Single Technology Appraisal

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from AbbVie
2. **Company summary of information for patients (SIP)** from AbbVie
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Blood Cancer UK
   b. Lymphoma Action
   c. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
5. **External Assessment Report** prepared by BMJ Technology Assessment Group
6. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company**
   a. Technical engagement response
   b. Technical engagement appendix
   c. Company response regarding fully adjusted MAICs
   d. Severity and cost calculations
   e. Response to EAG critique of company technical engagement response
8. **Technical engagement responses and statements from experts:**
   a. Assoc. Professor David Lewis – clinical expert, nominated by National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

b. Dr Wendy Osborne – clinical expert, nominated by the British Society for Haematology

9. External Assessment Report critique of company response to technical engagement prepared by BMJ Technology Assessment Group

a. EAG critique of company technical engagement response
b. EAG critique of company technical engagement appendix

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments

[ID4045]

Document B

Company evidence submission

April 2023

File name	Version	Contains confidential information	Date
ID4045_Epcoritamab_NICE_Document B_Final_09June23 [ACIC]	Final: Updated ACIC highlighting	Yes	09 June 2023

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Instructions for companies 2
Contents 3
Tables 5
Figures 8
Abbreviations 10
B.1 Decision problem, description of the technology and clinical care pathway 14
B.1.1 Decision problem 15
B.1.2 Description of the technology being evaluated 18
B.1.3 Health condition and position of the technology in the treatment pathway 20
B.1.3.1 Disease overview and prognosis 20
B.1.3.2 Symptoms and health-related quality of life 24
B.1.3.3 Epcoritamab 25
B.1.3.4 Clinical pathway of care 26
B.1.4 Equality considerations 31
B.2 Clinical effectiveness 32
B.2.1 Identification and selection of relevant studies 33
B.2.2 List of relevant clinical effectiveness evidence 33
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence 35
B.2.3.1 Trial design and methodology 35
B.2.3.2 Patient characteristics 40
B.2.3.3 Patient disposition 46
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence 47
B.2.4.1 Trial populations 47
B.2.4.2 Statistical analyses 48
B.2.5 Critical appraisal of the relevant clinical effectiveness evidence 51
B.2.6 Clinical effectiveness results of the relevant studies 52
B.2.6.1 Overview of the clinical effectiveness results 53
B.2.6.2 Primary endpoint 53
B.2.6.3 Secondary endpoints 55
B.2.6.4 Patient reported outcomes 60
B.2.7 Subgroup analysis 62
B.2.8 Indirect and mixed treatment comparisons 64
B.2.8.1 Methods of the indirect treatment comparison 65
B.2.8.2 Results of the indirect treatment comparison 72
B.2.8.3 Uncertainties in the indirect and mixed treatment comparisons 82
B.2.9 Adverse reactions 84
B.2.9.1 Summary of treatment-emergent adverse events 84
B.2.9.2 Treatment-emergent adverse events 86
B.2.9.3 Serious TEAEs 87
B.2.9.4 Treatment-emergent adverse events leading to discontinuation 88
B.2.9.5 Adverse events of special interest 88
B.2.9.6 Patient deaths 89
B.2.10 Ongoing studies 89
B.2.11 Interpretation of clinical effectiveness and safety evidence 90
B.2.11.1 Principal findings from the clinical evidence base 90
B.2.11.2 Strengths and limitations of the clinical evidence base 91
B.2.11.3 Conclusions 93
B.3 Cost effectiveness 95
B.3.1 Published cost-effectiveness studies 96
B.3.2 Economic analysis 96
B.3.2.1 Patient population 97
B.3.2.2 Model structure 97

B.3.2.3 Intervention technology and comparators 102
B.3.3 Clinical parameters and variables 102
B.3.3.1 Baseline characteristics 102
B.3.3.2 Survival inputs and assumptions 104
B.3.3.3 Time-to-event analyses: Patients ineligible for, or chose not to receive, intensive therapies 105
B.3.3.4 Time-to-event analyses: Patients eligible for intensive therapies 114
B.3.3.5 Adverse events 124
B.3.3.6 Background mortality 127
B.3.4 Measurement and valuation of health effects 127
B.3.4.1 Health-related quality-of-life data from clinical trials 127
B.3.4.2 Mapping 128
B.3.4.3 Health-related quality-of-life studies 128
B.3.4.4 Age-related utility deterioration 128
B.3.4.5 Adverse reactions 129
B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis 129
B.3.5 Cost and healthcare resource use identification, measurement and valuation 130
B.3.5.1 Intervention and comparators' costs and resource use 130
B.3.5.2 Health-state unit costs and resource use 134
B.3.5.3 Adverse reaction unit costs and resource use 137
B.3.5.4 Miscellaneous unit costs and resource use 138
B.3.6 Severity 138
B.3.7 Uncertainty 139
B.3.8 Managed access proposal 139
B.3.9 Summary of base-case analysis inputs and assumptions 140
B.3.9.1 Summary of base-case analysis inputs 140
B.3.9.2 Assumptions 143
B.3.10 Base-case results 149
B.3.10.1 Base-case cost-effectiveness analysis results 149
B.3.11 Exploring uncertainty 154
B.3.11.1 Probabilistic sensitivity analysis 154
B.3.11.2 Deterministic sensitivity analysis 155
B.3.11.3 Scenario analysis 156
B.3.12 Subgroup analysis 163
B.3.13 Benefits not captured in the QALY calculation 163
B.3.14 Validation 163
B.3.14.1 Validation of cost-effectiveness analysis 163
B.3.15 Interpretation and conclusions of economic evidence 165
B.3.15.1 Generalisability of the analysis 165
B.3.15.2 Strengths and limitations of the analysis 165
B.3.15.3 Summary of the economic evidence for epcoritamab 166
B.3.15.4 Conclusions 166
References 167

Tables

Table 1: The decision problem 16
Table 2: Technology being appraised 18
Table 3: Dosing schedule for epcoritamab 18
Table 4: Overview of different subtypes of LBCL 22
Table 5: Clinical effectiveness evidence 34
Table 6: Summary of trial methodology 37
Table 7: Key demographic characteristics 40
Table 8: Baseline disease characteristics (FAS) 42
Table 9: Prior anticancer therapies (FAS) 44
Table 10: Disposition of patients (FAS; [redacted] data cut-off) 46
Table 11: Analysis sets used for the outcomes in EPCORE™ NHL-1 (aNHL cohort) 47
Table 12: Summary of statistical analyses in EPCORE™ NHL-1 48
Table 13: Quality assessment conducted for EPCORE™ NHL-1 51
Table 14: Overview of key clinical effectiveness results from EPCORE™ NHL-1 (FAS; [redacted] data cut-off) 53
Table 15: ORR and BOR based on IRC Assessment, Lugano Criteria (FAS; [redacted] data cut-off) 54
Table 16: DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 55
Table 17: PFS based on IRC assessment Lugano Criteria (FAS; [redacted] data cut-off) 57
Table 18: OS (FAS; [redacted] data cut-off) 58
Table 19: TTNT (FAS; [redacted] data cut-off) 60
Table 20: Mean scores for FACT-Lym total score and FACT-LymS while on treatment (FAS – DLBCL population [N=139]; [redacted] data cut-off) 61
Table 21: Mean scores for EQ-5D-3L health utility score while on treatment (FAS – DLBCL population [N=139]; [redacted] data cut-off) 61
Table 22: Comparator studies selected for inclusion in the ITC (base case and scenario analyses) 66
Table 23: Summary of key characteristics of the studies included in the ITC 67
Table 24: Outcome definition for PFS and response for each treatment included in the ITC 69
Table 25: Summary of the base case MAICs and the supportive MAICs conducted 74
Table 26: Baseline characteristics for base case analysis A (epcoritamab DLBCL population adjusted to Sehn *et al.* 3L+) 75
Table 27: Baseline characteristics for the pairwise comparison of epcoritamab versus axi-cel (epcoritamab DLBCL, CAR-T eligible – adjusted to match axi-cel) 76
Table 28: Baseline characteristics for the pairwise comparison of epcoritamab versus axi-cel (epcoritamab LBCL, CAR-T eligible – adjusted to match axi-cel) 77
Table 29: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (SCHOLAR-1) 78
Table 30: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, CAR-T eligible) versus axi-cel (ZUMA-1) 79
Table 31: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, CAR-T eligible) versus axi-cel (ZUMA-1) 81
Table 32: Summary of TEAEs (SAF; [redacted] data cut-off) 85
Table 33: Most common (at least 10% in any group) TEAEs by SOC and PT (SAF; [redacted] data cut-off) 86
Table 34: Most common (2% or more in any group) serious TEAEs by SOC and PT (SAF; [redacted] data cut-off) 87
Table 35: Summary of AESIs (SAF; [redacted] data cut-off) 88
Table 36: Summary of fatal TEAEs by PT (SAF; [redacted] data cut-off) 89
Table 37: Features of the economic analysis compared to previous NICE evaluations in the population of interest[a] 100
Table 38: Epcoritamab dosing schedule 102

Table 39: Baseline patient characteristics applied in the cost-effectiveness model, base case approach 103
Table 40: Goodness of fit statistics for OS (AIC and BIC): base case analysis A – ineligible for, or choose not to receive, intensive therapy 107
Table 41: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy 108
Table 42: Goodness of fit statistics for PFS (AIC and BIC): base case analysis A – ineligible for, or choose not to receive, intensive therapy 109
Table 43: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy 110
Table 44: Goodness of fit statistics for ToT (AIC and BIC): base case analysis A – ineligible for, or choose not to receive, intensive therapy 111
Table 45: Predicted and observed ToT for epcoritamab at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy 112
Table 46: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (base case analysis A) 113
Table 47: Goodness of fit statistics for OS (AIC and BIC): base case analysis B – eligible for intensive therapy 116
Table 48: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy 117
Table 49: Goodness of fit statistics for PFS (AIC and BIC): base case analysis B – eligible for intensive therapy 119
Table 50: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy 120
Table 51: Goodness of fit statistics for ToT (AIC and BIC): base case analysis B – eligible for intensive therapy 121
Table 52: Predicted and observed ToT for epcoritamab at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy 122
Table 53: Epcoritamab populations included in scenario analyses: Patients eligible for intensive therapies 123
Table 54: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – Patients eligible for intensive therapies 124
Table 55: AEs incidence and duration inputs applied in the cost-effectiveness model 126
Table 56: Summary of utility values derived from EPCORE™ NHL-1 – linear mixed models ... 128
Table 57: Summary of utility values from ZUMA-1 used in prior NICE evaluations[3, 14, 44] 128
Table 58: Adverse event-related utility decrements applied in the cost-effectiveness model 129
Table 59: Summary of utility values for the cost-effectiveness analysis 130
Table 60: Drug dosage inputs applied in the cost-effectiveness model 131
Table 61: Drug acquisition costs for intervention and comparators 131
Table 62: One-time drug acquisition, administration, or monitoring cost inputs applied in the cost-effectiveness model 132
Table 63: Drug administration cost inputs applied in the cost-effectiveness model 133
Table 64: Proportion of patients receiving subsequent treatments and the distribution of subsequent treatments used in the cost-effectiveness model 133
Table 65: Subsequent treatment cost inputs applied in the cost-effectiveness model 134
Table 66: Disease management-related resource use by health state and cost inputs applied in the cost-effectiveness model 135
Table 67: Disease progression-related resource use and cost inputs applied in the cost-effectiveness model 136
Table 68: Terminal care-related resource use and cost inputs applied in the cost-effectiveness model 136
Table 69: AE cost inputs applied in the cost-effectiveness model 137
Table 70: Summary features of QALY shortfall analysis 138

Table 71: Summary of health state benefits and utility values for QALY shortfall analysis 138
Table 72: Summary of QALY shortfall analysis 139
Table 73: Summary of variables applied in the economic model 140
Table 74: Key model assumptions for the base case cost-effectiveness analysis 143
Table 75: Base-case probabilistic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies 149
Table 76: Base-case probabilistic results (no severity modifier; epcoritamab list price): ineligible for, or choose not to receive, intensive therapies 150
Table 77: Net health benefit (probabilistic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies 150
Table 78: Net health benefit (probabilistic; no severity modifier; at epcoritamab list price): ineligible for, or choose not to receive, intensive therapies 150
Table 79: Base-case probabilistic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies 151
Table 80: Base-case probabilistic results (epcoritamab list price): ineligible for, or choose not to receive, intensive therapies 151
Table 81: Net health benefit (probabilistic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies 151
Table 82: Net health benefit (probabilistic; at epcoritamab list price): ineligible for, or choose not to receive, intensive therapies 152
Table 83: Base-case probabilistic results (epcoritamab PAS price): eligible for intensive therapies 152
Table 84: Base-case probabilistic results (epcoritamab list price): eligible for intensive therapies 153
Table 85: Net health benefit (probabilistic; at epcoritamab PAS price): eligible for intensive therapies 153
Table 86: Net health benefit (probabilistic; at epcoritamab list price): eligible for intensive therapies 153
Table 87: Scenario analysis B.1– HRs applied to the epcoritamab curves to derive the time-to-event outcomes for axi-cel 157
Table 88: Resource use estimates applied to the PD health state based on previous NICE appraisals in R/R LBCL and clinical expert feedback 158
Table 89: Scenario analyses results (epcoritamab PAS price) 160

Figures

Figure 1: Mechanism of action of epcoritamab 26
Figure 2: Current clinical pathway of patients with LBCL in the UK, including the proposed positioning of epcoritamab 28
Figure 3: EPCORE™ NHL-1 trial design 36
Figure 4: Waterfall plot of best reduction in SPD based on IRC assessment per Lugano Criteria (FAS; [redacted] data cut-off) 54
Figure 5: KM plot of DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 56
Figure 6: KM plot of PFS based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 57
Figure 7: KM plot of PFS based on IRC assessment, Lugano Criteria, by BOR (FAS; * [redacted] data cut-off) 58
Figure 8: KM plot of OS (FAS; [redacted] data cut-off) 59
Figure 9: Mean change from baseline in EQ-5D-3L Health Utility Score (PRO-evaluable Set – DLBCL population [N=139]; [redacted] data cut-off) 62
Figure 10: Forest plot of ORR in prespecified subgroups based on IRC assessment determined by Lugano Criteria - DLBCL patients (FAS; [redacted] data cut-off) 63
Figure 11: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to Sehn *et al.* 3L+ 78
Figure 12: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population 80
Figure 13: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population 80
Figure 14: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population 81
Figure 15: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population 82
Figure 16: Determination of state membership in a standard three-state PSM 98
Figure 17: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT) 106
Figure 18: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT) 106
Figure 19: Long-term OS extrapolations for epcoritamab: base case analysis A – ineligible for, or choose not to receive, intensive therapy 107
Figure 20: Long-term PFS extrapolations for epcoritamab: base case analysis A – ineligible for, or choose not to receive, intensive therapy 110
Figure 21: Long-term ToT extrapolations for epcoritamab: base case analysis A – ineligible for, or choose not to receive, intensive therapy 112
Figure 22: KM plot of PFS, OS and ToT in the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population (N=[redacted]) from EPCORE™ NHL-1 ([redacted] data cut-off) 114
Figure 23. Log-cumulative hazard curve – OS (epcoritamab versus axi-cel) 115
Figure 24. Schoenfeld residual curve – OS (epcoritamab versus axi-cel) 115
Figure 25: Long-term OS extrapolations for epcoritamab: base case analysis B – eligible for intensive therapy 117
Figure 26. Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel) 118
Figure 27. Schoenfeld residual curve – PFS (epcoritamab versus axi-cel) 119
Figure 28: Long-term PFS extrapolations for epcoritamab: base case analysis B – eligible for intensive therapy 120
Figure 29: Long-term ToT extrapolations for epcoritamab: base case analysis B – eligible for intensive therapy 122
Figure 30: Cost-effectiveness scatter plot for epcoritamab versus R-based CIT (epcoritamab PAS price) 154
Figure 31: Cost-effectiveness acceptability curve for epcoritamab versus R-based CIT (epcoritamab PAS price) 154
Figure 32: Cost-effectiveness scatter plot for epcoritamab versus axi-cel (epcoritamab PAS price) 155

Figure 33: Cost-effectiveness acceptability curve for epcoritamab versus axi-cel (epcoritamab PAS price) 155
Figure 34: DSA tornado plot for epcoritamab versus R-based CIT (epcoritamab PAS price) 156
Figure 35: DSA tornado plot for epcoritamab versus axi-cel (epcoritamab PAS price) 156

Abbreviations

Abbreviation	Definition
ABC	Activated B-cell
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
ALDVMM	Adjusted limited dependent variable mixture models
Allo-SCT	Allogenic stem cell transplantation
ALT	Alanine transaminase
aNHL	Aggressive B-cell non-Hodgkin lymphoma
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase
Axi-cel	Axicabtagene ciloleucel
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BR	Bendamustine and rituximab
BSA	Body surface area
BSH	British Society of Haematology
CAR-T	Chimeric antigen receptor T-cell
CDF	Cancer Drugs Fund
CI	Confidence interval
CIT	Chemoimmunotherapy
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTLS	Clinical tumour lysis syndrome
CXDX	Cycle X Day X
DHAP	Dexamethasone, cytarabine, cisplatin
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DOCR	Duration of complete response
DOR	Duration of response
DSA	Deterministic sensitivity analysis
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eMIT	Electronic market information tool
EOT	End of treatment
Epco	Epcoritamab
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
ESMO	European Society for Medical Oncology
FACT-Lym	The Functional Assessment of Cancer Therapy
FACT-LymS	Functional Assessment of Cancer Therapy – Lymphoma Subscale
FAS	Full analysis set
FDG	Fluorodeoxyglucose
FISH	Fluorescence in situ hybridisation
FL	Follicular lymphoma
FL Gr 3B	Follicular lymphoma grade 3B
GCB	Germinal centre B-cell
GDP	Gemcitabine, dexamethasone and cisplatin
GEP	Gene expression profiling
GP	General practitioner
HS	Health state
HGBCL	High-grade B-cell lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
HTA	Health Technology Appraisals
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio
ID	Identification
IHC	Immunohistochemistry
iNHL	Indolent B-cell non-Hodgkin lymphoma
IPD	Individual patient data
IPI	International Prognostic Index
IRC	Independent Review Committee
ITC	Indirect treatment comparison
IVE	Ifosfamide, etoposide and epirubicin
IWG	International Working Group
KM	Kaplan–Meier
LBCL	Large B-cell lymphoma
LDH	Lactate dehydrogenase
LLM	Linear mixed models
LYG	Life years gained
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MAIC	Matching adjusted indirect comparisons
Max	Maximum
MCL	Mantle cell lymphoma

MD	Mean difference
MID	Minimum important difference
Min	minimum
MRD	Minimal residual disease
mRES	Modified response evaluable set
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NE	Non evaluable
NHB	Net health benefit
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NHSEI	National Health Service England and National Health Service Improvement
NICE	National Institute for Health and Care Excellence
NR	Not reached or not reported
ORR	Overall response rate
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient access scheme
PD	Partial disease
PET	Positron emission tomography
PFS	Progression-free survival
PF	Progression-free
PK	Pharmacokinetic
PMBCL	Primary mediastinal B-cell lymphoma
Pola + BR	Polatuzumab vedotin with rituximab and bendamustine
Pola + BR/R	Polatuzumab vedotin plus rituximab with or without bendamustine
Pola + R-CHP	Polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone
PPS	Post-progression survival
PRO	Patient-reported outcome
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
R	Rituximab
R-Gem	Rituximab and gemcitabine

R-GemOX	Rituximab, gemcitabine and oxaliplatin
R/R	Relapsed and/or refractory
R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
RCT	Randomised controlled trial
RES	Response evaluable set
RP2D	Recommended phase 2 dose
RWE	Real-world evidence
SAE	Serious adverse event
SAF	Safety analysis set
SC	Subcutaneous
SCT	Stem cell transplant
SD	Stable disease or standard deviation
SE	Standard error
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ class
SPD	Sum of the product of the diameters
TA	Technology appraisal
TdT	Terminal deoxynucleotidyl transferase
TEAE	Treatment-emergent adverse events
TFL	Transformed follicular lymphoma
ToT	Time on treatment
TTCR	Time to complete response
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTR	Time to response
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WHO	World Health Organisation
X	The dose level where the trigger (grade 2 non-haematological toxicity etc.) is observed: switch from single patient cohort to three patient cohort
Y	The highest investigated dose level
3L+	Third-line and beyond

B.1 Decision problem, description of the technology and clinical care pathway

Relapsed and/or refractory LBCL

- Malignant lymphoma is a disease characterised by malignant transformation of the cells from lymphoid tissue. Historically, lymphomas have been divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Large B-cell lymphoma (LBCL) represents almost 30% of all cases of NHL and diffuse large B-cell lymphoma is the most common form of NHL. LBCL has an estimated one-year prevalence of 4,310 cases in the United Kingdom (UK; based on data from 31st December 2019) and 150,000 new cases per year worldwide.[1, 2]
- Numerous subtypes of LBCL exist, with diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma Grade 3B (FL Gr 3B) all considered within this submission. The disease characteristics and treatment pathways of each of these LBCL subtypes are all highly similar.
- Overall, the outcomes for patients with relapsed and/or refractory (R/R) LBCL are poor and there are few potentially curative treatment options for patients with R/R LBCL, especially at third-line and beyond (3L+).[3] In addition, patients with R/R LBCL experience poor health-related quality of life (HRQoL) and disease burden is heavily linked to response and survival.[4]

Epcoritamab

- Epcoritamab is anticipated to be licenced for use in [redacted]
- Epcoritamab is a humanised IgG1-bispecific antibody that binds to the T-cell antigen CD3 and the B-cell antigen CD20, and represents the first and only subcutaneous treatment available for adult patients with R/R LBCL after two or more lines of systemic therapy.[5]
- The subcutaneous (SC) administration enables quick administration across different practice settings when compared with intravenous (IV) administration, and greater flexibility and convenience for both clinicians and patients when compared with currently available IV therapies.[6]

Current clinical pathway of care

- The treatment pathway for most forms of LBCL, including PMBCL, HGBCL and FL Gr 3B, is very similar to that for DLBCL.[7, 8]
- First-line treatment usually comprises chemotherapy and rituximab (R), with radiotherapy in some cases.[4, 9] However, in February 2023, the National Institute for Health and Care Excellence (NICE) recommended polatuzumab with rituximab, cyclophosphamide, doxorubicin and prednisolone (Pola + R-CHP) as a treatment option for untreated DLBCL.[10]
- At second-line, treatment choice for R/R disease is primarily dependent on eligibility for intensive therapies with the main treatment options being chemoimmunotherapy (CIT), followed by consolidation with autologous stem cell transplant (ASCT).[9, 11]
- Approximately 30% of patients will progress from second-line to third-line treatment.[12] At 3L+ there is no universal standard of care that is accessible to a broad range of patients. Those eligible for intensive therapies primarily receive chimeric antigen receptor T-cell (CAR-T) therapy, namely axicabtagene ciloleucel, and for those ineligible for, or choose not to receive, intensive therapies at third-line, a number of rituximab (R)-based chemotherapy combinations are the primary treatment options, considering UK clinicians' hesitancy to retreat with polatuzumab, following the recommendation of Pola + R-CHP.[13]
- Following relapse at third-line, treatment options are limited to CIT regimens and outcomes are poor.[4]
- For patients with R/R LBCL at 3L+, there remains a significant unmet need for tolerable, effective and readily available treatments that drive deep and durable responses across the patient population.

B.1.1 *Decision problem*

The objective of this appraisal is to determine the clinical and cost-effectiveness of epcoritamab in line with its anticipated marketing authorisation, for the treatment of [redacted]

The submission covers the technology's full marketing authorisation for this indication. The decision problem addressed in this submission is compared to that specified in the final scope issued by NICE in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory large B-cell lymphoma who have had 2 or more systemic therapies	[redacted]	N/A
Intervention	Epcoritamab	Epcoritamab, administered via subcutaneous injection	N/A

Comparator(s)	Established clinical management without epcoritamab including but not limited to:
	• Salvage chemotherapy with rituximab:
	  ○ DHAP (dexamethasone, cytarabine, cisplatin)
	  ○ ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
	  ○ GDP (gemcitabine, dexamethasone, cisplatin)
	  ○ GEMOX (gemcitabine and oxaliplatin)
	  ○ ICE (ifosfamide, carboplatin, etoposide)
	  ○ IVE (ifosfamide, etoposide, epirubicin)
	• Pixantrone
	• Pola + BR (only when stem cell transplantation is not suitable)
	• Axicabtagene ciloleucel for treating refractory or relapsed DLBCL after 2 or more systemic therapies (subject to NICE appraisal process)
		The comparators considered in this submission include:
		• R-based CIT
		• CAR-T therapy (axicabtagene ciloleucel)
			The comparators considered within this submission align with current UK clinical practice.
			
			Based on consultation with UK clinical experts, pixantrone monotherapy is not used in UK clinical practice due to a lack of efficacy and high toxicity. This is supported by the recent appraisal by NICE of tafasitamab with lenalidomide [ID3795],in which clinical experts and NHSEI confirmed that pixantrone is not prescribed due to a lack of efficacy and high toxicity.[14] As such, pixantrone is not considered a relevant comparator in this submission.
			
			Tafasitamab with lenalidomide is not recommended by NICE following its appraisal and therefore is not yet routinely used in UK clinical practice.[14]As such, it is not considered a relevant comparator in this submission.
			
			Pola + BR is recommended by NICE as a treatment option for R/R DLBCL. However, following the NICE recommendation of

	• Tafasitamab with lenalidomide (only when stem cell transplantation is unsuitable and subject to NICE appraisal process)		Pola + R-CHP for untreated DLBCL in February 2023, UK clinicians stated that Pola + BR will no longer be used for the majority of patients who have previously received polatuzumab as a component of frontline treatment.[10, 13] As such, Pola + BR is not considered a relevant comparator in this submission but has been considered in a scenario analysis for completeness.
Outcomes	**The outcome measures to be considered include:** • OS • PFS • Response rates • Adverse effects of treatment • HRQoL • ToT	**The outcome measures to be considered include:** • OS • PFS • Response rates (including ORR, CR, PR and DOR) • Adverse effects of treatment • HRQoL • TTD • TTNT	All outcomes requested in the final scope are presented, with additional outcomes that are important to demonstrate the benefits of epcoritamab.

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; CR: complete response; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; HRQoL: health-related quality of life; ID: identification; N/A: not applicable; NHS: National Health Service; NHSEI: National Health Service England and National Health Service Improvement; NICE: National Institute for Health and Care Excellence; ORR; overall response rate; OS: overall survival; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; Pola + R-CHP: polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone; PR: partial response; R/R: relapsed and/or refractory; ToT: time on treatment; TTD: time to treatment discontinuation; TTNT: time to next treatment; UK: United Kingdom.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with epcoritamab are presented in Table 2. Please refer to Appendix C for the summary of product characteristics and the United Kingdom (UK) public assessment report.

Table 2: Technology being appraised

UK approved name and brand name	Epcoritamab ([redacted]
Mechanism of action	Epcoritamab is a humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B-cells and to CD3 on T cells. CD20 is an antigen expressed on most human B-cell lymphomas. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T cell activation and T cell-mediated killing of CD20-expressing cells, as epcoritamab does not have direct immune effector mechanisms. This is a different mechanism of action to that of chemotherapy or conventional CD-20 targeting monoclonal bispecific antibodies, which can induce cytotoxicity through Fc-mediated effector functions.[5]
Marketing authorisation/CE mark status	The marketing authorisation for epcoritamab is anticipated to be granted by the [redacted].
Indications and any restriction(s) as described in the SmPC	Epcoritamab is anticipated to be licenced for use in [redacted] Contraindications for epcoritamab include hypersensitivity to epcoritamab or any of the following excipients:[5] • Sodium acetate trihydrate • Acetic acid • Sorbitol • Polysorbate 80 • Water for injections Other restrictions also include pregnancy and lactation. Women of childbearing age should be advised to use effective contraception during treatment with epcoritamab and for at least six months after the last dose. The effect of epcoritamab on male and female fertility is unknown.[5]
Method of administration and dosage	Epcoritamab is for SC injection only and should be administered by a licensed healthcare professional preferably in the lower part of abdomen or the thigh.[5] Epcoritamab should be administered according to the following dosing schedule in 28-day cycles:[5]

Table 3: Dosing schedule for epcoritamab

Cycle	**1**				**2 and 3**				**4–9**		**10+**
Day of cycle	1	8	15	22	1	8	15	22	1	15	1
Dose (mg)[a]	0.16	0.8	48	48	48	48	48	48	48	48	48

	[a] 0.16 mg is a priming dose, 0.8 mg is an intermediate dose and 48 mg is a full dose. **Source:** AbbVie, epcoritamab draft SmPC 2022.[5] Change of injection site from left to right side or vice versa is recommended especially during the weekly administration (Cycles 1–3).[5] Epcoritamab should be administered until disease progression or unacceptable toxicity occurs.[5]
Additional tests or investigations	No additional tests or investigations are required to determine eligibility for epcoritamab in NHS clinical practice.
List price and average cost of a course of treatment	• Epcoritamab is available at a list price of [redacted] • Average cost of a course of treatment with epcoritamab (PAS price): ○ Base case A: [redacted] ○ Base case B: [redacted]
Patient access scheme	A simple PAS is in place for epcoritamab. The proposed epcoritamab price with the PAS applied is [redacted]

Abbreviations: DLBCL: diffuse large B-cell lymphoma; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade-B-cell lymphoma; LBCL: large B-cell lymphoma; NHS: National Health Service; PAS: patient access scheme; PMBCL: primary mediastinal B-cell lymphoma; SC: subcutaneous; SmPC: summary of product characteristics; UK: United Kingdom.

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 Disease overview and prognosis

Large B-cell lymphoma

Malignant lymphoma is a disease characterised by malignant transformation of the cells from lymphoid tissue, which can originate from B-cells, T-cells or NK cells. In more than 90% of cases, lymphoma originates in B-cells.[15] Historically, lymphomas have been divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), based on the presence (or absence) of Reed-Sternberg lymphocytes (which are present in HL but absent in NHL).[16] NHL represent approximately 90% of all malignant lymphomas.[17]

LBCL is the most common form of NHL, representing almost 30% of all cases of NHL with approximately 150,000 new cases per year worldwide.[1, 2] In the UK, there are an estimated 8.3 cases of LBCL diagnosed per 100,000 people each year (based on diagnoses between 2010 and 2019), and LBCL has an estimated one-year prevalence of 4,310 cases in the UK (based on data from 31st December 2019).[218] LBCL is characterised by proliferation of atypical irregular large B-cells that can have a distinct growth pattern; this is usually a diffuse infiltration of a lymph node or tissue outside a lymph node (extra-nodal), or the large cells may form a follicular (nodular) growth pattern.[19] Therefore, numerous subtypes of LBCL exist. The diagnosis of LBCL is based on the investigation of tumour material, often a whole lymph node or, less commonly, a core needle biopsy of a lymph node.[19] The prognosis of these malignancies is dependent on a number of factors, including the type of lymphoma and the stage of the disease. The subtypes of LBCL included within this submission are discussed further in subsequent paragraphs.

The population of interest in this submission is R/R LBCL following two or more lines of systemic therapy. The term relapsed refers to disease that returns following a period of remission, oftendefined as disease that recurs at least six months after completion of therapy. Refractory refers to disease that does not respond to treatment, or the response does not last long; it is typically defined as progression either during therapy or within six months of completion of therapy.[20, 21] In addition, LBCL can be either *de novo* or transformed; transformed disease occurs when low-grade lymphoma develops into a different type of lymphoma, commonly DLBCL.[22]

DLBCL

DLBCL is the most common subtypes of LBCL, accounting for approximately 90% of LBCL cases in the UK; the estimated incidence of DLBCL in the UK is 7.4 per 100,000 individuals (based on diagnoses between 2010 and 2019) and the estimated one-year prevalence of DLBCL is 4,000 cases (based on UK data from 31st December 2019).[2, 18] Further, it affects slightly more men than women and it typically affects older adults, with a peak incidence in people aged 65–74 years.[23]

DLBCL is characterised by an aggressive clinical course with heterogeneity in clinical, pathological and molecular presentation; this can result in varying prognosis for different patients.[24] It is generally composed of large neoplastic B lymphoid cells that express CD19, CD20, CD22, CD79a (pan B-cell antigens).[1, 25] In most cases, the causes of DLBCL are unknown.[8] However, occasionally, it is associated with autoimmune conditions (e.g., rheumatoid

arthritis and systemic lupus erythematosus), infections (human immunodeficiency virus, human T-cell leukaemia, Epstein-Barr virus), and prior organ transplantation. [7,8]

HGBCL

The World Health Organisation (WHO) classification 2016 recognises some aggressive lymphomas as separate entities, such as HGBCL.[19] This is because <10% of DLBCL cases express *MYC* (a regulator gene that modulates cell proliferation, differentiation, survival, and metabolism) rearrangements. [26-28] In approximately half of these cases a *BLC2* and/or *BCL6* rearrangement is noted. [26-28] These are referred to as double-hit lymphomas (when rearrangements involve *MYC* and either *BCL2* or *BCL6*) and triple-hit lymphomas (if all 3 rearrangements are observed), or collectively as HGBCL.[29] Approximately 5% of DLBCLs have rearrangements of the *MYC* and *BCL2* and/or *BCL6* genes and are thus called HGBCL.[27] Based on WHO's updated 2022 classification, DLBCL tumours expressing terminal deoxynucleotidyl transferase (TdT) are also classified as HGBCL.[30]

Due to these rearrangements, HGBCL has some distinct pathobiological features compared with DLBCL, and it is associated with poorer prognosis and increased risk of central nervous system involvement.[26] Despite this, HGBCL is commonly treated following the same clinical pathway of care as DLBCL (Section B.1.3.4).[7, 31]

PMBCL

PMBCL is another (relatively rare [2–4% of NHL cases]) subtype of LBCL, that mainly affects young adults (25–40 years) and women.[7 32] In the UK, the estimated incidence of PMBCL is 0.2 cases per 100,000 individuals and the estimated one-year prevalence is approximately 120 cases, constituting ~3% of all LBCL cases.[2] Similarly to DLBCL, CD19/20 are expressed in PMBCL.[33] However, PMBCL has a distinct phenotype compared with DLBCL due to CD30, CD23, PDL1, PDL2 expression, as well as a unique gene expression profiling signature.[1] Further, PMBCL primarily develops within the mediastinal area. As such, a majority of the symptoms associated with PMBCL arise due to pressure of the lymphoma on the chest. [32] This results in symptoms such as cough, tachypnoea, superior vena caval obstruction, vein thrombosis, chest pain, or dysphagia.[32] PMBCL follows a similar clinical pathway of care to DLBCL (Section B.1.3.4).[34]

FL Gr 3B

Lastly, follicular lymphoma (FL) is the most common type of low-grade NHL.[35] It accounts for approximately 22% of all NHLs and roughly 2,200 people are diagnosed with the disease each year in the UK.[35, 36] FL may be graded according to the number of large cells (cetroblasts) seen under a miscrope.[36] FL Gr 3B is a subtype of FL, defined by the presence of follicles exclusively comprised of centroblasts (activated B-cell that is enlarged), which is associated with a much poorer prognosis, when compared with other forms of FL.[37 38] FL can be characterised as either Grade 1/2 and Grade 3A, or Grade 3B (Gr 3B) depending on the proportion of centroblasts present; FL Gr 3B has been defined as FL with more than 15% centroblast per high resolution field present as solid sheets, whilst FL1/2 have a less extensive centroblast component and a predominance of centrocytes.[37, 38] The molecular characteristics of FL Gr 3B are highly similar to DLBCL.[17]

The estimated one-year prevalence of FL in the UK is approximately 2,430 cases.[2] It is estimated that approximately 80–90% of FL are FL 1/2 and approximately 5–10% of FL cases are FL Gr

3B. In addition, approximately 50% of FL Gr 3B cases coexist with either lower-grade FL or DLBCL.[2, 38] FL Gr 3B is more prevalent in females than males, at a ratio of approximately 1.7:1.[37]

Although distinct from DLBCL, as FL Gr 3B originates from FL, many aspects of FL Gr 3B are reminiscent of *de novo* DLBCL, including clinical presentation.[37-40] As such, treatment of FL Gr 3B typically follows the same treatment pathway as that of DLBCL (Section B.1.3.4) and it has been suggested that FL Gr 3B may be a follicular growing variant of DLBCL. Symptoms of FL Gr 3B commonly include swelling in the neck, armpit or groin due to lymphoma cells building up in the lymph nodes.[41]

A summary of the key subtypes of LBCL is provided in Table 4.

Table 4: Overview of different subtypes of LBCL

Subtype	Diagnosis	Clinical features and outcomes
DLBCL	• Diffuse proliferation of medium or large lymphoid B-cells • Expresses CD19, CD20, CD22, CD79a, PAX5, and surface or cytoplasmic immunoglobulin	• Median age: 65–70 years • Nodal presentation most common • 30–40% of cases are primary extranodal • Prognosis varies
HGBCL	• Variable morphology • Includes DLBCL • Blastoid features; *MYC* and *BCL2* and/or *BCL6* rearrangements • DLBCL tumours expressing TdT	• Frequently aggressive clinical presentation • Higher risk of CNS involvement • Poor prognosis
PMBCL	• Putative thymic B-cell origin • Medium-to-large B-cells, frequently with sclerosis • Expresses CD30, CD23, PDL1, PDL2 • Unique GEP signature • Frequent 9p21 amplification • Genomic alterations of CIITA	• Most common in young adults and females • Primarily develops within the mediastinal region, with local invasion • Can involve other nodal or extranodal sites (kidney and liver) • Prognosis varies
FL Gr 3B	• Lack CD10 expression • Lower probability of *BCL2* expression • Increased *TP53* expression • Features resemble DLBCL	• Clinical presentation resembles DLBCL • More common in females than males • Poor prognosis, when compared to other forms of FL

Abbreviations: CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; FL Gr 3B: follicular lymphoma grade 3B; GEP: gene expression profiling; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; TdT: terminal deoxynucleotidyl transferase.
Sources: Salaverria et al , 2011;[37] Sehn et al, 2021;[1] Falini et al, 2023.[30]

Data on LBCL as a whole and the rarer subtypes of LBCL, including PMBCL, HGBCL and FL Gr 3B, are limited. As such, due to limited data across the rarer subtypes of LBCL, the following sections primarily focus on DLBCL, with supplementary info on the other subtypes where available. Given that the disease characteristics and treatment pathways of the other subtypes of LBCL, including PMBCL, HGBCL and FL Gr 3B, are highly similar to DLBCL, the following information on prognosis and disease burden is considered generalisable to all subtypes of

LBCL.[28, 32, 36] This was supported by feedback from UK clinical experts who stated that prognosis at relapse is highly similar between LBCL subtypes.[17]

Prognosis for patients with LBCL

For patients with DLBCL specifically, outcomes differ between treatment stage; the five-year survival rates are around 65–70% for stage 1 and 2 disease, dropping to 50% for advanced stages 3 and 4.[3, 42] Although many patients are cured at first-line with 6–8 cycles of R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone) CIT, approximately 10–15% have primary refractory disease and a further 20–30% relapse.[9] Similarly, recent data on patients receiving Pola + R-CHP at first-line shows that 76.7% of patients are expected to remain progression-free after 24 months.[3]

Following relapse at first-line, the primary treatment option is chemotherapy re-induction consolidated with high-dose chemotherapy and stem cell transplant (SCT). However, of patients who relapse at first-line and receive chemotherapy in combination with SCT, approximately 50% of patients will experience a subsequent relapse .[43] In the NICE technology appraisal (TA) of polatuzumab vedotin with bendamustine plus rituximab (Pola + BR) [TA649], a patient expert estimated that the median overall survival (OS) for patients with R/R DLBCL is less than 1 year.[44] In addition, patients with R/R DLBCL who are not candidates for intensive therapies have a particularly poor prognosis; approximately only 50% of these patients survive longer than six to 12 months.[43]

In the real-world setting, OS and progression-free survival (PFS) for patients with R/R DLBCL have been demonstrated to be short.[34] A real-world study by Northend *et al.* (2022) provides data on the survival of patients with R/R DLBCL in the UK specifically, following treatment with Pola + BR after one or more prior therapies. In this study, median OS was 8.2 months (95% CI: 5.9, 14.3) and median PFS was 4.8 months (95% CI: 3.7, 9.3).[45] In this real-world study, the median number of prior lines of therapy was two (range: 1–6), however 33.8% of patients had only received one prior line of therapy. As the decision problem for this submission focuses on patients with R/R LBCL who have received two or more prior lines of therapy, outcomes in the population of interest (i.e. the 3L+) are likely to be poorer than those observed in this real-world study. For this reason, and due to recent changes with Pola + BR now only being used in a minority of patients in the third-line and beyond setting, this real-world study cannot be used directly to inform efficacy estimates for current clinical practice in the 3L+ setting in the UK, but provide useful context to the wider LBCL population.

Considering the other subtypes of LBCL, PMBCL (like DLBCL) was historically treated with R-CHOP, often with consolidation radiotherapy.[32] With improving supportive care patients with PMBCL now have a 5-year survival rate exceeding 70%.[46] Data on patients with R/R PMBCL after two or more lines of systemic therapy specifically is limited; however the available data demonstrates that prognosis of patients with R/R PMBCL not responding to CIT is poor.[46]

The lymphomas included within the term HGBCL are among the most clinically aggressive types of LBCL. They are characterised by high-risk clinical features at presentation, often have a poor response to standard therapy, and they are associated with higher central nervous system infiltration. These factors can lead to an increased risk of relapse and a worse prognosis when compared to other B-cell lymphomas.[47]

There are limited data on the prognosis of patients with FL Gr 3B specifically. For patients with FL, median survival ranges from 8 to 15 years with 5-year survival outcomes ranging from 53% to 91%.[36] Based on the data available, prognosis of patients with FL Gr 3B is considerably worse than the prognosis of patients with other forms of FL.[37] Further, histological transformation of FL to DLBCL is generally associated with shortened survival, with a median OS of less than two years.[36]

Overall, the outcomes for patients with R/R LBCL are poor and there are few potentially curative treatment options for patients with R/R LBCL, especially after two or more prior therapies.[3]

B.1.3.2 Symptoms and health-related quality of life

Disease burden of LBCL

Patients with LBCL typically present with swollen lymph nodes in the neck, armpit or groin, but a mass of malignant lymphoma can occur in any region or tissue; in the case of PMBCL, the swollen lymph nodes occur in the area behind the breastbone and between the lungs (mediastinum). Patients with LBCL may experience a range of symptoms, such as fever, night sweats and unexplained weight loss (collectively known as 'B symptoms'), fatigue, pain and severe itching.[48] A range of other symptoms can be experienced depending on the organs and tissues that are affected by the disease. Given the range of symptoms experienced, LBCL can have a substantial, detrimental impact on patients HRQoL.[4] For patients with DLBCL specifically, health status and functioning have been shown to be negatively impacted when compared with the general population and patients who report symptoms exhibit significantly lower HRQoL when compared with patients who do not report symptoms from the disease.[4] Furthermore, patients with DLBCL are subsequently more prone to infections and hospital admissions which can negatively affect HRQoL.[4]

In addition to the burden of the disease itself, current treatments for LBCL are associated with a number of adverse events (AEs). The side effects of chemotherapy such as infection, anaemia, nausea and vomiting, fatigue, mouth ulcers and bowel changes impart a substantial humanistic burden on patients with LBCL.[49] Several later-line treatments for R/R LBCL, are also associated with frequent toxicity, including sepsis and mucositis, and severe AEs, including cytokine release syndrome and neurotoxicity; these can require frequent and/or prolonged stays in hospital.[50] In addition, all currently available third-line treatments for R/R LBCL require an IV infusion, which can have long infusion times and result in capacity issues in hospitals.[51, 52] Furthermore, this mode of administration is expected to negatively impact patients' HRQoL; a study conducted in patients with R/R DLBCL or FL demonstrated that the majority of patients prefer SC treatment when compared with IV treatment.[53] Therefore, an effective SC treatment for R/R LBCL would be expected to help alleviate some of the burden associated with the disease.

Not only do patients experience the AEs associated with treatment, the manufacturing process of CAR-T therapies, including axi-cel, means that patients cannot receive treatment with CAR-T therapies immediately. According to UK clinical experts, patients in the UK wait approximately seven weeks from being approved for treatment with axi-cel to receiving the infusion. In patients with rapidly progressing disease, this represents an additional source of disease burden and patients may experience rapid deterioration in their health whilst waiting for the treatment [17] An effective therapy that is readily available in hospital pharmacies is expected to be welcomed by patients and health care professionals.

There are limited data on HRQoL of patients with R/R LBCL specifically; however, these patients would be expected to experience a similar or worse HRQoL when compared with those at diagnosis or receiving first-line treatment. Patients who achieve a complete response (CR) after first-line treatment have demonstrated significant improvements in HRQoL compared with non-responders.[54] However, the cycle of remission and relapse when having successive treatments imparts a substantial psychological and physical burden on people with the disease, potentially due to uncertainties around the prognosis of their disease and fears of relapse.[3] During an advisory board conducted by AbbVie in July 2022 that focused on DLBCL, clinical experts agreed that the disease burden of DLBCL was heavily linked to response and survival; if a patient is responding well to therapy, then the burden of disease is lessened.[4] However, patients who relapse or become refractory to later lines of treatment experience poor HRQoL.[4] This is supported by studies identified in an economic systematic literature review (SLR; Appendix G), which demonstrated that HRQoL in patients with R/R LBCL generally improves on all subdomains measured when responding to active treatment.

Economic burden of LBCL

Data on the economic burden of R/R LBCL are limited. However, available data from the US demonstrate that patients who do not respond to first-line therapy and are not eligible for SCTs have substantial health care resource utilisation and associated costs, especially during the first 12 months following initiation of treatment, due to the requirement for hospitalisations, skilled nursing and long-term care facilities.[23]

This is further supported by clinical expert opinion gathered during an advisory board conducted by AbbVie in July 2022 where UK clinicians highlighted how patients who receive CAR-T therapy may require a live-in carer for four weeks post-infusion and are not able to drive for eight weeks.[4] The disease also results in absenteeism especially as many patients cannot work whilst on treatment.[4] Furthermore, as highlighted in the NICE appraisal of axi-cel as a treatment for DLBCL following one prior therapy [ID1684], a special tariff is paid in UK clinical practice when CAR-T therapies are administered in the UK; therefore, in addition to the high costs associated with the acquisition of CAR-T therapies, their administration represent a substantial economic burden on the UK National Health Service (NHS).[55] Also, UK clinical experts highlighted that it is now common practice for patients to receive bridging therapy between apheresis and CAR-T infusion, which adds an additional cost onto the long wait times for patients.[17]

Furthermore, CAR-T therapy is associated with issues surrounding accessibility due to there being a limited number of centres that can deliver CAR-T therapy.[56] As a result, some patients have to travel long distances to access CAR-T therapy and this can impart a substantial economic burden on patients and/or their family/carers.

Moreover, a study conducted by Moertl *et al.* (2022) which looked at the economic burden of third-line treatment for R/R DLBCL versus fourth-line and beyond treatment demonstrated that the economic burden of treatment increases as patients move from third-line treatment to fourth-line and beyond.

B.1.3.3 Epcoritamab

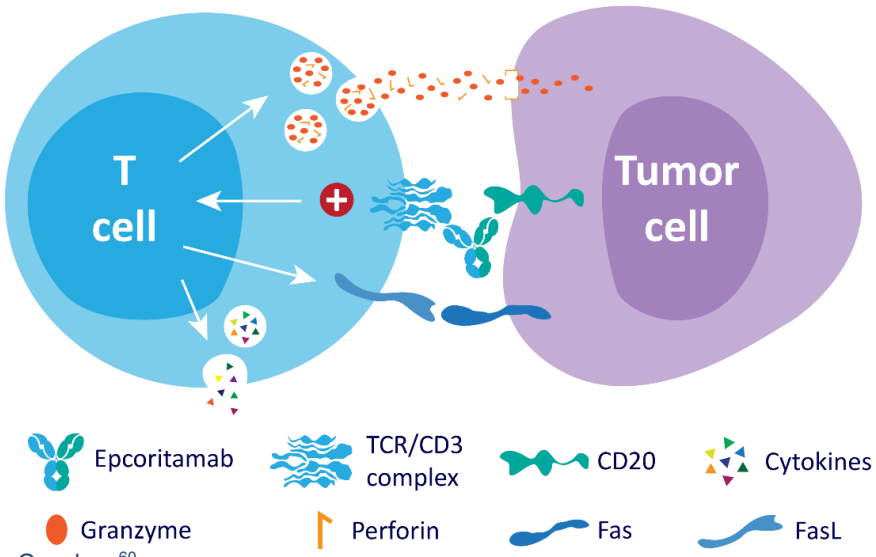
Epcoritamab is a humanised IgG1-bispecific antibody that binds to the T-cell antigen CD3 and the B-cell antigen CD20.[5] The activity of epcoritamab requires simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T-cells; this induces specific

T-cell activation and T-cell-mediated killing of CD20-expressing cancer cells.[5] A diagram presenting the mechanism of action of epcoritamab is presented in Figure 1.

Targeting of CD20-expressing cells with CD20-specific monoclonal antibodies has been shown to be a robust and highly successfully mechanism for the treatment of B-cell malignancies.[57] However, the epcoritamab mechanism of action differs when compared with that of conventional CD20-targeting monoclonal antibodies (such as obinutuzumab and rituximab) which can induce cytotoxicity through Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity, antibody-dependent cell-mediated phagocytosis, and complement-dependent cytotoxicity and, in some cases, programmed cell death.[21] Instead, epcoritamab requires binding to both T-cells and malignant B-cells to initiate cell death. Furthermore, epcoritamab binds to a distinct epitope when compared with conventional CD20-specific monoclonal antibodies, demonstrating in vitro anti-tumour activity in the presence of excess levels of CD20 antibody.[57-59]

Epcoritamab is the first and only SC treatment available for adult patients with R/R LBCL after two or more prior lines of systemic therapy. The SC administration enables quick administration across different practice settings when compared with currently available IV therapies.[6] This allows for greater flexibility and convenience for both clinicians and patients, and decreased healthcare resource use. In addition, epcoritamab is a readily available treatment option; as such, once it is decided that a patient should receive treatment with epcoritamab, this allows access to the treatment almost immediately.

Figure 1: Mechanism of action of epcoritamab



Source: AbbVie Oncology[60]

B.1.3.4 Clinical pathway of care

Current treatment pathway

The treatment pathway for most forms of LBCL, including PMBCL, HGBCL and FL Gr 3B, is similar to that for DLBCL; this was confirmed by UK clinicians during an advisory board conducted by AbbVie and during subsequent validation interviews with UK clinical experts.[7, 8, 13, 17]

Guidelines for the treatment of DLBCL, and other forms of LBCL, are available from a number of sources including NICE Clinical Pathway NG52, the British Society of Haematology (BSH) and the European Society for Medical Oncology (ESMO).[9, 11, 61] Furthermore, there are a number of treatments currently recommended by NICE for patients with R/R DLBCL and other subtypes of LBCL. For example, Pola + BR is recommended for the treatment of R/R DLBCL in patients who are ineligible for SCT and pixantrone monotherapy is recommended for treating multiple R/R aggressive NHL B-cell lymphomas.[44, 62] In addition, in January 2023, NICE recommended axi-cel for routine commissioning for treating R/R DLBCL and PMBCL after two or more systemic therapies; tisagenlecleucel is also recommended for the treatment of R/R DLBCL after two or more systemic therapies within the Cancer Drugs Fund (CDF).[3, 63]

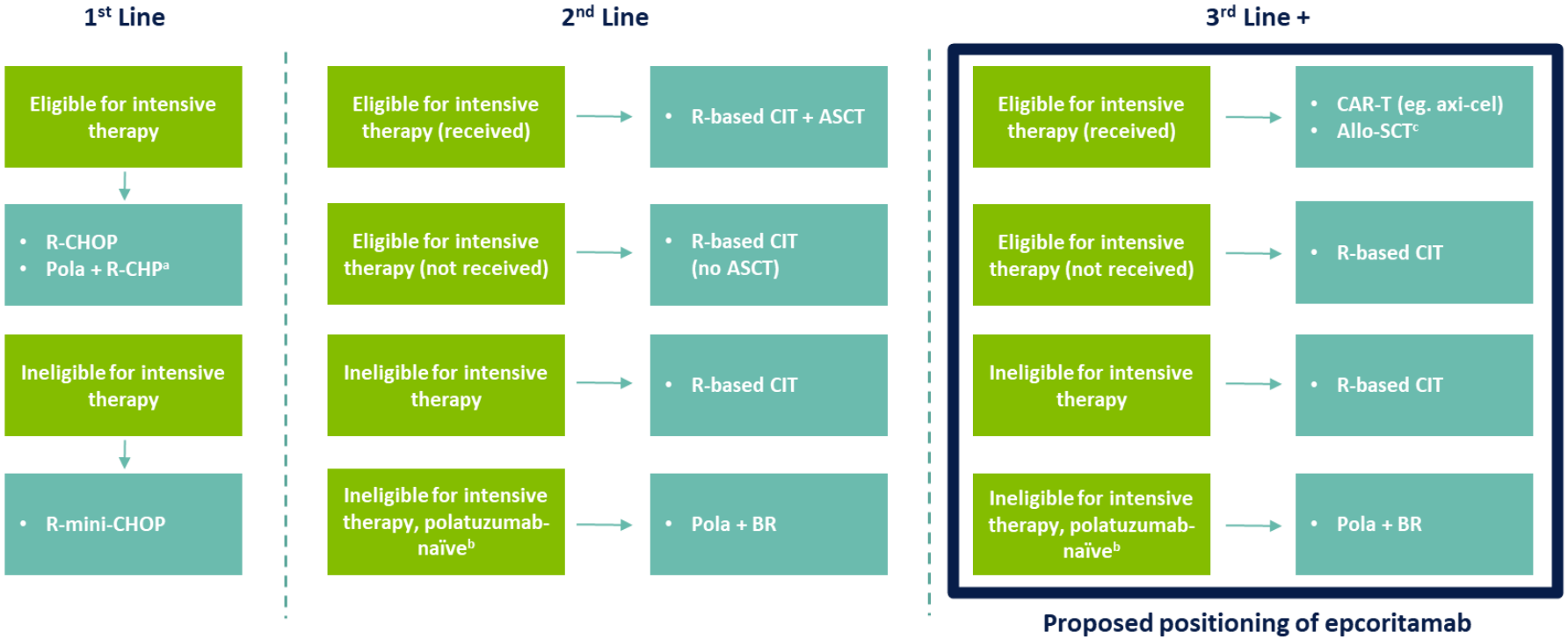
Although recommended by NICE, UK clinicians stated that pixantrone monotherapy is rarely used in UK clinical practice to treat R/R LBCL due to limited efficacy and high toxicity and this was supported by clinical experts during the NICE appraisal of tafasitamab with lenalidomide.[14] As such, in line with the rational outlined in Table 1, pixantrone monotherapy is not considered a relevant comparator in this submission.

The current treatment pathway for patients with DLBCL in UK clinical practice and the proposed positioning of epcoritamab within this pathway is presented in Figure 2.

In this submission, due to differing clinical pathways of care and differing levels of patient fitness, economic analyses are presented separately for two separate patient populations, as supported by feedback from UK clinical experts:

- Base case analysis A: Patients who are ineligible for, or choose not to receive, intensive therapies
- Base case analysis B: Patients who are eligible to receive intensive therapies

Figure 2: Current clinical pathway of patients with LBCL in the UK, including the proposed positioning of epcoritamab



[a] Feedback from clinical experts indicated that patients would receive Pola + R-CHP at the first-line; [b] With the introduction of Pola-R-CHP as a first-line treatment for DLBCL, the proportion of newly diagnosed patients entering the treatment pathway who receive Pola + BR in the second or third-line is expected to fall below 20% over the next 12 months and to as low as 5% in 24 months. Based on market share estimates included in the budget impact analysis alongside this submission, the market share of Pola + BR is anticipated to fall to [redacted] in five years; [c] Clinical experts stated that allo-SCT has minimal use at third-line in UK clinical practice.
Abbreviations: Allo-SCT: allogenic stem cell transplantation; ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; Pola + BR: polatuzumab vedotin in combination with bendamustine plus rituximab; Pola + R-CHP: polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone; R: rituximab; R-CHOP: rituximab in combination with cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; UK: United Kingdom.
Source: AbbVie Advisory Board, 2022;[4] AbbVie Medical Advisory Board, 2023.[13]

First-line treatment of LBCL

First-line treatment usually comprises chemotherapy with R, which may be consolidated with radiotherapy; the most common combination of drugs used at first-line is 6–8 cycles R-CHOP.[4, 9] The exact treatment regimen used (i.e. the number of cycles of R-CHOP and whether radiotherapy is used) depends on a number of factors, including the stage of the disease, whether the disease is bulky or non-bulky and the level of response to initial treatment with R-CHOP.[11] Relevant guidelines state that R-CHOP is the primary first-line treatment option. Patients who are ineligible for this treatment may also receive R-mini-CHOP, which consists of a reduced dose of R-CHOP.[11] In those with cardiac comorbidities, doxorubicin may be substituted with gemcitabine or etoposide.

However, since the publication of these guidelines, Pola + R-CHP was recommended by NICE for untreated DLBCL in February 2023 [TA874].[10] Following an advisory board organised by AbbVie, which took place in February 2023 after the NICE recommendation of Pola + R-CHP was published, UK clinical and economic experts stated that the recommendation of Pola + R-CHP as a treatment for first-line DLBCL is expected to change the treatment pathway for later lines of treatment as patients would not be retreated with polatuzumab.[13]

Second-line treatment of R/R LBCL

At second-line, treatment choice for R/R disease is primarily dependent on eligibility for intensive therapies. NICE CG52 recommends that patients with R/R DLBCL who have received one prior line of therapy and who are fit enough to tolerate intensive therapy should be offered treatment with CIT, followed by consolidation with autologous stem cell transplantation (ASCT), if deemed eligible.[9, 11]

For those ineligible for intensive therapies such as ASCT at second-line or CAR-T therapy at third-line, R-based CIT, such as rituximab, gemcitabine and oxaliplatin (R-GemOX), was the most common treatment option, until Pola + BR received a positive recommendation from NICE in September 2020; since this recommendation, Pola + BR became the primary treatment choice.[4, 44] However following the NICE recommendation of Pola + R-CHP for untreated DLBCL, Pola + BR is anticipated to now be used in only a minority of patients at second-line who have not previously been treated with polatuzumab.[13, 17] Moreover, UK clinical experts highlighted that Pola + BR is not used for patients who might be expected to receive treatment with CAR-T therapy at later lines, due to the adverse impact of bendamustine on T-cell number and function which could increase the risk of a poor response to CAR-T therapy.[17]

Third-line and beyond treatment of R/R LBCL

Despite the curative intent of some treatments at second-line, approximately 30% of patients will progress from second-line to third-line treatment.[12] At 3L+, there is no universal standard of care that is accessible to a broad range of patients. As with earlier lines of therapy, treatment at 3L+ is largely dependent on eligibility for intensive therapies, and whether patients wish to receive intensive therapies.

Those eligible for intensive therapies mainly receive CAR-T therapy, primarily axi-cel. Tisagenlecleucel is an alternative CAR-T therapy for the treatment of R/R LBCL, however it is currently recommended by NICE on the CDF so is not available under routine commissioning in UK clinical practice.[7, 63] Alternatively, for patients who experience relapse following ASCT, further CIT followed by alloSCT may be considered.[9] However, clinical experts consulted as part of an

advisory board which took place in July 2022 stated that alloSCT has minimal use at third-line in UK clinical practice.[4] As such, for patients who are eligible for intensive therapies, the primary treatment option currently, and relevant comparator for epcoritamab, is axi-cel.

Despite the availability of CAR-T therapies at third-line, approximately 26% of patients with R/R LBCL who are approved for treatment with CAR-T therapy by the National CAR-T Clinical Panel do not receive it.[64] For all patients eligible for treatment with CAR-T therapy (i.e. including both patients who are not approved for treatment with CAR-T therapy and those who do not wish to receive it), this figure is likely to be higher.[64] For those ineligible for, or choose not to receive, intensive therapies at third-line, the primary treatment options are a number of R-based CIT combinations, such as R-GemOx and R-Gem. During an advisory board conducted by AbbVie in July 2022, UK clinicians stated that BR is rarely used in UK clinical practice.[4]

In addition, treatment guidelines state that Pola + BR remains a treatment option for patients who are ineligible for, or choose not to receive, intensive therapy at third-line. However, based on feedback from UK clinicians during an advisory board conducted in February 2023 and validation interviews, Pola + BR is anticipated to no longer be used as a primary treatment option at third-line following the recommendation of Pola + R-CHP at first-line, as patients would not be retreated with polatuzumab.[13, 17] For the minority of patients who are ineligible to receive intensive therapies and are polatuzumab-naïve, Pola + BR would remain a treatment option at third-line. However, UK clinicians stated that they would now expect less than 5% of patients with R/R LBCL at third-line to receive Pola + BR.[13] As such, Pola + BR is not considered to be a relevant comparator for epcoritamab in this submission.

Following relapse at third-line, treatment options are therefore limited to R-based CIT regimens only and outcomes are poor. However, there is no consensus on specific regimens used and the benefit of continuation of treatment is often carefully considered in such a heavily pre-treated population; at fourth-line, many patients will have relapsed following, or be refractory to, R-based CIT.[4] Although pixantrone monotherapy is recommended by NICE for treating multiple R/R aggressive NH B-cell lymphomas, UK clinical experts stated that it is rarely used in clinical practice due to a lack of efficacy and toxicity.

Unmet need

Despite a number of treatment options for patients with LBCL at first-line, approximately 10–15% of patients have primary refractory disease and a further 20–30% will experience relapse.[9] Despite advances in treatment for R/R LBCL in the 3L+, such as the development of CAR-T therapies, there is no standard of care that is accessible for a broad range of patients. As such, OS and PFS for patients with R/R LBCL have been demonstrated to be poor in the real-world setting. Furthermore, CAR-T therapies are associated with waiting times (approximately 7 weeks from approval by the National CAR-T Clinical Panel to re-infusion) due to manufacturing and preparation of the therapy, as well as issues associated with accessibility due to requiring support from carers and there being a limited number of centres that can deliver CAR-T therapy.[56] As a result, some patients have to travel long distances to access CAR-T therapy; this can impart a substantial economic burden on patients and/or their family/carers and drive inequity in access to CAR-T therapy. For patients with R/R LBCL at third-line and beyond, there remains a significant unmet need for tolerable, effective and readily available treatments that drive deep and durable responses across the patient population.

Epcoritamab is the first and only SC bispecific antibody for the treatment of R/R LBCL at third-line and beyond, which enables rapid administration across practice settings, and greater flexibility and convenience for both clinicians and patients compared with existing IV therapies. Moreover, epcoritamab is a readily available treatment option, allowing administration almost immediately for patients with rapidly progressing disease; feedback from UK clinical experts highlighted this as an important benefit associated with epcoritamab. Epcoritamab adds a novel mechanism of action to the existing R/R LBCL treatment landscape and it has demonstrated clinically meaningful efficacy in a heavily pre-treated population, alongside a manageable safety profile. Data from EPCORE™ NHL-1 demonstrated that epcoritamab is well tolerated whilst driving deep and durable responses in challenging-to-treat, highly refractory patients with R/R LBCL making it a potential core therapy for patients with LBCL (Section B.2).

Comparators

Epcoritamab is anticipated to be licensed for the treatment of [redacted].[5] As described above, at third-line, patients typically receive axi-cel or R-based CIT. Following relapse at third-line, clinicians are limited to R-based CIT. As such, the comparators for epcoritamab in this submission are axi-cel and R-based CIT.

B.1.4 *Equality considerations*

It is not anticipated that the provision (or non-provision) of epcoritamab within its licensed indication would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

An SLR identified one trial (EPCORE™ NHL-1) for epcoritamab in the relevant patient population as defined by the NICE scope

- The efficacy and safety evidence base to support the use of epcoritamab in patients with R/R LBCL after two or more lines of systemic therapy comes from EPCORE™ NHL-1: a phase 1/2, open-label, dose-escalation and expansion trial of epcoritamab as a treatment for R/R LBCL in adult patients.
- The primary endpoint in EPCORE™ NHL-1 was overall response rate (ORR) based on an Independent Review Committee (IRC) assessment determined by Lugano criteria.
- Secondary outcomes included duration of response (DOR) and PFS based on IRC assessment, as determined by Lugano criteria, as well as OS, time to next treatment (TTNT), HRQoL and safety (treatment-emergent AEs [TEAEs]).
- The results of the EPCORE™ NHL-1 study are aligned with the decision problem specified in the NICE scope. The patient population in EPCORE™ NHL-1 was considered by clinicians to be reflective of patients with R/R LBCL in UK clinical practice and the results of the trial are directly relevant to UK clinical practice.[40]

Results of EPCORE™ NHL-1 demonstrate that epcoritamab drives clinically meaningful, deep and durable responses in patients with R/R LBCL after two or more systemic therapies

- The cohort of patients included in the EPCORE™ NHL-1 trial represents a heavily pre-treated population with a median number of three prior lines of therapy (range [min, max]: 2, 11), in which effective treatment options are currently limited.
  - In total, 46 (29.3%) and 50 (31.8%) patients received two or three prior lines of therapy, respectively. 61 (38.9%) patients received 4 or more prior lines of therapy.
- All efficacy results are reported based on the [redacted] data cut-off, unless otherwise stated, with a median duration of study follow-up of [redacted] months.
- The ORR in patients with DLBCL (N=139) was [redacted] with [redacted] and [redacted] achieving best response of CR and partial response (PR), respectively. Overall, results throughout the trial were consistent for patients with other LBCL subtypes and all patients with LBCL.
- For patients with DLBCL, the median DOR was [redacted] and median PFS was [redacted] based on IRC assessment determined by Lugano criteria.
  - Among patients in CR, median PFS was [redacted] Median PFS was [redacted] among patients in PR when compared with non-responders ([redacted] versus [redacted].
- Median OS among patients with DLBCL was [redacted] and median TTNT was [redacted].
- Based on the [redacted] data cut-off, whilst on treatment, there were [redacted] in the total Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) score and the Functional Assessment of Cancer Therapy-Lymphoma Subscale (FACT-LymS) from C1D1 to C9D1.

The matching adjusted indirect comparisons (MAICs) support the evidence from EPCORE™ NHL-1 that epcoritamab is clinically beneficial for patients with R/R LBCL

- The results of the MAICs demonstrate that epcoritamab is associated with a [redacted] versus R-based CIT with regards to OS hazard ratio (HR) ([redacted]), difference in CR rate ([redacted]) and difference in ORR ([redacted]).
- For the comparison of epcoritamab versus axi-cel, the results of the MAIC demonstrate that there is [redacted] treatment benefit for patients receiving epcoritamab

versus axi-cel in terms of the OS HR (and PFS HR). was also observed for CR rate and ORR for epcoritamab versus axi-cel, with the difference in CR rate of and a difference in ORR of .

Epcoritamab has been demonstrated to be tolerable, with a manageable AE profile

- AEs were generally manageable with appropriate monitoring and mitigation measures including dose delays and/or supportive care. Data on AEs are reported from the data cut-off of EPCORE™ NHL-1.
- with LBCL had experienced at least one TEAE. Of these, experienced TEAEs considered related to epcoritamab by the investigator.
- A total of with LBCL experienced or higher TEAEs and had or higher TEAEs considered related to epcoritamab by the investigator.
- Serious TEAEs were reported in with LBCL and were considered related to epcoritamab by the investigator in .
- A total of experienced a TEAE leading to treatment discontinuation and had a TEAE leading to dose delay/interruption.
- Fatal TEAEs were reported in with LBCL; was considered related to epcoritamab by the investigator, which was .
- Of the patients with LBCL that had ≥1 CRS event ( ), most events were (and , respectively). Events of CTLS were reported in with LBCL. Further details on AESI are provided in Section B.2.9.5.

The overall safety profile of epcoritamab is considered manageable and acceptable in this R/R LBCL patient population with limited and predominantly CIT-based treatment options.

Epcoritamab is the first and only SC treatment available for patients with R/R LBCL after two or more lines of therapy, adding a novel mechanism of action to the existing treatment pathway

- Epcoritamab is expected to provide a significant benefit to patients with deep and durable treatment effects and offering an advantage that is clinically meaningful to patients and clinicians when compared with currently available therapies.
- It represents a treatment option that would be available to a broad range of patients, for underserved subtypes of LBCL and regardless of eligibility for intensive therapies. The introduction of epcoritamab would be expected to enhance equity to access as it will not be limited by manufacturing times and specialist delivery centres.

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence from randomised controlled trials (RCTs) on the efficacy and safety of epcoritamab or any other pharmacological intervention for the treatment of adult patients with R/R LBCL after two or more lines of systemic therapies. A total of 322 publications were eligible for inclusion based on the pre-specified criteria, of which 119 publications were relevant for reporting as they presented clinical evidence in the ≥3rd line LBCL or DLBCL population (≥20 patients) in a European, Northern American or global perspective.

Full details of the SLR search strategy, study selection process and results can be found in .

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical SLR identified one clinical trial for epcoritamab in patients with LBCL. EPCORE™ NHL-1 (NCT03625037) provides the clinical evidence for the efficacy of epcoritamab as a

treatment for adult patients with R/R LBCL after two or more lines of systemic therapy.[21] EPCORE™ NHL-1 is a phase 1/2, open-label, dose-escalation and expansion trial of epcoritamab as a treatment for relapsed, progressive or refractory LBCL in adult patients. This is in line with the target population for this submission. Data from EPCORE™ NHL-1 are provided in the following sections and the clinical study report (CSR) located in the reference pack accompanying this submission.[21, 65, 66]

A further trial for epcoritamab is ongoing. EPCORE™ DLBCL-1 (NCT04628494) is a phase 3 clinical trial evaluating the comparative efficacy of epcoritamab versus Investigators' choice of BR or R-GemOx in patients with LBCL who are ineligible for or have failed high-dose therapy followed by ASCT.[67] This trial is ongoing and results from the trial are not yet available. As such, EPCORE™ DLBCL-1 is not considered within this submission.

Table 5: Clinical effectiveness evidence

Study	**EPCORE™ NHL-1 (NCT03625037)**		
Study design	A phase 1/2, open-label, multicentre trial including a Dose Escalation Part and an Expansion Part.		
Population	Adult patients with relapsed, progressive, or refractory b-cell lymphoma. The Expansion Part of the trial was initiated with parallel enrolment in three cohorts of patients, including patients with aNHL (i.e., LBCL), iNHL, and MCL. This submission considers the aNHL (i.e., LBCL, including DLBCL, PMBCL, HGBCL and FL Gr 3B) cohort of the Expansion Part of the trial only.		
Intervention(s)	Epcoritamab, administered via subcutaneous injection		
Comparator(s)	N/A		
Indicate if study supports application for marketing authorisation	Yes	**Indicate if study used in the economic model**	Yes
Rationale if study not used in model	N/A		

Reported outcomes specified in the decision problem	**Primary endpoint**: ORR determined by Lugano criteria as assessed by IRC
	
	Secondary endpoints:
	• Response rates
	  ○ ORR (including CR, BOR, SD, PD)
	  ○ DOR determined by Lugano criteria as assessed by IRC
	• PFS determined by Lugano criteria as assessed by IRC
	• ToT
	• OS
	• AEs
	• Patient-reported outcomes (FACT-Lym and EQ-5D-3L)		

All other reported outcomes	• TTNT • DOCR, TTCR, TTR determined by Lugano criteria as		

	assessed by IRC • Rate of MRD negativity

Abbreviations: aNHL: aggressive B-cell non-Hodgkin lymphoma; AE: adverse event; BOR; best overall response; CR: complete response; DLBCL: diffuse large B-cell lymphoma; DOCR: duration of complete response; DOR: duration of response; EQ-5D-3L: EuroQoL-5 diminesions-3 levels; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade-B-cell lymphoma; iNHL: indolent B-cell non-Hodgkin lymphoma; IRC: Independent Review Committee; LBCL: large B-cell lymphoma; MCL: mantle cell lymphoma; MRD: minimal residual disease; N/A: not applicable; ORR: overall response rate; OS: overall survival; PD: partial disease; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; SD: stable disease; ToT: time on treatment; TTCR: time to complete response; TTNT: time to next (anti-lymphoma) therapy; TTR: time to response.
Source: AbbVie, epcoritamab draft SmPC 2022;[5] AbbVie, EPCORE™ NHL-1 CSR, [redacted].[21]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design and methodology

The clinical evidence base for epcoritamab as a treatment for adult patients with R/R LBCL after two or more lines of systemic therapy is provided by EPCORE™ NHL-1. A summary of the trial design is illustrated in Figure 3 and an overview of the trial methodology is presented in Table 6.

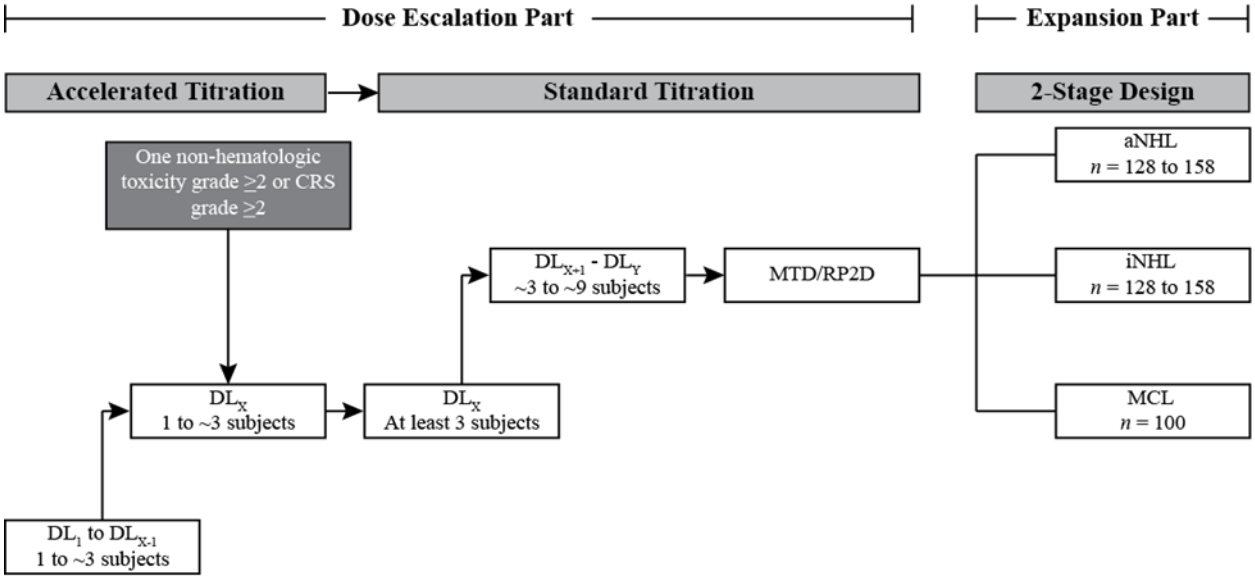
The trial consisted of two parts:

- The Dose Escalation Part enrolled patients from Denmark, the Netherlands, the UK and Spain. Patients received priming and intermediate doses of epcoritamab followed by full doses administered in 28-day cycles. Each subsequent cohort involved escalation of the priming, intermediate or full dose (0.0128–60 mg)[68]
    - Results from the Dose Escalation Part of the trial were used to determine the epcoritamab recommended phase 2 dose (RP2D) regimen. This consisted of: 0.16 mg (Cycle 1 Day 1A [C1D1]), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg (C1D15, C1D22). The full dose of 48 mg was used for all administrations thereafter (Cycle 2 and 3: Day 1, 8, 15, and 22; Cycle 6–9: Day 1 and 15; Cycle 10+ [until progression or unacceptable toxicity]: Day 1).
- The Expansion Part to evaluate the clinical efficacy and safety of epcoritamab in patients with R/R LBCL at RP2D

The Expansion Part of the trial was initiated with parallel enrolment in three cohorts of patients with distinct B-cell lymphoma subtypes who were treated with the RP2D of epcoritamab: aggressive NHL (aNHL) (i.e., LBCL), indolent B-cell non-Hodgkin lymphoma (iNHL), or mantle cell lymphoma (MCL).

Data from the aNHL cohort from the Expansion Part of the EPCORE™ NHL-1 trial are presented in this submission, as this represents the population that is consistent with the decision problem and the anticipated licensed indication for epcoritamab of relevance to this submission. Results from the other cohorts are not relevant to and therefore not considered within this submission.

Figure 3: EPCORE™ NHL-1 trial design



Abbreviations: aNHL: aggressive non-Hodgkin lymphoma subtypes; CRS: cytokine release syndrome; DL: dose level; iNHL: indolent non-Hodgkin lymphoma subtypes; MCL: mantle cell lymphoma; MTD: maximum tolerated dose; RP2D: recommended phase 2 dose; X: the dose level where the trigger (grade 2 non-haematological toxicity etc.) is observed: switch from single patient cohort to three patient cohort; Y: the highest investigated dose level.
Source: Figure 9-1 AbbVie, EPCORE™ NHL-1 CSR, 2022.[21]

An overview of the trial methodology, including the key eligibility criteria for EPCORE™ NHL-1 is provided in Table 6. The full eligibility criteria are presented in Appendix M.

Table 6: Summary of trial methodology

Trial name	EPCORE™ NHL-1 (NCT03625037) – aNHL cohort
Location	International, multicentre trial with [redacted] sites across [redacted]: Australia ([redacted]), South Korea ([redacted]), United States ([redacted]), France ([redacted]), Netherlands ([redacted]), Spain ([redacted]), Denmark ([redacted]), Germany ([redacted]), United Kingdom ([redacted]), Poland ([redacted]), Singapore ([redacted]), Canada ([redacted]), and Italy ([redacted]).
Trial design	A phase 1/2, open-label, dose escalation and expansion trial

Eligibility criteria for participants	**Inclusion criteria:**
	• ≥18 years
	• ECOG performance status of 0, 1, or 2
	• CD20+ mature B-cell neoplasm according to WHO classification[a]
	• Measurable disease, defined as:
	  ○ CT/MRI scan with at least one measurable lesion and an FDG-PET scan that demonstrated positive lesion(s) (for FDG-avid lymphomas only)
	  ○ DLBCL diagnosis including patients diagnosed with DH or TH DLBCL, with MYC and BCL2 and/or BCL6 rearrangements, or other LBCL (including PMBCL, HGBCL, or FL Gr 3B)
	  ○ Relapsed or refractory disease[b]
	  ○ Previous treatment with ≥2 lines of systemic antineoplastic therapy including at least one anti-CD20 mAb-containing therapy.
	  ○ Have failed prior ASCT or be ineligible for ASCT due to age, ECOG performance status, comorbidities, and/or insufficient response to prior treatment
	Exclusion criteria:
	• Known primary CNS lymphoma or known CNS involvement or a past or current malignancy other than inclusion diagnosis
	• AST or ALT >3 × ULN
	• Total bilirubin >1.5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
	• CrCl <45 mL/min
	• Clinically significant cardiac disease, chronic ongoing infectious diseases, diseases or treatments resulting in immunosuppression or seizure disorders requiring therapy
	• CAR T-cell therapy within 30 days or an ASCT within 100 days prior to first dose of epcoritamab, or any prior allogeneic HSCT or solid organ transplantation

Trial drugs and method of administration	Epcoritamab, administered as a SC injection.

	The epcoritamab dosing regimen consisted of an initial priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg at C1D15, C1D22. The full dose of 48 mg is used for all administrations thereafter (Cycle 2 and 3: Day 1, 8, 15, and 22; Cycle 4–9: Day 1 and 15; Cycle 10+ [until progression or unacceptable toxicity]: Day 1). Patients were hospitalised for at least 24 hours after the first full dose of epcoritamab. This planned hospitalisation was not reported as an SAE.	
Permitted and disallowed concomitant medication	Concomitant medications were allowed to provide adequate care and were given as clinically indicated, except for anti-lymphoma therapy. All concomitant medications were recorded except for vitamins or nutrient supplements.	
	Permitted concomitant medications: • Supportive care for treatment of CRS[d] • Hydration and prophylactic treatment with a uric acid lowering agent for patients with increased risk of CTLS ○ Supportive therapy, including rasburicase, was allowed if CTLS occurred • Prophylactic antibiotic, antiviral, and antifungal therapies • Growth factors for neutropenia such as granulocyte colony stimulating factor • Local palliative radiotherapy on non-target lesions	**Prohibited concomitant medications**: • Any anti-lymphoma therapy (e.g., chemotherapy, radiotherapy, or experimental therapy[c]) • Corticosteroid that exceeded a total daily dose of 10 mg of prednisolone or equivalent administered for more than ten days (unless for the management of AEs)[e] • Vaccination with live or live attenuated vaccines
Primary outcome	Overall response rate determined by Lugano criteria as assessed by IRC	
Key secondary outcomes	• DOR, CR, DOCR, PFS, TTR, and TTCR determined by Lugano criteria as assessed by IRC • ORR, DOR, CR, DOCR, PFS, TTR and TTCR determined by LYRIC as assessed by IRC[f] • OS and TTNT • Rate of MRD negativity • Safety[g] • PK parameters • ADAs to epcoritamab[f] • FACT-Lym	
Duration of study and follow-up	For each patient, the treatment period continued until disease progression unless the patient fulfilled one of the discontinuation criteria. The trial will run for a maximum of five years after the last patient's first dose.	

[a] World Health Organization (WHO) classification 2016 or WHO classification 2008 based on representative pathology report; [b] Relapsed disease was defined as disease that had recurred ≥6 months after completion of therapy; [c] Local palliative radiotherapy on non-target lesions was allowed; [d] This included infusion of saline, systemic glucocorticosteroids, antihistamines, antipyretics, support for blood pressure (vasopressin, vasopressors), support for low-flow and high-flow oxygen and positive pressure ventilation and/or mAbs against IL-6R (e.g., intravenous administration of tocilizumab); [e] Excluding corticosteroids given as prophylactic corticosteroid administration pre- and post-epcoritamab administration or concomitant medication for CRS; [f] Outcomes not presented within this submission; [g] AEs, laboratory parameters [biochemistry, haematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers], hospitalisations, and cytokine measures.
Abbreviations: ADA: anti-drug antibody (i.e., anti-epcoritamab antibody); AE: adverse events; ALT: alanine transaminase; ASCT: autologous stem cell transplantation; AST: aspartate transaminase; CAR: chimeric antigen receptor; CNS: central nervous system; CXDX: Cycle X Day X; CR: complete response; CrCl: creatinine clearance; CRS: cytokine release syndrome; CT: computed tomography; CTLS: clinical tumour lysis syndrome; DH: double-hit; DLBCL: diffuse large B-cell lymphoma; DOCR: duration of complete response; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; FACT-Lym: Functional Assessment of Cancer Therapy – Lymphoma; FDG: fluorodeoxyglucose; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high grade B-cell lymphoma; HSCT: hematopoietic stem cell transplantation; IRC: Independent Review Committee; LBCL: large B-cell lymphoma; LYRIC: Lymphoma Response to Immunomodulatory Therapy Criteria; MRD: minimal residual disease; MRI: magnetic resonance imaging; ORR: overall response rate; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; PMBCL: primary mediastinal B-cell lymphoma; SAE: serious adverse event; SC: subcutaneous; TH: triple-hit; TTCR: time to complete response; TTNT: time to next treatment; TTR: time to response; ULN: upper limit of normal; WHO: World Health Organization.
Source: AbbVie, EPCORE™ NHL-1 CSR, Jan 2022.[21]

B.2.3.2 Patient characteristics

Demographic characteristics

The demographic characteristics for the full analysis set (FAS) in the EPCORE™ NHL-1 trial aNHL cohort are summarised in Table 7 below. As highlighted in Table 6, a high proportion of patients enrolled in the EPCORE™ NHL-1 trial were from European countries ([redacted] [redacted]), with [redacted] from the UK.

More than half of patients with LBCL (94 [59.9%] patients) were male. The median age was 64.0 years (range: 20, 83), with 48 (30.6%) patients aged 65 to <75 years, and 29 (18.5%) patients aged ≥75 years. More than half of patients with LBCL were white (96 [61.1%] patients), and 30 (19.1%) patients were Asian. Race was not reported in [redacted] of patients due to country specific data protection laws and was reported as "other" in [redacted] of patients. Most patients had a baseline ECOG performance status of 0 (74 [47.1%] patients) or 1 (78 [49.7%] patients) (a status of 0, 1, or 2 was required for inclusion). Median body weight of patients with LBCL at baseline was [redacted] (range [min, max]: [redacted]).

Most patients with LBCL (approximately [redacted]) had normal or mildly impaired renal function at trial entry based on creatine clearance; [redacted] patients had moderately impaired renal function and [redacted] had severely impaired renal function. Most patients (approximately [redacted]) had normal hepatic function or mild dysfunction; [redacted] had moderate dysfunction and [redacted] had severe dysfunction.

Demographic characteristics were similar in patients with DLBCL specifically, with [redacted] male patients, median age of [redacted] (range [min, max]: [redacted]), [redacted] white patients, and [redacted] Asian patients. Demographic characteristics differed slightly in patients with other subtypes, with a lower proportion of male patients ([redacted]) and a lower median age ([redacted] years [range {min, max}: [redacted]]). However, all other characteristics were generally similar.

Table 7: Key demographic characteristics

Number of treated patients, n (%)	aNHL Cohort (N=157)		
	DLBCL (N=139)	Other subtypes[a] (N=18)	LBCL (N=157)
Age (years)			
Median (range: min, max)	[redacted]	[redacted]	64.0 (20, 83)
Age category (years)			
<65 years	[redacted]	[redacted]	80 (51.0%)
65 to <75 years	[redacted]	[redacted]	48 (30.6%)
≥75 years	[redacted]	[redacted]	29 (18.5%)
Sex (at birth)			
Male	[redacted]	[redacted]	94 (59.9%)
Female	[redacted]	[redacted]	63 (40.1%)
Race			
White	[redacted]	[redacted]	96 (61.1%)
Asian	[redacted]	[redacted]	30 (19.1%)
Other	[redacted]	[redacted]	[redacted]

Number of treated patients, n (%)	aNHL Cohort (N=157)		
	DLBCL (N=139)	Other subtypes[a] (N=18)	LBCL (N=157)
Not reported[b]	[redacted]	[redacted]	[redacted]
Ethnic origins			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Weight (kg) at baseline			
Median (range: min, max)	[redacted]	[redacted]	[redacted]
ECOG performance status			
0	[redacted]	[redacted]	74 (47.1%)
1	[redacted]	[redacted]	78 (49.7%)
2	[redacted]	[redacted]	5 (3.2%)
Baseline renal function (CrCl, mL/min)			
Normal (≥90)	[redacted]	[redacted]	[redacted]
Mildly impaired (60–<90)	[redacted]	[redacted]	[redacted]
Moderately impaired (30–<60)	[redacted]	[redacted]	[redacted]
Severe impaired (15–<30)	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Baseline hepatic function per NCI criteria			
Normal	[redacted]	[redacted]	[redacted]
Mild dysfunction	[redacted]	[redacted]	[redacted]
Moderate dysfunction	[redacted]	[redacted]	[redacted]
Severe dysfunction	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

[a] Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL; [b] Not reported in non-US countries; [c] Baseline renal function calculated based on estimate creatine clearance using the Cockcroft Gault method.
Abbreviations: aNHL: aggressive B-cell non-Hodgkin lymphoma; CrCl: creatinine clearance; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FL Gr 3B: follicular lymphoma grade 3; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; max: maximum; min: minimum; NCI: National Cancer Institute; PMBCL: primary mediastinal B-cell lymphoma; US: United States.
Source: Table 14.1.1.2 AbbVie, EPCORE™ NHL-1 CSR, Jan 2022;[21] Thieblemont 2022.[65]

Baseline disease characteristics

The baseline disease characteristics for the full analysis set in the EPCORE™ NHL-1 trial aNHL cohort are summarised in Table 8 below.

Most patients (139 [88.5%] patients) had DLBCL histology at trial entry. In total, 97 (69.8%) patients with DLBCL had de novo disease, 40 (28.8%) patients had transformed disease and two (1.4%) patients had unknown DLBCL type. As outlined in Section B.1.3.1, transformed disease is disease that originated from a low-grade lymphoma and becomes a different type of lymphoma, most commonly DLBCL. Patients with other LBCL subtypes included nine (5.7%) patients with HGBCL, five (3.2%) patients with FL Gr 3B and four (2.5%) patients with PMBCL.

For patients with DLBCL, the cell origin classification per local laboratory was most commonly germinal centre B-cell (65 [46.8%] patients). [redacted] of patients with DLBCL ([redacted]) had IPI ≥3 at trial entry. At trial entry, [redacted] with DLBCL had local laboratory results to assess genetic rearrangements. Of these, [redacted] had *MYC*, *BCL2*, and/or *BCL6* rearrangements, classified as HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements according to WHO 2016 criteria.[19]

An additional, retrospective fluorescence in situ hybridisation (FISH) analysis was performed at a central laboratory on available diagnostic baseline tumour tissue sections to minimise selection bias. Based on central laboratory FISH analysis of screening tumour tissue available from [redacted] patients enrolled as having DLBCL, [redacted] had tumours with *MYC, BCL2*, and/or *BCL6* rearrangements and thus classified as HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements according to the WHO 2016 criteria.[19] In addition, [redacted] with DLBCL, who had no screening tumour tissue available for central laboratory FISH analysis, had been identified as having *MYC* and *BCL2* and/or *BCL6* rearrangements (i.e., DH or TH lymphoma) based on local laboratory results at trial entry.

Table 8: Baseline disease characteristics (FAS)

Number of treated patients, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Disease type at trial entry			
DLBCL	139 (100%)	0 (0.0%)	139 (88.5%)
HGBCL	0 (0.0%)	9 (50.0%)	9 (5.7%)
PMBCL	0 (0.0%)	4 (22.2%)	4 (2.5%)
FL Gr 3B	0 (0.0%)	5 (27.8%)	5 (3.2%)
DLBCL type			
De novo	97 (69.8%)	N/A	97 (61.8%)
Transformed	40 (28.8%)	N/A	40 (25.5%)
Disease type at initial diagnosis			
FL	[redacted]	[redacted]	[redacted]
MZL	[redacted]	[redacted]	[redacted]
SLL	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	2 (1.4%)	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]	[redacted]
DLBCL cell of origin classification per local laboratory[b]			
GCB	65 (46.8%)	[redacted]	65 (41.4%)
ABC/non-GCB	56 (40.3%)	[redacted]	56 (35.7%)
Unknown	18 (12.9%)	[redacted]	18 (11.5%)
Not applicable	0 (0.0%)	[redacted]	18 (11.5%)
***MYC* and *BCL2* and/or *BCL6* rearrangements per local laboratory**			
Number evaluated	[redacted]	[redacted]	[redacted]
Double-hit lymphoma	[redacted]	[redacted]	[redacted]

Number of treated patients, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Triple-hit lymphoma	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
***MYC* and *BCL2* and/or *BCL6* rearrangements per central laboratory FISH analysis**			
Number evaluated	[redacted]	[redacted]	[redacted]
Double-hit lymphoma	[redacted]	[redacted]	[redacted]
Triple-hit lymphoma	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ann Arbor stage at Screening			
I	[redacted]	[redacted]	[redacted]
IE	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIE	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
IIIE	[redacted]	[redacted]	[redacted]
IIIS	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
IPI (at study entry)			
0–2	[redacted]	[redacted]	55 (35.0%)
≥3	[redacted]	[redacted]	82 (52.2%)
Unknown	[redacted]	[redacted]	2 (1.3%)
Not applicable	[redacted]	[redacted]	18 (11.5%)
Presence of constitutional symptoms	[redacted]	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]	[redacted]
Weight loss (>10% over last 6 months)	[redacted]	[redacted]	[redacted]
Fever	[redacted]	[redacted]	[redacted]
Extreme fatigue	[redacted]	[redacted]	[redacted]

[a] Other includes 9 patients with HGBCL, 5 patients with FL Gr 3B and 4 patients with PMBCL; [b] Patients who had results from local laboratory analysis collected as medical history; [c] Time from diagnosis of disease recorded at time of trial entry; [d] Time from diagnosis of disease recorded at time of study entry.
Abbreviations: ABC: activated B-cell; aNHL: aggressive B-cell non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FISH: fluorescence in situ hybridisation; FL: follicular lymphoma; FL Gr 3B: follicular lymphoma grade 3B; GCB: germinal centre B-cell; HGBCL: high-grade B-cell lymphoma; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; max: maximum; min: minimum; MZL: marginal zone lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; SLL: small lymphocytic lymphoma.
Source: Table 14.1.1.3 and Table 14.1.1.3.1 AbbVie, EPCORE™ NHL-1 CSR, Jan 2022;[21] Thieblemont 2022.[65]

Prior medications and procedures

An overview of the prior cancer therapies received by patients in the EPCORE™ NHL-1 trial is shown in Table 9. As required by the protocol, all patients had R/R disease and had previously received at least two lines of systemic anti-lymphoma therapy, including at least one anti CD20 monoclonal antibody-containing therapy. Patients must have also failed prior ASCT or been ineligible for ASCT. For patients who are ineligible for ASCT, ineligibility must have been due to age, ECOG performance status, comorbidities, and/or insufficient response to prior treatment.

The median number of prior lines of anti-lymphoma therapy was 3.0 (range [min, max]: 2, 11), with [redacted] having received three prior lines of therapy and [redacted] having received ≥4 prior lines of therapy. The median time from the end of the last-line anti-lymphoma therapy to the first dose of epcoritamab in patients with LBCL was [redacted]).

Over half of the patients (96 [61.1%] patients) with LBCL had primary refractory disease and 119 (75.8%) patients were refractory to ≥2 consecutive prior lines of anti-lymphoma therapy. Most patients (130 [82.8%]) were refractory to the last line of systemic antineoplastic therapy. Overall, 61 (38.9%) patients with LBCL had received prior CAR-T cell therapy and, of these, 46 (75.4%) patients were refractory to CAR T-cell therapy (defined as disease that either progressed during therapy or progressed <6 months after completion of therapy).

A total of 31 (19.7%) patients with LBCL had a prior ASCT and [redacted] had received a prior allogeneic HSCT. Of the 31 (19.7%) patients with LBCL who had prior ASCT, more than half of those patients (18 of 31 patients) relapsed within 12 months of ASCT treatment.

Thus, the population of patients enrolled in the aNHL expansion cohort represents a heavily pre-treated, highly refractory, high-risk LBCL patient population.

Table 9: Prior anticancer therapies (FAS)

Number of treated patients, n (%)	**aNHL Cohort**		
	DLBCL (N=139)	**Other Subtypes[a] (N=18)**	**LBCL (N=157)**
Prior radiotherapy	[redacted]	[redacted]	[redacted]
Prior stem cell transplant	[redacted]	[redacted]	[redacted]
ASCT	[redacted]	[redacted]	31 (19.7%)
Patient relapsed ≤12 months after ASCT	[redacted]	[redacted]	[redacted]
Allogeneic SCT	[redacted]	[redacted]	[redacted]
Prior systemic therapy received			
Anti-CD20	[redacted]	[redacted]	[redacted]
Anti-CD19	[redacted]	[redacted]	[redacted]
Alkylating-containing Agents	[redacted]	[redacted]	[redacted]
Anthracyclines	[redacted]	[redacted]	154 (98.1%)
Nucleotide	[redacted]	[redacted]	[redacted]
Topo inhibitor	[redacted]	[redacted]	[redacted]
PI3K inhibitor	[redacted]	[redacted]	[redacted]
BCL2 inhibitor	[redacted]	[redacted]	[redacted]
PolyV	[redacted]	[redacted]	[redacted]
CAR-T	[redacted]	[redacted]	61 (38.9%)
Other	[redacted]	[redacted]	[redacted]
Median number (min, max) of prior lines of anti-lymphoma therapy	[redacted]	[redacted]	3.0 (2, 11)
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	46 (29.3%)

Number of treated patients, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
3	[redacted]	[redacted]	50 (31.8%)
≥4	[redacted]	[redacted]	61 (38.9%)
Median time (min, max) from end of last-line anti-lymphoma therapy to first dose of epcoritamab (months)	[redacted]	[redacted]	2.4 (0, 153)
Patients with primary refractory disease[b]	[redacted]	[redacted]	96 (61.1%)
Patients refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[c]	[redacted]	[redacted]	119 (75.8%)
Last-line systemic antineoplastic therapy			
Refractory[c]	[redacted]	[redacted]	130 (82.8%)
No response	[redacted]	[redacted]	[redacted]
Relapsed within six months after therapy completion	[redacted]	[redacted]	[redacted]
Relapsed[d]	[redacted]	[redacted]	[redacted]

[a] Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL; [b] Patient was considered primary refractory if the patient is refractory to frontline anti-lymphoma therapy; [c] Patient was considered refractory if the patient experienced disease progression or stable disease as best response or disease progression within six months after therapy completion; [d] Patient was considered relapsed if the patient experienced disease progression >6 months after last treatment.
Abbreviations: aNHL: aggressive B-cell non-Hodgkin lymphoma; ASCT: autologous stem cell transplantation; CAR-T: chimeric antigen receptor T-cells; DLBC: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; max: maximum; min: minimum; PMBCL: primary mediastinal B-cell lymphoma; SCT: stem cell transplantation.
Source: Table 14.1.1.6.1 AbbVie, EPCORE™ NHL-1 CSR, Jan 2022; [21] Thieblemont 2022.[65]

Clinician opinion on patient characteristics

During an AbbVie-organised advisory board held in July 2022, UK clinical experts provided feedback on the generalisability of the EPCORE™ NHL-1 trial population to UK clinical practice. Generally, UK clinical experts stated that the baseline characteristics of patients in the EPCORE™ NHL-1 trial were aligned with those of patients in UK clinical practice. The clinicians however noted that the proportion of patients who had failed CAR-T therapy was higher than expected in UK clinical practice.[4] Clinical experts highlighted that treating LBCL after patients have received CAR-T therapy is challenging; therefore the higher proportion of patients post-CAR-T in the EPCORE™ NHL-1 trial would be expected to bias against epcoritamab in terms of reduced survival outcomes, compared with patients in UK clinical practice.[4]

The clinicians also highlighted that a high number of patients in the EPCORE™ NHL-1 trial had refractory disease compared with UK clinical practice, in which patients are more often seen with relapsing disease. This was also proposed to bias against epcoritamab in the trial, compared with UK clinical practice, as clinical outcomes for patients with relapsing disease are typically worse than for patients with refractory disease.[4] Despite the above differences, overall, the clinicians considered the population included in the study to be reflective of patients with R/R LBCL in UK clinical practice.[4]

B.2.3.3 Patient disposition

Full CONSORT diagrams of the population flow for the trial can be found in Appendix D.

As of the [redacted] data cut-off, a total of [redacted] were screened and 157 patients received at least one dose of epcoritamab in the aNHL expansion cohort. Of the [redacted] who were enrolled but not treated with epcoritamab, the primary reason for not being treated was due to ineligibility; this was the reason for not being treated in [redacted], whilst the remaining [redacted] was due to an otherwise uncategorised reason ([redacted]). A total of 157 patients with LBCL, including 139 patients with DLBCL and 18 patients with other LBCL subtypes (nine patients with HGBCL, five patients with FL Gr 3B, and four patients with PMBCL) were treated with the RP2D.

As of the [redacted] data cut-off, [redacted] with LBCL remained on epcoritamab treatment. A total of [redacted] with LBCL had discontinued epcoritamab treatment at the time of the data cut-off. The most frequent primary reasons for treatment discontinuation were disease progression ([redacted]) and AEs ([redacted]). For [redacted], the decision to proceed with transplant was the primary reason for treatment discontinuation; the option to proceed with transplant following treatment with epcoritamab is an important clinical benefit. Lastly, a total of [redacted] with LBCL permanently discontinued the trial. The most common reason for trial discontinuation was death ([redacted]).

Considering patients with DLBCL specifically, as of the [redacted] data cut-off, [redacted] with DLBCL remained on epcoritamab treatment. A total of [redacted] with DLBCL had discontinued epcoritamab treatment at the time of the data cut-off. The most frequent primary reasons for treatment discontinuation were disease progression ([redacted]), AEs ([redacted]), and the decision to proceed with transplant ([redacted]). A total of [redacted] with DLBCL permanently discontinued the trial. The most common reason for trial discontinuation was death ([redacted]).

Table 10: Disposition of patients (FAS; [redacted] data cut-off)

Number of Treated Patients, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Ongoing study treatment	[redacted]	[redacted]	[redacted]
Discontinued study treatment	[redacted]	[redacted]	[redacted]
Primary reason for treatment discontinuation			
Progressive disease[b]	[redacted]	[redacted]	[redacted]
Clinical progression	[redacted]	[redacted]	[redacted]
Disease progression according to response criteria	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Decision to proceed with transplant	[redacted]	[redacted]	[redacted]
Other[c]	[redacted]	[redacted]	[redacted]

Number of Treated Patients, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Patients remain on trial	[redacted]	[redacted]	[redacted]
Discontinued from trial	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Patient withdrew consent from trial	[redacted]	[redacted]	[redacted]

[a] Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with primary mediastinal B-cell lymphoma (PMBCL); [b] Progressive disease includes both clinical progression and documented radiographic disease progression; [c] [redacted] discontinued treatment following a partial response on epcoritamab to proceed to CAR-T therapy.
Abbreviations: AE: adverse event; aNHL: aggressive B-cell non-Hodgkin lymphoma; CAR-T: chimeric antigen receptor T-cells; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma.
Source: Table 14.1.1.1.1 EPCORE™ NHL-1, 2022.[21]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Trial populations

A total of 157 patients, including 139 with DLBCL and 18 with other LBCL subtypes, were included in the aNHL cohort and treated with the RP2D of epcoritamab.

As per the statistical analysis plan, all analyses for the aNHL cohort were conducted for the overall aNHL population (i.e. LBCL), the DLBCL group and other subtypes. The DLBCL group includes patients with DLBCL (de novo or transformed from all indolent subtypes) and double-hit or triple-hit DLBCL (classified in WHO 2016 as HGBCL with *MYC* and *BCL2* or *BCL6* translocations). Other subtypes include patients with PMBCL, HGBCL (neither double-hit or triple-hit; based on WHO 2016 classification) and FL Gr 3B.

The definitions used for the analysis sets in the trial that were used for the analysis outcomes presented in this submission are presented in Table 11. All efficacy analyses were performed on the FAS (N=157). The FAS of the aNHL expansion cohort included 157 patients who received at least one dose of epcoritamab. All safety analyses were performed on the safety analysis set (SAF), which was identical to the FAS.

Table 11: Analysis sets used for the outcomes in EPCORE™ NHL-1 (aNHL cohort)

Analysis Set	Definition
FAS	All patients who received at least one dose of epcoritamab. All efficacy analyses were performed on the FAS (N=157)
SAF	All patients who received at least one dose of epcoritamab (same as FAS; N=157).
MRD-evaluable set	All patients who had at least one baseline or on-treatment MRD sample and were either MRD positive or not evaluated at baseline ([redacted])

PRO-evaluable set	All patients in the FAS with a baseline and at least one postbaseline PRO score ([redacted])

[a] A patient was considered having measurable disease at baseline based on investigator assessment if baseline CT or MRI scan was indicative of disease involvement of two or more lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm, or one lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm.
Abbreviations: aNHL: aggressive B-cell non-Hodgkin lymphoma; CT: computed tomography; FAS: full analysis set; MRD: minimal residual disease; MRI: magnetic resonance imaging; PRO: patient-reported outcome; SAF: safety analysis set.
Source: AbbVie, EPCORE™ NHL-1 CSR, Jan 2022. [21]

B.2.4.2 Statistical analyses

The statistical analyses used in EPCORE™ NHL-1, alongside sample size calculations and methods for handling missing data, are presented in Table 12.

Table 12: Summary of statistical analyses in EPCORE™ NHL-1

Hypothesis objective	• The expansion part of the trial was carried out in two stages. In the aNHL cohort, 28 patients with DLBCL were enrolled in Stage 1. If the futility criteria were met no further expansion would have continued:
	  ○ Null hypothesis: H_0: ORR is at most 35% (i.e. no more than seven responders out of 25 response evaluable patients with up to 12 weeks of follow up)
	  ○ Alternative hypothesis: H_1: ORR is at least 50%
	• As the futility criteria were not met, an additional 100 patients with DLBCL were enrolled to Stage 2, along with up to 30 patients with other types of aNHL (HGBCL, PMBCL and FL Gr 3B); Up to 158 patients were to be enrolled in total.
	• No formal statistical hypotheses were formulated for Stage 2 of the trial

Statistical analysis	• For categorical or ordinal variables, frequencies and percentages of patients in each category were displayed in contingency tables. The denominator was determined by the analysis set used for the summary. Percentages provided in the contingency tables were rounded to the first decimal place. Non-zero percentages less than 0.1 were displayed as '<0.1'. • For continuous variables, descriptive statistics included number of non-missing values (n), mean, standard deviation, median, minimum and maximum values. In addition, 25th percentile and 75th percentile may also have been provided. • Time to event variables were analysed using KM estimates (median time, first and third quartiles) with the number and percentage of patients with event or censoring reported. If specified, 95% confidence intervals were provided using Brookmeyer and Crowley method with log-log transformation. Landmark event-free rates may also have been presented together with the 95% confidence intervals. • All main efficacy analyses were based on FAS, with sensitivity analyses for primary analysis in the PP, RES and mRES populations. • Unless stated otherwise, all analyses for aNHL were performed for the DLBCL group, other subtypes, and the overall aNHL population.
Sample size, power calculation	• Assuming a non-evaluable rate of 10%, a sample size of [redacted] in the DLBCL group was estimated to provide approximately 90% power to detect the alternative hypothesis of at least 50% ORR while ensuring a 2-sided significance level of 0.05 using one-sample exact binomial test under the null hypothesis of at most 35% ORR. The probability of futility at the end of Stage 1 was approximately 30% under the null hypothesis and 2.1% under the alternative hypothesis.

Data management, patient withdrawals	**Primary endpoint analysis:** ***IRC-assessed ORR determined by Lugano criteria*** • ORR is defined as the proportion of patients who achieved BOR of complete response or partial response. As per the statistical analysis plan, the primary analysis was conducted approximately nine months after the last patient's first dose of epcoritamab. • ORR, disease control rate (BOR of stable disease and better) and the corresponding 95% CI are provided for the DLBCL, other subtypes and the overall aNHL cohort. **Secondary endpoint analyses:** ***Time to response and duration of response*** • TTR and DOR were derived for patients who achieved BOR of PR or CR. TTR is defined as the time from Day 1 of Cycle 1 to first documentation of objective tumour response (PR or better). DOR is defined as the time from the first documentation of response (CR or PR) to the date of PD or death, whichever occurs earlier. Date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment. • DOR was estimated using the KM product-limit method and displayed graphically. Median, first and third quantile along with two-sided 95% CI were computed based on log-log transformation. ***Complete response rate, time to complete response and duration of complete response*** • CR rate is defined as the proportion of patients with BOR of CR. Duration of complete response (DoCR) is defined as the time from the first documentation of CR to the date of PD or death, whichever occurs earlier. DoCR was derived for patients reaching CR. CR rate analyses were performed in a similar manner as ORR, and DoCR analyses were conducted using similar methods for DOR in the FAS. • Time to CR (TTCR) is defined as the time from Day 1 of Cycle 1 to first documentation of objective tumour response of CR. TTCR was derived for those patients who achieve the best of response of CR. ***Progression-free survival*** • PFS is defined as the time from Day 1 of Cycle 1 to the date of PD or death due to any cause, whichever occurs earlier. Date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment. PFS was derived for all patients and analysed using similar methods as DOR. The duration of disease follow-up, defined as the time between Day 1 of Cycle 1 to the date of PD or death due to any cause, whichever occurs earlier, was calculated based on reverse Kaplan-Meier method. • Two definitions of PFS were included in the statistical analysis plan; results in this submission are presented for the primary definition. The primary definition of PFS accounts for subsequent anti-lymphoma therapy and censor PFS at the last evaluable tumour assessment on or prior to the date of subsequent anti-lymphoma therapy. The subsequent anti-lymphoma therapies for PFS censoring in general consist of systemic anti-lymphoma therapy, and curative intent radiotherapy on one and only target lesion. ***Overall survival*** • OS is defined as the time from Day 1 of Cycle 1 to death from any cause. If a patient is not known to have died, then OS was censored at the latest

	date the patient was known to be alive. Survival status was assessed at least every three months after last administration of epcoritamab until the patient died or withdrew from the trial. OS was derived for all patients and analysed in the FAS using similar methods as DOR.

Abbreviations: aNHL: advanced non-Hodgkin's lymphoma; BOR: best overall response; CR: complete response; DLBCL; diffuse large B-cell lymphoma; DoCR: duration of complete response; DOR: duration of response; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade diffuse large B-cell lymphoma; KM: Kaplan–Meier; mRES: modified response evaluable set; ORR: overall response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; PP: per protocol; PR: partial response; RES: response evaluable set; TTR: time to response.

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

A summary of the quality assessment conducted for all clinical trials included in the SLR is presented in Appendix D. A summary of the quality assessment conducted for EPCORE™ NHL-1 is provided in Table 13.

Table 13: Quality assessment conducted for EPCORE™ NHL-1

Author year	Genmab/AbbVie CSR, 2022
Trial acronym	EPCORE NHL-1
What is the study design of this study?	Single-arm trial
Was the study a prospective study or a retrospective study?	Prospective
In case of a case-control study, were the groups similar at the outset of the study in terms of prognostic factors?	N/A
Was the intervention used appropriately?	Yes
Were the outcome measures in the study reliable?	Yes
Were the outcome measures in the study valid?	Yes
Was the statistical analysis conducted appropriately in the study?	Yes
Was the quality of reporting appropriate in the study?	Yes
Can the study results be generalised to routine practice?	Yes

Abbreviations: CSR: clinical study report; RCT: randomised controlled trial.

B.2.6 *Clinical effectiveness results of the relevant studies*

- The following section presents results from the [redacted] data cut-off of EPCORE™ NHL-1. Median duration of study follow-up was [redacted] months.
- The cohort of patients included in the EPCORE™ NHL-1 trial represents a heavily pre-treated population with a median number of three prior lines of therapy (range [min, max]: 2, 11), in which effective treatment options are currently limited.
    - In the overall cohort, 50 (31.8%) patients received 3 prior lines of therapy and 61 (38.9%) patients received 4 prior lines of therapy.
    - [redacted] had received prior CAR-T cell therapy and of these, [redacted] were refractory to CAR-T.
- Based on the [redacted] data cut-off, the ORR in patients with DLBCL (N=139) was [redacted] with [redacted] achieving best response of CR and PR, respectively. Overall, results were consistent for patients with other LBCL subtypes and all patients with LBCL.
- For patients with DLBCL, the median DOR, based on IRC assessment determined by Lugano criteria, was [redacted]. The estimated percentage of patients remaining in response at three, six and nine months was [redacted] (95% CI: [redacted], [redacted] (95% CI: [redacted] and [redacted] (95% CI: [redacted], respectively.
- Median PFS was [redacted] based on IRC assessment determined by Lugano criteria.
    - Among patients in CR, median PFS was [redacted]
    - Among patients in PR, median PFS was longer when compared with non-responders ([redacted] versus 1.2 months [redacted]
- Median OS among patients with DLBCL was [redacted] and median TTNT was [redacted]
- Based on the January 2022 data cut-off, whilst on treatment, there were marked HRQoL improvements in the patient reported symptoms across all six symptoms of the FACT-Lym questionnaire from Cycle 2 to Cycle 13.

In the EPCORE™ NHL-1 trial, results were assessed by IRC assessment, per the Lugano criteria, as well as by investigator assessment, per the Lugano criteria. IRC-assessed and investigator-assessed results were generally consistent. Investigator-assessed results for ORR and PFS are presented in Appendix M to demonstrate the consistency between IRC-assessment and Investigator-assessment. All results are presented from the [redacted] data cut-off.

Efficacy assessments were conducted as scheduled imaging assessments during Weeks 6, 12, 18, 24, 36, 48, and then every 24 weeks thereafter, including physical examination (including constitutional symptoms), ECOG performance status, MRD status, and other procedures as necessary. All efficacy assessments were conducted throughout the trial until disease progression or withdrawal of consent from trial participation occurred. Response assessments according to the imaging assessment were performed by the investigators at the site to make decisions for continuation of treatment.

As outlined in Section B.2.8, efficacy data from the DLBCL cohort are used to inform the comparative efficacy analyses to reduce heterogeneity between the EPCORE™ NHL-1 trial and comparator trials. The trial results in this section therefore focus on the DLBCL population from the aNHL cohort of EPCORE™ NHL-1. However, results were consistent with the full LBCL and other subtypes (i.e. non-DLBCL) populations; the LBCL and other subtype data are provided in Appendix M.

B.2.6.1 Overview of the clinical effectiveness results

A summary of the key clinical outcomes from the EPCORE™ NHL-1 trial for the FAS population aNHL patients are shown in Table 14.

Table 14: Overview of key clinical effectiveness results from EPCORE™ NHL-1 (FAS; [redacted] data cut-off)

Outcome	DLBCL (N=139)	Other Subtypes (N=18)[a]	LBCL (N=157)
ORR (IRC, Lugano criteria)[a]	[redacted]	[redacted]	[redacted]
(95% CI)[b]	[redacted]	[redacted]	[redacted]
CR (IRC, Lugano criteria)	[redacted]	[redacted]	[redacted]
(95% CI)[b]	[redacted]	[redacted]	[redacted]
DOR (months) all responders (IRC, Lugano criteria)			
Number of responders	[redacted]	[redacted]	[redacted]
Min, max[c]	[redacted]	[redacted]	[redacted]
Median (95% CI)[d]	[redacted]	[redacted]	[redacted]
PFS (months) (IRC, Lugano criteria)			
Number of events	[redacted]	[redacted]	[redacted]
Min, Max[c]	[redacted]	[redacted]	[redacted]
Median (95% CI)[d]	[redacted]	[redacted]	[redacted]
OS (months)			
Number of events	[redacted]	[redacted]	[redacted]
Number of censored	[redacted]	[redacted]	[redacted]
Min, max[c]	[redacted]	[redacted]	[redacted]
Median (95% CI)[d]	[redacted]	[redacted]	[redacted]
TTNT (months)			
Number of events[e]	[redacted]	[redacted]	[redacted]
Number of censored	[redacted]	[redacted]	[redacted]
Min, Max[c]	[redacted]	[redacted]	[redacted]
Median (95% CI)[c,d]	[redacted]	[redacted]	[redacted]

[a] Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL; [b] Based on the Clopper and Pearson method; [c] Symbol '+' indicates a censored value; [d] Based on Kaplan–Meier estimate; [e] Event is defined as administration of subsequent anti-lymphoma therapy with curative intent or death due to disease progression.
Abbreviations: CI: confidence interval; CR: complete response rate; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; IRC: independent review committee; LBCL: large B-cell lymphoma; Max: maximum; Min: minimum; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; TTNT: time to next treatment.
Source: Table 14.2.1.1.1; Table 14.2.1.7.1; Table 14.2.1.12.1, Table 14.2.1.17, and Table 14.2.1.18 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.6.2 Primary endpoint

ORR based on IRC assessment, Lugano Criteria (FAS)

The ORR in patients with DLBCL (N=139) was [redacted] ([redacted]; 95% CI: [redacted]) with [redacted] and [redacted] achieving best response of CR and PR, respectively, as shown in Table 15.

Overall, results were consistent for patients with other LBCL subtypes and patients with DLBCL (Appendix N).

Table 15: ORR and BOR based on IRC Assessment, Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
ORR[a]	[redacted]
(95% CI)[b]	[redacted]
CR rate	[redacted]
(95% CI)[b]	[redacted]
BOR	
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
NE	[redacted]

[a] CR+PR. Includes [redacted] who had a PR or CR after an assessment of PD or indeterminate response (i.e., pseudo progression); [b] Based on the Clopper and Pearson method.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; NE: non evaluable; ORR: overall response rate; PD: partial disease; PR: partial response; SD: stable disease.
Source: Table 14.2.1.1.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

A waterfall plot of best reduction in sum of the product of the diameters by IRC assessment determined by Lugano criteria is provided for patients with DLBCL in Figure 4. The same figure for the LBCL population is presented in Appendix M.

Figure 4: Waterfall plot of best reduction in SPD based on IRC assessment per Lugano Criteria (FAS; [redacted] data cut-off)

Stars indicate that there is an increase of more than 100% in sum of product perpendicular diameters.
Abbreviations: FAS: full analysis set; IRC: Independent Review Committee; SPD: Sum of Product Perpendicular Diameter.
Source: Figure 14.2.1.8.1 EPCORE™ NHL-1, 2022.[21]

B.2.6.3 Secondary endpoints

DOR based on IRC assessment, Lugano Criteria (FAS)

In patients with DLBCL who had achieved PR or CR ([redacted]), the median DOR was [redacted] (95% CI: [redacted]). The estimated percentage of patients remaining in response at three, six, and nine months was [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively. In patients with DLBCL who had achieved CR ([redacted]), the median DOR was [redacted]. The estimated percentage of patients remaining in response at three, six, and nine months was [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively. These results are shown in Table 16 and a Kaplan–Meier (KM) plot of DOR for DLBCL, LBCL and other subtypes is shown in Figure 5.

It is important to note that most CRs were achieved by the first or second assessment; however, nine patients converted from a PR to a CR at or after the Week 36 tumour assessment (range [min, max]: 32.3–48.1 weeks), eight of these patients had ongoing responses, thereby suggesting added clinical benefit with continuous treatment of epcoritamab in a subset of patients.[65]

DOR among patients with LBCL and other subtypes of LBCL were consistent with that of patients with DLBCL. The data for all LBCL subtypes are provided in Appendix M.

Table 16: DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
All responders (PR or CR)	
Number of responders	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
DOR (months)	
Min, max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimate percentage of patients remaining in response (95% CI)[b]	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]
CR	
Number of patients with CR	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
DOR (months)	
Min, max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]

	DLBCL (N=139)
Estimate percentage of patients remaining in response (95% CI)[b]	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on Kaplan–Meier estimate
Abbreviations: CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; FAS: full analysis set; IRC: independent review committee; max: maximum; min: minimum; NR: not reached; PR: partial response.
Source: Table 14.2.1.7.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

Figure 5: KM plot of DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; NR: not reached; PMBCL: primary mediastinal B-cell lymphoma.
Source: Figure 14.2.1.9.1 AbbVie, EPCORE™ NHL-1, 2022.[21]

PFS based on IRC assessment, Lugano Criteria (FAS)

PFS was defined as the time from C1D1 to date of disease progression or death due to any cause, whichever occurred earlier. Among patients with DLBCL, [redacted] patients experienced a PFS event (disease progression or death) as assessed by IRC. The median PFS was [redacted]). The estimated percentage of patients remaining progression-free at six and nine months was [redacted] and [redacted], respectively.

Based on the [redacted] data cut-off, for patients with DLBCL, among patients in CR, median PFS was [redacted]. Among patients in PR, median PFS was [redacted] when compared with non-responders ([redacted] versus [redacted]).

The PFS based on IRC assessment (Lugano criteria) are presented in Table 17 and a KM plot of PFS based on IRC assessment for patients with DLBCL, LBCL and other subtypes is presented in Figure 6. The PFS data for all LBCL subtypes are provided in Appendix M.

Table 17: PFS based on IRC assessment Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events	[redacted]
Number of censored	[redacted]
PFS (months)	
Min, Max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimated percentage of patients remaining progression-free (95% CI)[b]	
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; LBCL: large B-cell lymphoma; Max: maximum; Min: minimum; NR: not reached; PFS: progression-free survival.
Source: Table 14.2.1.12.1 EPCORE™ NHL-1 CSR, 2022.[21]

Figure 6: KM plot of PFS based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

[redacted]

Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL. [redacted]

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma.
Source: Figure 14.2.1.12.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

Figure 7: KM plot of PFS based on IRC assessment, Lugano Criteria, by BOR (FAS; [redacted] data cut-off)

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PR: partial response.
Source: Figure 14.2.1.12.11 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

OS (FAS)

OS was defined as the time from C1D1 to death from any cause. If a patient was not known to have died, then OS was censored at the latest date the patient was known to be alive. Among patients with DLBCL, [redacted] had died and [redacted] were still alive. After a median follow up of [redacted], median OS was [redacted] (95% CI: [redacted]). The estimated percentage of patients with DLBCL who remained alive at 6, 9, and 12 months was [redacted], [redacted], and [redacted], respectively. This is shown below in Table 18 and a KM plot of OS for DLBCL, LBCL and other subtypes is shown in Figure 8. The data for LBCL and other subtypes are provided in Appendix N.

Table 18: OS (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events	[redacted]
Number of censored	[redacted]
OS (months)	
Min, max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimated percentage of patients remaining alive (95% CI)[b]	
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]

	DLBCL (N=139)
15-month	[redacted]
18-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; Max: maximum; Min: minimum; NR: not reached; OS: overall survival.
Source: Table 14.2.1.17 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

Figure 8: KM plot of OS (FAS; [redacted] data cut-off)

Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; PMBCL: primary mediastinal B-cell lymphoma; NR: not reached.
Source: Figure 14.2.1.13.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

TTNT (FAS)

TTNT was defined as the time from C1D1 to first recorded administration of subsequent anti-lymphoma therapy with curative intent or death, whichever occurred earlier. Patient death due to disease progression was considered an event. Death due to other reasons was censored at the death date. The subsequent anti-lymphoma therapies for TTNT events in general consisted of systemic anti-lymphoma therapy, and curative intent radiotherapy for one and only target lesion. The exception is censoring patient without disease progression while receiving subsequent stem cell transplant after responding to epcoritamab to be consistent with the intent to measure duration of clinical benefit using TTNT. Patients alive and without initiation of subsequent anti-lymphoma therapy were censored at the last known alive date.

Among patients with DLBCL ([redacted]), [redacted] experienced a TTNT event (of which [redacted] events were due to receiving subsequent anti-lymphoma therapy and [redacted] events were due to death) and [redacted] were censored. Median TTNT was [redacted] (95% CI: [redacted]). The estimated percentage of patients not initiating subsequent therapy at three, six, nine, and 12 months was [redacted], [redacted], [redacted], and [redacted], respectively. This is shown below in Table 19. The TTNT data for LBCL and other subtypes are provided in Appendix M.

Table 19: TTNT (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events[a]	[redacted]
Number of censored	[redacted]
TTNT (months)	
Min, Max[b]	[redacted]
25% quartile (95% CI)[c]	[redacted]
Median (95% CI)[c]	[redacted]
75% quartile (95% CI)[c]	[redacted]
Estimated percentage of patients not initiating next line of therapy (95% CI)[b]	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]
15-month	[redacted]

[a] Event is defined as administration of subsequent anti-lymphoma therapy with curative intent or death due to disease progression; [b] Symbol '+' indicates a censored value; [c] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; Max: maximum; Min: minimum; NR: not reached; TTNT: time to next anti-lymphoma therapy.
Source: Table 14.2.1.18 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.6.4 Patient reported outcomes

FACT-Lym

FACT-Lym is a fully validated quality of life questionnaire applicable for patients with lymphoma which includes a module that assesses specific concerns of patients with lymphoma. The Lymphoma Subscale (LymS) module consists of 15 statements for patients to respond to on an identical 5-point scale. An overview of the results of the FACT-Lym total score and the FACT-LymS are provided in Table 20.

All the statements included in the FACT-Lym questionnaire are provided in Appendix M. Six questions from the FACT-Lym (P2 [body pain], BRM3 [fever], ES3 [night sweats], GP1 [lack of energy], BMT6 [tires easily], and C2 [weight loss]) were considered relevant to key symptoms of lymphoma and as such, were secondary endpoints of the EPCORE™ NHL-1 trial.

While on treatment, there were marked improvements in the patient reported symptoms across all six symptoms of the FACT-Lym (body pain, fever, night sweats, lack of energy, tires easily, and weight loss) from Cycle 2 to Cycle 13. The results for the whole LBCL population and other LBCL subtypes are provided in Appendix M.

Table 20: Mean scores for FACT-Lym total score and FACT-LymS while on treatment (FAS – DLBCL population [N=139]; [redacted] data cut-off)

Time point	Sample size	FACT-Lym total score, mean (Sd)	FACT-LymS, mean (SD)
C1D1	[redacted]	[redacted]	[redacted]
C3D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C5D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]

Abbreviations: CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; FAS: full analysis set; SD: standard deviation.
Source: EPCORE™ NHL-1 Data Tables, [redacted].[21]

EQ-5D-3L results

Changes in HRQoL as evaluated by EuroQoL-5 dimensions-3 levels (EQ-5D-3L) were included as an exploratory endpoint in EPCORE™ NHL-1.

Based on the [redacted] data cut-off, for patients with DLBCL, consistent and steady improvements in patient-reported quality of life were observed as reflected by improvements in mean (standard deviation) EQ-5D-3L health utility scores from [redacted] ([redacted]; N=[redacted]) at baseline to [redacted] ([redacted]; N=[redacted]) at C9D1. The mean changes are presented below in Table 21 and graphically in Figure 9. Similar improvements were observed in the LBCL cohort (Appendix M).

Table 21: Mean scores for EQ-5D-3L health utility score while on treatment (FAS – DLBCL population [N=139]; [redacted] data cut-off)

Time point	Sample size	Health utility score, mean (SD)
C1D1	[redacted]	[redacted]
C3D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
C5D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
C7D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
C9D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]

Abbreviations: CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma; EQ-5D-3L: EuroQoL-5 diminesions-3 levels; FAS: full analysis set; SD: standard deviation.
Source: EPCORE™ NHL-1 Data Tables, [redacted].[21]

Figure 9: Mean change from baseline in EQ-5D-3L Health Utility Score (PRO-evaluable Set – DLBCL population [N=139]; [redacted] data cut-off)

Horizontal reference line indicates [redacted]; Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; MID: minimum important difference; PMBCL: primary mediastinal B-cell lymphoma; PRO: patient-reported outcome.
Source: Figure 14.2.3.5.5 EPCORE™ NHL-1 CSR, [redacted].[21]

B.2.7 *Subgroup analysis*

For most pre-specified subgroups, the ORRs were generally consistent with the ORR of the overall DLBCL population ([redacted]; 95% CI: [redacted]) (Figure 10). Furthermore, for most subgroups, the ORRs were generally consistent with the ORR of the overall LBCL population. Key observations from the subgroup analysis of patients within the full LBCL population are provided in Appendix M.

Of particular interest, in the DLBCL population, ORR was [redacted] in the no prior CAR-T subgroup (N=[redacted]) versus the prior CAR-T subgroup (N=[redacted]) ([redacted] versus [redacted]). Although a numerical difference was observed, the 95% confidence intervals overlapped and there was [redacted] difference. Relatedly, in the subgroup of patients refractory to prior CAR-T (N=[redacted]), ORR was [redacted]; again, although a numerical difference was observed, there was [redacted] difference.

Figure 10: Forest plot of ORR in prespecified subgroups based on IRC assessment determined by Lugano Criteria - DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: ABC: activated B-cell; ADA: anti-drug antibody; ASCT: autologous stem cell transplantation; CAR-T: Chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; GCB: germinal centre B-cell; IPI: International Prognostic Index; IRC: independent review committee; ORR; overall response rate.
Source: Figure 14.2.1.1.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.8 *Indirect and mixed treatment comparisons*

- EPCORE™ NHL-1 is a single-arm trial and no head-to-head trials with available data comparing epcoritamab to the relevant comparators were identified in the clinical SLR. Therefore, an indirect treatment comparison (ITC), in the form of a matching-adjusted indirect comparison (MAIC), was conducted to inform the relative efficacy estimates for epcoritamab versus the relevant comparators for this appraisal: axi-cel and R-based CIT.
  - The relative efficacy of epcoritamab versus Pola + BR is also determined for use in a scenario analysis.
- In the MAIC informing base case analysis A (patients who are ineligible for, or choose not to receive, intensive treatments; epcoritamab versus R-based CIT), the epcoritamab DLBCL, no prior CAR-T population is adjusted to match the Sehn *et al.* population after two or more prior lines of therapy and then compared to R-based CIT. This approach was taken following feedback from UK clinical experts and to ensure that the adjusted population is most reflective of the population of interest in this submission.
- In the MAIC informing base case analysis B (patients who are eligible for intensive therapy; epcoritamab versus axi-cel), the epcoritamab DLBCL, no prior CAR-T, eligible for CAR-T population is unadjusted to match the axi-cel population from ZUMA-1. This is a conservative approach that biases against epcoritamab when compared with the adjusted results.
- The results of the MAICs demonstrate that epcoritamab is associated with a [redacted] versus R-based CIT with regards to OS HR ([redacted]), difference in CR rate ([redacted]) and difference in ORR ([redacted]).
- For the comparison of epcoritamab versus axi-cel, the results of the MAIC demonstrate that there is [redacted] treatment benefit for patients receiving epcoritamab versus axi-cel in terms of the OS HR ([redacted] and PFS HR [redacted]). [redacted] was also observed for CR rate and ORR for epcoritamab versus axi-cel, with the difference in CR rate of [redacted] and a difference in ORR of [redacted].
- Extensive supportive analyses have also been conducted to explore the uncertainty associated with any assumptions used in the base case approaches, including using the LBCL population from EPCORE™ NHL-1 to inform the epcoritamab efficacy data.
  - Overall, the supportive analyses demonstrated that the efficacy estimates for epcoritamab based on the DLBCL population are similar to those based on the LBCL population, and the base case is biasing against the true efficacy of epcoritamab in R/R LBCL in patients who have received two or more prior therapies.

EPCORE™ NHL-1 is a single-arm trial and no head-to-head trials with available data comparing epcoritamab to the relevant comparators were identified in the clinical SLR. EPCORE™ DLBCL-1, in which epcoritamab is compared with BR or R-GemOx was identified in the clinical SLR, but as stated in Section B.2.2, this trial is ongoing and data are not yet available; as such, EPCORE™ DLBCL-1 is not considered within this submission document.

Therefore, ITCs, in the form of a MAICs, were conducted to inform the relative efficacy estimates for epcoritamab versus the relevant comparators for this appraisal: axi-cel and R-based CIT. The relative efficacy of epcoritamab versus Pola + BR is also determined for use in a scenario analysis. The following section provides an overview of the MAIC methodology and results. Additional details are presented in Appendix N.

B.2.8.1 Methods of the indirect treatment comparison

Choice of MAIC methodology

Due to the single-arm nature of the EPCORE™ NHL-1 trial, no network could be created between EPCORE™ NHL-1 and comparator trials. Therefore, a network meta-analysis was not deemed to be feasible. As a result, given the availability of individual patient data (IPD) for epcoritamab and based on NICE TSD 18 guidance on population-adjusted indirect comparisons based on propensity score reweighting methods, unanchored MAICs were conducted.[69]

The unanchored MAIC methodology was preferred to simulated treatment comparisons (STCs) (i.e. outcome regressions) due to small numbers of events available. Parametric or semiparametric regression analyses rely on the number of events (not the number of patients) to determine the degrees of freedom; the lower the number of events, the lower the number of predictors that can be included in the model. In addition, MAICs produce marginal (population-level) treatment effect estimates which is considered more appropriate for Health Technology Appraisals (HTA), whereas STCs only produce conditional (patient-level) treatment effects.[69]

Data sources

The ITC was conducted using IPD from the EPCORE™ NHL-1 trial ([redacted] data cut-off) and aggregated data from comparator studies. In this submission, economic analyses are presented separately for two separate patient populations due to differing clinical pathways of care and differing levels of patient fitness, as supported by feedback from UK clinical experts. As such, MAICs are conducted with the separate base case populations in mind:

- Base case analysis A: Patients who are ineligible for, or choose not to receive, intensive therapies
- Base case analysis B: Patients who are eligible to receive intensive therapies

As detailed in Appendix D, a clinical SLR was conducted to identify relevant clinical evidence for patients initiating 3L+ therapies for R/R LBCL, including R/R DLBCL, in line with the expected indication for epcoritamab. A total of 13,356 publications were identified and a total of 227 peer-reviewed publications were deemed eligible for inclusion in the clinical SLR. An additional 80 relevant abstracts were identified through searches of conference proceedings, and three additional publications were included from citation review. A total of 164 publications were considered eligible for data extraction.

The clinical SLR identified a number of studies reporting survival and/or response outcomes of R/R LBCL treatments, including evidence from HTA bodies and oncology conferences. RCT evidence was prioritised for inclusion but in instances where the included study could not provide appropriate information on the exact treatment line of interest or baseline characteristics to enable the matching and adjustment, real-world evidence (RWE) that could serve these purposes was considered (Appendix N).

Of the studies identified from the SLR, one study for each comparator of interest in the base case (axi-cel and R-based CIT) and for scenario analyses (Pola + BR) was selected, along with other observational sets where appropriate, for inclusion in the ITC based on the following additional criteria:

- Included patients that had received two or more prior lines of therapy

- Reported key baseline patient characteristics
- Included a KM curve for OS and PFS that clearly displays the survival and progression events or enough information to extract or estimate curves for the population of interest
- Reported outcomes that were similarly defined as in the EPCORE™ NHL-1 trial

If no appropriate data were available, the comparator population that was most representative of the epcoritamab population was selected, using the above inclusion criteria, aligned with the PICOS criteria for the SLR (Appendix D).

The studies selected for inclusion in the ITC, based on the above criteria, are presented in Table 22.

Table 22: Comparator studies selected for inclusion in the ITC (base case and scenario analyses)

Analysis	Treatment	Source	Comparator population(s) included in ITC
Base case analysis A	R-based CIT	SCHOLAR-1 (Neelapu *et al.* [2021])[70]	No prior CAR-T therapy
Base case analysis B/Scenario analysis B.1	Axi-cel	ZUMA-1 (Locke *et al.* [2019])[71]	No prior CAR-T therapy and CAR-T eligible population
Scenario analysis A.1	Pola + BR	• EUnetHTA submission for Pola + BR[a] • Sehn *et al.* (2019) and Sehn et al. (2022) extension study[72,b]	Two or more prior therapies, no prior CAR-T therapy (PICO 1b subgroup)
Scenario analysis A.2/A.3	Pola + B/R	Liebers *et al.* (2019) real-world observation study (Liebers *et al.* [2019])[73]	Overall population

[a] Data from the EUnetHTA submission for Pola + BR were used to inform baseline characteristics of the 3L+ population. [b] Data from Sehn *et al.* (2019) and Sehn *et al.* (2022) were used to estimate 3L+ survival curves and inform best response outcomes.
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; ITC: indirect treatment comparison; Pola + BR: polutuzumab vedotin with bendamustine plus rituximab; Pola + B/R: polutuzumab vedotin plus rituximab with or without bendamustine; R: rituximab.

Summary

A summary of the key characteristics of the trials included in the ITC is presented in Table 23.

Table 23: Summary of key characteristics of the studies included in the ITC

Trial	Treatment	Trial design	Indication of study	Main patient selection criteria	Median follow-up (months)
EPCORE™ NHL-1	Epcoritamab	Phase 1/2, open-label trial; LBCL patients: N=157; DLBCL patients: N=139	LBCL, including DLBCL	2+ prior lines of treatment	[redacted]
SCHOLAR-1[70]	R-based CIT	Observational RWE study; N=340	LBCL	1+ prior line of treatment	5.4 months
ZUMA-1[71]	Axi-cel	Phase 1/2, open-label trial; N=101	LBCL	2+ prior lines of treatment, ECOG PS <2	27.1
Sehn *et al.* (2019); data also obtained from Sehn et al. (2022) extension study and PICO 1b subgroup of EUnetHTA submission for Pola + BR [72, 74, 75]	Pola + BR	Phase 2, randomised, controlled trial; N=29 The extension cohort included an additional 102 patients treated with Pola + BR after 2+ prior therapies	DLBCL	2+ prior lines of treatment (PICO 1b subgroup from EUnetHTA submission)	22.3
Liebers *et al.* (2019)[73]	Pola + BR/R	Observation RWE study; N=54	LBCL	2+ prior lines of treatment	7.5

Abbreviations: axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; ITC: indirect treatment comparison; LBCL: large B-cell lymphoma; Pola + BR: polutuzumab vedotin with bendamustine plus rituximab; Pola + BR/R: polatuzumab vedotin plus rituximab with or without bendamustine; R: rituximab; RWE: real-world evidence.

Methodology

Overview

The ITCs were conducted based on the following key methodology steps:

- Using the comparator studies outlined above, published survival data were digitised
- In order to make the comparator populations and the epcoritamab population more comparable, patients with no prior CAR-T therapy from the epcoritamab population were selected; EPCORE™ NHL-1 included patients who had previously received CAR-T therapy, whereas Sehn *et al.* (2019), SCHOLAR-1 and ZUMA-1 did not include patients who had previously received CAR-T therapy[70-72]
- The populations were adjusted for imbalances in prognostic factors and effect modifiers using IPD from EPCORE™ NHL-1 on epcoritamab and aggregate data on the comparators
- Propensity score weights resulting from the adjustments were applied to estimate the difference in ORR and complete response (CR) rate for epcoritamab versus comparators, and weighted Cox proportional hazards models were used to estimate the PFS and OS HRs for epcoritamab versus the comparators

The methodology of the ITCs is described in more detail in the following sections.

Endpoints of interest

Comparative efficacy data were derived for PFS, OS, ORR and CR using the following estimates:

- HR and 95% CI of PFS
- HR and 95% CI of OS
- KM survival curves
- Mean difference (MD) and 95% CI for ORR
- MD and 95% CI for CR

Outcome definitions used in the trials were comparable across sources used. PFS and response outcomes from EPCORE™ NHL-1 were based on IRC assessment, as IRC assessment is typically considered to be more robust. As such, when available, IRC assessment was used for comparators to ensure comparability of outcomes and to reduce the risk of bias. A summary of the definitions for PFS and response used in the indirect comparisons for each treatment is provided in Table 24.

Table 24: Outcome definition for PFS and response for each treatment included in the ITC

Epcoritamab versus comparator treatment	Outcome definition for epcoritamab[a]	Outcome definition for comparator
R-based CIT	IRC Lugano	IWG as per investigator
Pola + BR (EUnetHTA submission)[74]		Modified IRC Lugano[b]
Pola + B/R (Liebers *et al.*)		Investigator-assessed using CT/clinical judgement; CT scans available in 75.9% of patients
Axi-cel		IWG as per IRC

[a] Full definitions for PFS and response endpoints in EPCORE™ NHL-1 are reported in Section B.2.4.2 and Section B.2.6. [b] As the Pola + BR on two or more prior therapies population (PICO 1B) in EUnetHTA submission did not report best response in that population, the estimate for best response among those on two or more prior therapies (N=102) in the extension of the Sehn *et al* trial was used.[75] This was deemed to be a justified assumption for the analysis given that authors of the extension study concluded that *"the baseline characteristics in the extension cohort were similar to the [original] randomized pola+BR cohort",* which is where the PICO 1b population was derived from in the EUnetHTA submission.
Abbreviations: axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; CT: computed tomography; IRC: independent review committee; ITC: indirect treatment comparison; IWG: International Working Group; Pola + BR: polutuzumab vedotin with bendamustine plus rituximab; Pola + BR/R: polatuzumab vedotin plus rituximab with or without bendamustine; PFS: progression-free survival; R: rituximab.

Statistical methods: Propensity score weighting

Unanchored indirect treatment comparisons, in the form of MAICs, were conducted for epcoritamab versus the relevant comparators based on propensity score (PS) reweighting methods. The MAICs were conducted in alignment with suggested best practice, as outlined in NICE DSU TSD18.[76]

PS methods were used to mimic the effect of randomisation by creating a balance between two treatment groups in respect to important baseline covariates. In the adjusted analyses, the EPCORE™ NHL-1 trial data were reweighted to match the baseline characteristics of those reported in the comparator trial.[77, 78] As part of this process, each patient was given a weight representing the inverse of the odds of being in the EPCORE™ NHL-1 trial versus being in the comparator trial. This means that the patients who were less likely to be among the comparator trial population (based on the reported baseline characteristics) were assigned less weight in the analysis and vice versa. Whenever indicated, adjustment weights were truncated at 1% and 99% of their distribution to reduce the occurrence of extreme weights, while still preserving the resulting balance in adjusted baseline characteristics.[79]

In these analyses, the epcoritamab population was reweighted to match the comparator trials. As such, the effective sample size, N_{eff}, of the epcoritamab trials is reduced when compared to the original sample size.

In unadjusted analyses, the epcoritamab data were compared to other treatments without an adjustment of their baseline characteristics; each patient was given a weight of one and the data were unchanged.

Statistical methods: Assessment of proportional hazards

In alignment with NICE DSU TSD 14, the proportional hazards (PH) assumption between the treatment arms was tested for all of the MAICs conducted, using R. [80, 81] As part of the assessment of PH, three tests were carried out:

- **Visual inspection of the log-cumulative hazards against log-time**: If the lines on the graph are approximately parallel then it can be said that the PH assumption holds. Should the curves not be parallel and show evidence of crossing then there is evidence that under this test that proportionality does not hold.
- **Visual inspection of the Schoenfeld residuals to examine the model fit**: The Schoenfeld residuals present the difference between the observed covariate and the expected value over time. If PH holds then the plot of Schoenfeld residuals should be flat and centred around zero.
- **The Grambsch and Therneau test (a chi-square test)**: This tests whether the slope is zero between the Schoenfeld residuals and the survival time. If the p-value is significant (<0.05), the null hypothesis of PH (i.e., the slope is zero) is rejected.

There is not one test which can assess whether proportional hazards holds and so the final determination was based upon the conclusions from all the tests.

Statistical methods: HR for survival

For survival endpoints, the EPCORE™ NHL-1 data and the simulated patient-level outcomes data for comparators were analysed using a weighted Cox model with robust standard errors within the 'survival' package in R.[82] The outcome of the survival ITCs were the HRs and 95% CIs of epcoritamab relative to comparators. A HR <1 indicates lower risk of progression or death for epcoritamab than for the comparator treatment.

Statistical methods: Percentage difference for response outcomes

For response comparisons, mean difference in response on the absolute scale was estimated using weighted regression models with Gaussian distribution, implemented in the "survey" package in R.[83] The weighted regression models in effect modelled the difference between ORR and CR rates between epcoritamab and comparators.

Weighted generalised regression models were implemented using the "survey" package in order to calculate robust standard errors of the weighted mean estimates by accounting for clustering on the patient ID level.[84]

Variables for adjustment

In alignment with NICE DSU TSD18, the effect modifiers and prognostic variables to be included for adjustment were carefully considered. As outlined in NICE DSU TSD18, including too many variables will reduce the effective sample size, negatively affecting the precision of the estimate and failure to include relevant variables will result in biased estimates.

The selection of covariates to adjust for in the MAICs were identified based on published literature (including peer-reviewed published ITCs and consideration of previous NICE evaluations in the indication of interest), empirical testing of prognostic status in the EPCORE™ NHL-1 trial and input from UK clinical experts as to whether certain characteristics are important to adjust for in a R/R LBCL population.[70, 85, 86] Based on these sources, the following covariates were identified as potential variables to adjust for in the analyses:

- Age
- Gender
- ECOG performance status

- Histology
- IPI score
- Disease stage
- Primary refractoriness
- Response to recent prior therapy
- Number of prior lines of treatment
- Prior ASCT
- Prior CAR-T therapy

To ensure all key variables were adjusted for, a validation exercise with UK clinical and health economic experts was conducted. UK clinical experts stated that adjustment for IPI score was not necessary if adjustment for disease stage is included, as disease stage contributes to IPI score. Based on the validation exercise, the following covariates were identified as the most relevant for adjustment:

- Age ≥65 years of age
- Gender
- DLBCL histology (including transformed FL) vs not DLBCL
- Primary refractoriness
- Refractory to ≥2 consecutive lines of therapy
- Refractory to last prior anti-CD20 agent
    - Refractoriness to last treatment when information on last prior anti-CD20 or primary refractoriness is not available
- Prior CAR-T therapy
- Prior ASCT
- Relapse within 12 months of autologous stem cell transplant
- ECOG PS >1
- Disease stage III-IV

Within each MAIC, the availability of the above characteristics in the comparator studies guided the final list of adjusted variables in that analysis.

In addition, due to variability in the number of prior lines of therapy in each trial, exact regimens administered and corresponding sequence of administration, the number of prior lines of therapy were not adjusted for. Refractory to last therapy was only adjusted for when comparator information on primary refractoriness or prior anti-CD20 was missing. This approach was followed to avoid multicollinearity with other variables of refractoriness that were included for adjustment post clinical validation.

B.2.8.2 Results of the indirect treatment comparison

Comparisons conducted

Patients ineligible for, or choose not to receive, intensive therapies: Base case analysis A

For the ITC informing base case analysis A (ineligible for intensive therapies), an approach was taken that allows for one PFS and OS reference curve across multiple comparisons, thereby allowing fully incremental cost-effectiveness analysis, if required. NICE have previously criticised pairwise comparisons where each individual adjusted comparison leads to a change in the reference survival curve, such as during ID3795, and this approach addresses that concern.[14]

In order to do so, UK clinical experts were consulted on which comparator population represents the population that is generalisable to patients with R/R LBCL in the UK. After consultation with UK clinical experts during an AbbVie-organised advisory board in July 2022, clinical experts suggested that adjustment of the epcoritamab population to match the Sehn *et al.* 3L+ population was appropriate, as the Sehn *et al.* 3L+ baseline characteristics are reflective of the comparator populations in the decision problem: patients with R/R LBCL after two or more prior lines of therapy in UK clinical practice.[4]

Therefore, in the ITC informing base case analysis A, the epcoritamab population was adjusted to match the Sehn *et al.* 3L+ population and then compared to R-based CIT based on data from SCHOLAR-1.[70]

The EPCORE™ NHL-1 trial included a population of heavily pre-treated patients, including those who had received prior CAR-T therapies, as well as patients with different subtypes of LBCL (including DLBCL, HGBCL, PMBCL and FL Gr 3B). In the Sehn *et al.* trial, ZUMA-1 trial and SCHOLAR-1 dataset, no patients had received prior CAR-T therapy. Furthermore, in the Sehn *et al.* trial, almost all patients had DLBCL rather than other subtypes of LBCL. In the overall population (regardless of number of prior lines of therapy), only two patients (5%) had subtypes other than DLBCL. However, for the subpopulation that have received two or more prior lines of therapy, it is assumed that 100% of patients had DLBCL.

Therefore, following feedback from UK clinicians during an advisory board which took place in July 2022, to reduce heterogeneity between the study populations, the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 was selected for inclusion in the ITC and adjusted to the Sehn *et al.* 3L+ population in base case analysis A. This population is hereafter referred to as the 'DLBCL population adjusted to Sehn *et al.* 3L+'.

As outlined in Section B.1.3, the clinical characteristics and disease pathways of DLBCL and other subtypes of LBCL are largely similar; as such, the comparative efficacy evidence of treatments for DLBCL provided by this ITC is considered to be generalisable to other subtypes of LBCL. This is further supported by the pairwise comparisons of epcoritamab versus axi-cel and Pola + BR in which the LBCL population from EPCORE™ NHL-1 was used (Appendix N). In addition, as highlighted in Section B.2.6, [redacted] differences in ORR were observed based on prior CAR-T experience, so results from the no prior CAR-T population are expected to be generalisable to all patients.

Patients eligible for intensive therapies: Base case analysis B and scenario analysis B.1

For the ITC informing base case analysis B (eligible for intensive therapies), the epcoritamab population is unadjusted to match the axi-cel population from ZUMA-1. An analysis was conducted in which the epcoritamab population was adjusted to match the ZUMA-1 population (Section B.2.8.2), however the analysis using the unadjusted epcoritamab population produced conservative results (i.e., results in favour of axi-cel) when compared to the adjusted analysis, so was subsequently considered for use in the base case in order to maximise the sample size. Furthermore, the baseline characteristics were deemed similar enough to use the unadjusted epcoritamab population in this analysis.

As outlined above, in the ZUMA-1 trial, no patients had received prior CAR-T therapy. Therefore, to reduce the heterogeneity between the EPCORE™ NHL-1 population and the ZUMA-1 population, and to align with the expected population in UK clinical practice, the no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 was selected for inclusion in the ITC informing base case analysis B.

In line with the rationale outlined above, and the fact that 92.1% of patients in ZUMA-1 had DLBCL, rather than other subtypes of LBCL, the DLBCL population from EPCORE™ NHL-1 was also selected for inclusion in the ITC informing base case analysis B. A scenario analysis was conducted whereby the LBCL population from EPCORE™ NHL-1 was included in the MAIC (scenario analysis B.1).

Summary

A summary of the base case analyses and the supportive analysis also conducted is presented in Table 25, including the epcoritamab populations used in the analyses. Results from the MAICs informing the base case analyses and scenario analysis B.1 are presented in the following section. Results from other supportive analyses informing scenario analyses are presented in Appendix N.

Table 25: Summary of the base case MAICs and the supportive MAICs conducted

	Epcoritamab population	Epcoritamab versus comparator	Comparator population adjusted to
Ineligible for, or choose not to receive, intensive therapy			
Base case analysis A: Ineligible for, or choose not to receive, intensive therapy	DLBCL, no prior CAR-T therapy (N=[redacted])	R-based CIT (SCHOLAR-1)	PICO 1b subgroup, EUnetHTA submission (based on Sehn et al. 3L+)
Eligible for intensive therapy			
Base case analysis B: Eligible for intensive therapy	DLBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Unadjusted to match ZUMA-1[b]
Scenario analysis B.1: Eligible for intensive therapy	LBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Unadjusted to match ZUMA-1[b]

[a] The comparisons of EPCORE™ NHL-1 versus Liebers *et al.* were unadjusted as the population in Liebers *et al.* was considered to be similar enough to the EPCORE™ NHL-1 population to not require adjustment. The baseline characteristics of the epcoritamab population prior to and following adjustment are presented in Appendix N. [b] The comparisons of EPCORE™ NHL-1 versus ZUMA-1 were unadjusted as the unadjusted population maintains the full sample size, produces conservative results that bias against epcoritamab, and the unadjusted populations were considered similar enough to not require adjustment.
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; MAIC: matching adjusted indirect comparisons; Pola + BR; polatuzumab vedotin with bendamustine plus rituximab: Pola + BR/R: polatuzumab vedotin with rituximab, with or without bendamustine; R: rituximab.

Adjusted baseline characteristics

Patients ineligible for, or choose not to receive, intensive therapies: Base case analysis A

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy population). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the decision problem and Sehn *et al.* 3L+ (based on synthetic survival data; see Section B.2.8.1 and Appendix N for more detail). An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 26.

Table 26: Baseline characteristics for base case analysis A (epcoritamab DLBCL population adjusted to Sehn *et al.* 3L+)

	Unadjusted epcoritamab (N=[redacted])	Epcoritamab adjusted to Sehn *et al.* 3L+ (N^{eff}=[redacted])[a]	Pola + BR 3L+, EUnetHTA submission (N=29)[b,72, 74]	R-based CIT, SCHOLAR-1 (N=340)[70]
Age				
Median (years)	[redacted]	[redacted]	65	55
≥65 years	[redacted]	[redacted]	**51.7%**	16.5%
Male	[redacted]	[redacted]	**72.4%**	67.9%
DLBCL (including TFL)	[redacted]	[redacted]	Assumed 100%	-
ECOG PS 0–1 (vs 2)	[redacted]	[redacted]	**89.3%**	100.0%
Disease stage III–IV	[redacted]	[redacted]	**86.2%**	64.5%
IPI score ≥3	[redacted]	[redacted]	55.2%	27.7%
Number of prior lines				
2 lines of prior therapy	[redacted]	[redacted]	37.9%	-
≥3 lines of chemo and ASCT	[redacted]	[redacted]	62.1%	28.8%
Primary refractory	[redacted]	[redacted]	-	37.1%
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]	-	50.0%
Refractory to second-line or subsequent therapy	[redacted]	[redacted]	-	-
Refractory to last prior anti-CD20 agents[c]	[redacted]	[redacted]	**51.7%**	-
Refractory to last prior anti-lymphoma therapy[d]	[redacted]	[redacted]	93.1%	-
Prior ASCT	[redacted]	[redacted]	**34.5%**	-
Relapse within 12 months of ASCT	[redacted]	[redacted]	-	21.8%
SCT any time after refractory disease			-	37.1%

[a] Population adjusted for **bold** highlighted values: age (≥65 years), male, ECOG performance status, disease stage, refractory to last prior anti-CD20 agents, and prior ASCT; [b] Data from the EUnetHTA submission for Pola + BR were used to inform baseline characteristics of the 3L+ population. Data from Sehn *et al.* (2019) and Sehn *et al.* (2022) were used to estimate 3L+ survival curves and inform best response outcomes. [c] Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date in patients whose last prior regimen contained anti-CD20; [d] Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab; SCT: stem cell transplant; TFL: transformed follicular lymphoma; 3L+: third-line and beyond.

Patients eligible for intensive therapies: Base case analysis B

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy, eligible for CAR-T therapy population). An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the axi-cel population included in the analysis is presented in Table 27. As outlined previously, the unadjusted epcoritamab population was selected for use in the MAIC informing base case analysis B.

Table 27: Baseline characteristics for the pairwise comparison of epcoritamab versus axi-cel (epcoritamab DLBCL, CAR-T eligible – adjusted to match axi-cel)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])[a]	Axi-cel, ZUMA-1 (N=101)
Age			
Median, years	[redacted]	[redacted]	58
≥65 years	[redacted]	[redacted]	**23.8%**
Male	[redacted]	[redacted]	**67.3%**
DLBCL (including TFL)	[redacted]	[redacted]	92.1%
ECOG PS 0 or 1 (versus 2)	[redacted]	[redacted]	**100.0%**
Disease stage III–IV	[redacted]	[redacted]	**85.1%**
IPI score ≥3	[redacted]	[redacted]	47.5%
Number of prior lines of treatment			
≥3 prior lines of treatment	[redacted]	[redacted]	69.3%
History of primary refractory disease	[redacted]	[redacted]	**25.7%**
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]	**53.5%**
Refractory to second-line or subsequent therapy	[redacted]	[redacted]	77.2%
Relapse after autoSCT within 12 months	[redacted]	[redacted]	**20.8%**

[a] Population adjusted for **bold** highlighted values: age (≥65 years), male, ECOG PS (0 or 1), disease stage III–IV, history of primary refractory disease, history of resistance to two consecutive lines of therapy and relapse after autoSCT within 12 months.
Abbreviations: autoSCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; TFL: transformed follicular lymphoma.

Patients eligible for intensive therapy: Scenario analysis B.1

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, no prior CAR-T, eligible for CAR-T). The unadjusted and adjusted baseline characteristics for the pairwise comparison of epcoritamab versus axi-cel are presented in Table 28.

Table 28: Baseline characteristics for the pairwise comparison of epcoritamab versus axi-cel (epcoritamab LBCL, CAR-T eligible – adjusted to match axi-cel)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])[a]	Axi-cel, ZUMA-1 (N=101)
Age			
Median, years	[redacted]	[redacted]	58
≥65 years	[redacted]	[redacted]	**23.8%**
Male	[redacted]	[redacted]	**67.3%**
DLBCL (including TFL)	[redacted]	[redacted]	**92.1%**
ECOG PS 0 or 1 (versus 2)	[redacted]	[redacted]	**100.0%**
Disease stage III–IV	[redacted]	[redacted]	**85.1%**
IPI score ≥3	[redacted]	[redacted]	47.5%
Number of prior lines of treatment			
≥3 prior lines of treatment	[redacted]	[redacted]	69.3%
History of primary refractory disease	[redacted]	[redacted]	**25.7%**
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]	**53.5%**
Refractory to second-line or subsequent therapy	[redacted]	[redacted]	77.2%
Relapse after autoSCT within 12 months	[redacted]	[redacted]	**20.8%**

[a] Population adjusted for **bold** highlighted values: age (≥65 years), male, DLBCL, ECOG PS (0 or 1), disease stage III–IV, history of primary refractory disease, history of resistance to two consecutive lines of therapy and relapse after autoSCT within 12 months.
Abbreviations: autoSCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; TFL: transformed follicular lymphoma.

Proportional hazards assumption

Results of the assessment of the proportional hazards assumption for epcoritamab versus R-based CIT and epcoritamab versus axi-cel are presented in Section B.3.3.3 and Section B.3.3.4. The results of the assessment of the proportional hazards assumption relating to the scenario analyses are presented in **Appendix P**.

Efficacy results

Patients ineligible for, or choose not to receive, intensive therapy: Base case analysis A (epcoritamab versus R-based CIT)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 29. The unadjusted and adjusted OS KM curves for epcoritamab and the OS

KM for R-based CIT from SCHOLAR-1 are presented in Figure 11. No PFS KM data were available from SCHOLAR-1.

As presented in Table 29, the unadjusted OS HR for epcoritamab versus R-based CIT is [redacted]. Following adjustment, the adjusted OS HR for epcoritamab versus R-based CIT is [redacted], demonstrating that epcoritamab provides a [redacted] treatment benefit versus R-based CIT.

Table 29: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (SCHOLAR-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival; R: rituximab.

Figure 11: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to Sehn *et al.* 3L+

Abbreviations: EPCO: epcoritamab; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab.

Patients eligible for intensive therapy: Base case analysis B (epcoritamab versus axi-cel)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus axi-cel is presented in Table 30, alongside the unadjusted and adjusted KM curves for epcoritamab and axi-cel, in Figure 12 and Figure 13, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is a numerical benefit of epcoritamab versus axi-cel, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted]; adjusted HR: [redacted]). However, this difference is [redacted].

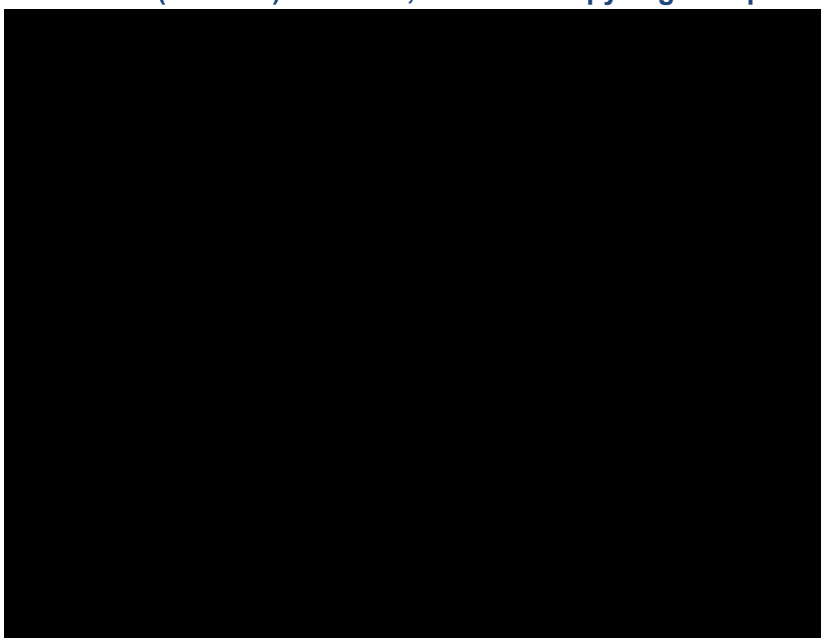
There was [redacted] in CR rate and ORR between epcoritamab and axi-cel.

Table 30: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, CAR-T eligible) versus axi-cel (ZUMA-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

Figure 12: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population



Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; epco: epcoritamab; KM: Kaplan–Meier; OS: overall survival.

Figure 13: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; epco: epcoritamab; KM: Kaplan–Meier; PFS: progression-free survival.

Patients eligible for intensive therapy: Scenario analysis B.1

A summary of the unadjusted and adjusted outcomes for epcoritamab versus axi-cel is presented in Table 31, alongside the unadjusted and adjusted KM curves for epcoritamab and axi-cel, in Figure 14 and Figure 15, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is a numerical benefit of epcoritamab versus axi-cel, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted]; adjusted HR: [redacted]). However, this difference is [redacted].

There was [redacted] in CR rate and ORR between epcoritamab and axi-cel.

Table 31: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, CAR-T eligible) versus axi-cel (ZUMA-1)

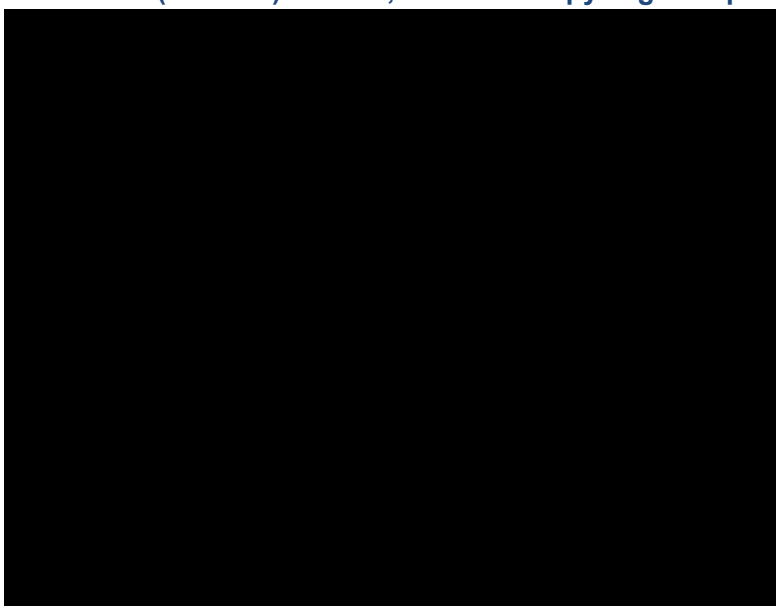
	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

Figure 14: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; PFS: progression-free survival.

Figure 15: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population



Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival.

B.2.8.3 Uncertainties in the indirect and mixed treatment comparisons

Strengths and weaknesses of the analyses

In alignment with NICE DSU TSD 18, the effect modifiers and prognostic variables to be included for adjustment were carefully considered; the variables to adjust for in the MAICs were identified based on an evidence-based process which included review of the published literature, empirical testing of prognostic status in EPCORE™ NHL-1 and feedback from clinical and health economic experts. With these variables in mind, the analyses were subsequently conducted with the robust methodologies suggested in NICE DSU TSD 18 to produce high-quality comparative efficacy evidence for epcoritamab versus R-based CIT and axi-cel.

Despite the comparative analyses being adjusted for clinically important variables, bias due to residual confounding and unaccounted unobserved residual bias cannot be excluded. For example, for the comparison of epcoritamab versus R-based CIT, after adjustment of the epcoritamab DLBCL population to Sehn *et al.* 3L+, patients in EPCORE™ NHL-1 were [redacted] than those included in SCHOLAR-1 ([redacted] years versus 55.0 years) and a [redacted] proportion of patients had disease stage III–IV in EPCORE™ NHL-1 than in SCHOLAR-1 ([redacted] versus 64.5%). Based on the observed baseline characteristics, this analysis may bias against epcoritamab. Moreover, the proportion of patients in SCHOLAR-1 that were refractory to previous treatment is not reported so it is unknown how this may impact the results.

For the ITC informing base case analysis A (ineligible for intensive therapies; epcoritamab versus R-based CIT), the epcoritamab DLBCL population is adjusted to match the Sehn *et al.* 3L+ population and then compared to R-based CIT. As highlighted previously, this approach was taken following feedback from UK clinical experts, to ensure alignment with the specific population of interest in this submission and as the Sehn *et al.* 3L+ baseline characteristics are reflective of the population of interest. This represents a conservative approach to accurately reflect UK clinical practice. However, it is important to note that adjustment to one core

comparator population will introduce some uncertainty in the comparative efficacy estimates as the epcoritamab population is not fully adjusted to match R-based CIT.

In addition, in the MAICs informing both base case analysis A and base case analysis B, the DLBCL population from EPCORE™ NHL-1 was selected to reduce heterogeneity between the trial populations, following feedback from four clinical and two health economic experts in the UK during an advisory board which took place in July 2022. As outlined in Section B.1, the clinical characteristics and disease pathways of DLBCL and other subtypes of LBCL are largely similar; as such, the comparative efficacy evidence of treatments for DLBCL provided by these MAICs is considered to be generalisable to other subtypes of LBCL, as demonstrated by the supportive analysis of epcoritamab versus axi-cel in patients with LBCL.

Due to the above limitations, a number of supportive pairwise MAICs that have been used in scenario analyses have been conducted. Therefore, the base case analyses should be interpreted alongside the sensitivity analyses, in which alternative epcoritamab populations and/or sources of comparator efficacy data are used. The adjusted HRs generated by the supportive pairwise analyses demonstrate that the base case ITCs are likely underestimating the treatment benefit associated with epcoritamab; despite the uncertainty in the base case ITCs, they can be considered to be conservative and bias against epcoritamab in terms of treatment benefit.

Summary of results of the ITC

For the comparisons of epcoritamab versus R-based CIT, the results of the MAIC demonstrate that epcoritamab is associated with a [redacted] treatment benefit in terms of the OS HR ([redacted]), difference in CR rate ([redacted]) and difference in ORR ([redacted]). No PFS data were available for R-based CIT from SCHOLAR-1; information on the derivation of PFS for R-based CIT for use in the economic analysis is presented in Section B.3.3.

For the comparison of epcoritamab versus axi-cel, the results of the MAIC using the unadjusted epcoritamab population demonstrate that there is [redacted] treatment benefit for patients receiving epcoritamab versus axi-cel in terms of the OS HR ([redacted] and PFS HR [redacted]). [redacted] was also observed for CR rate and ORR for epcoritamab versus axi-cel, with the difference in CR rate of [redacted] and a difference in ORR of [redacted]. Results of additional sensitivity analyses conducted are presented in **Appendix N**.

Overall, the ITCs conducted to generate comparative efficacy evidence for epcoritamab versus R-based CIT and axi-cel used the best available data to allow a comparison that is most reflective of the population of interest, based on feedback from UK clinical experts and suggested methods by NICE DSU TSD 18.[4, 76] Supportive analyses have also been conducted to explore the uncertainty associated with any assumptions used in the base case approaches; overall, the supportive analyses demonstrated that the base case is evidently biasing against the true efficacy of epcoritamab in R/R LBCL in patients who have received two or more prior therapies.

B.2.9 *Adverse reactions*

Epcoritamab is associated with a tolerable safety profile

- AEs were generally manageable with appropriate monitoring and mitigation measures including dose delays and/or supportive care. Data on AEs are reported from the [redacted] data cut-off of EPCORE™ NHL-1.
- [redacted] with LBCL had experienced at least one TEAE. Of these, [redacted] experienced TEAEs considered related to epcoritamab by the investigator.
- A total of [redacted] with LBCL experienced [redacted] or higher TEAEs and [redacted] had [redacted] or higher TEAEs considered related to epcoritamab by the investigator.
- Serious TEAEs were reported in [redacted] with LBCL and were considered related to epcoritamab by the investigator in [redacted].
- A total of [redacted] experienced a TEAE leading to treatment discontinuation and [redacted] had a TEAE leading to dose delay/interruption.
- Fatal TEAEs were reported in [redacted] with LBCL; [redacted] was considered related to epcoritamab by the investigator, which was [redacted].
- Of the patients with LBCL that had ≥1 CRS event ([redacted]), most events were [redacted] ([redacted] and [redacted], respectively). Events of CTLS were reported in [redacted] with LBCL. Further details on AESI are provided in Section B.2.9.5.
- The overall safety profile of epcoritamab is considered manageable and acceptable in this R/R LBCL patient population with limited and predominantly CIT-based treatment options.

All safety analyses were conducted using the SAF, and in the DLBCL and other subtypes subgroups. The SAF included 157 patients with LBCL (139 patients with DLBCL) who received at least one dose of epcoritamab. The AEs of special interest (AESIs) included CRS, clinical tumour lysis syndrome (CTLS), and immune effector cell-associated neurotoxicity syndrome (ICANS). All AEs were graded by the investigator according to National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0, except for CRS, CTLS, and ICANS. Events of CRS and ICANS were graded according to American Society for Transplantation and Cellular Therapy criteria (Lee *et al.,* 2019)[87] and CTLS was graded according to Cairo-Bishop (Coiffier *et al.*, 2008).[87, 88] Additional analyses of CRS by dose (priming, intermediate, full) are presented to evaluate the impact of step-up dosing on this AESI.

Other AEs of interest examined in this trial included neurological events, cytopenia events, infection events, and injection site reactions.

B.2.9.1 Summary of treatment-emergent adverse events

A summary of TEAEs reported in the EPCORE™ NHL-1 trials for patients with LBCL and patients with DLBCL is provided in Table 32. Further details on AEs are provided in subsequent sections. AEs among patients with LBCL and other subtypes were consistent with that of patients with DLBCL.

As of [redacted] data cut off, [redacted] with LBCL had experienced at least one treatment-emergent adverse event (TEAE). Of these, [redacted] experienced TEAEs considered related to epcoritamab by the investigator. A total of [redacted] experienced grade 3 or higher TEAEs and [redacted] had [redacted] or higher TEAEs considered related to epcoritamab by the investigator.

Serious TEAEs were reported in [redacted] with LBCL and were considered related to epcoritamab by the investigator in [redacted]. A total of [redacted] patients experienced a TEAE leading to treatment discontinuation and [redacted] had a TEAE leading to dose delay/interruption.

Fatal TEAEs were reported in [redacted], only [redacted] considered related to epcoritamab by the investigator, this was [redacted]

Adverse events of special interest (AESIs) included CRS, ICANS, and CTLS. Almost [redacted] of the trial patients ([redacted] patients) in the aNHL expansion cohort had an AESI of CRS; the AESI of ICANS occurred in [redacted] patients with LBCL. Events of CTLS were reported in [redacted] patients with LBCL. Further details on AESI are provided in Section B.2.9.5 and Appendix F.

Table 32: Summary of TEAEs (SAF; [redacted] data cut-off)

Number of patients (%)	LBCL (N=157)	DLBCL (N=139)
Number of patients with ≥1		
TEAE	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]
Grade 3 and higher TEAE	[redacted]	[redacted]
Grade 3 and higher related TEAE	[redacted]	[redacted]
TEAE by worst toxicity grade		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Serious related TEAE	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]
TEAE leading to dose delay/interruption	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]
Fatal related TEAE	[redacted]	[redacted]
AESI; Number of patients with ≥1		
CRS	[redacted]	[redacted]
ICANS	[redacted]	[redacted]
CTLS	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 14.3.1.1.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.9.2 Treatment-emergent adverse events

A summary of TEAEs in the DLBCL population in EPCORE™ NHL-1 is presented in Table 33.

Among patients with LBCL (N=157), the most frequent (≥20%) TEAEs by preferred term (PT) were CRS ([redacted]), fatigue ([redacted]), pyrexia (not associated with CRS; [redacted]), neutropenia ([redacted]), injection site reaction ([redacted]), diarrhoea ([redacted]), and nausea ([redacted]).

A total of [redacted] with LBCL had TEAEs considered related to epcoritamab by the investigator. The most frequent treatment-related TEAEs (≥10%) were CRS ([redacted]), injection site reaction ([redacted]), neutropenia ([redacted]), fatigue ([redacted]), and pyrexia ([redacted]).

Table 33: Most common (at least 10% in any group) TEAEs by SOC and PT (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
Patients with ≥1 TEAE	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]

Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRS: cytokine release syndrome' DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 14.3.1.2.2 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.9.3 Serious TEAEs

A summary of serious TEAEs in the LBCL population of EPCORE™ NHL-1 are presented in Table 34. Serious TEAEs were reported in [redacted] with LBCL. The most frequent (≥2%) serious TEAEs by PT in these patients were CRS ([redacted]), pleural effusion ([redacted]), sepsis, ICANS, febrile neutropenia, and pyrexia ([redacted] each), and COVID-19 and pneumonia ([redacted] and [redacted], respectively).

Treatment-related, serious TEAEs were reported in [redacted] with LBCL. The most frequent treatment-related, serious TEAEs by PT in these patients were CRS ([redacted]) and ICANS ([redacted]).

Table 34: Most common (2% or more in any group) serious TEAEs by SOC and PT (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
Patients with ≥1 serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
ICANs	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 14.3.2.3.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.9.4 Treatment-emergent adverse events leading to discontinuation

Among patients with LBCL (N=157), [redacted] experienced at least one TEAE that led to treatment discontinuation. The most common of these events were COVID-19 pneumonia, COVID-19 infection and myelodysplastic syndrome, each of which occurred in [redacted], [redacted] and [redacted], respectively.

B.2.9.5 Adverse events of special interest

AESIs were specified as ICANS, CRS and CTLS, of which the incidence of each are presented in Table 35. The full details of these AESIs, including time to onset and duration of event, can be found in Appendix F.

Events of ICANS were reported in [redacted]; [redacted] had [redacted] ICANS, [redacted] had [redacted] ICANS, and [redacted] had [redacted] ICANS. The fatal episode of ICANS, was in in [redacted], was an on treatment event with onset on [redacted], [redacted] after the patient's most recent dose of study drug and was considered related to study drug.

In patients with LBCL, [redacted] had at least one CRS event. The majority of these were [redacted] ([redacted]) or [redacted] ([redacted]) events and occurred most frequently after [redacted] dose of epcoritamab on [redacted]).

[redacted] with LBCL experienced events of CTLS, both of which were considered treatment-related within the setting of disease progression and were [redacted] in severity. Neither had resolved prior to the patients' deaths ([redacted]).

Table 35: Summary of AESIs (SAF; [redacted] data cut-off)

Number of patients (%)	LBCL (N=157)	DLBCL (N=139)
Patients with ≥1 ICANS event	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Patients with ≥1 CRS event	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Patients ≥1 CTLS event	[redacted]	[redacted]

Number of patients (%)	LBCL (N=157)	DLBCL (N=139)
Grade 3	[redacted]	[redacted]

CRS events are graded according to Lee et al, 2019.[87]
Abbreviations: AESI: adverse events of special interest; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set.
Source: Table 14.3.2.4, Table 14.3.2.5 and Table 14.3.1.6.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.9.6 Patient deaths

Overall, [redacted] with LBCL died during the trial, including [redacted] who died within 60 days of last dose of study treatment. Most deaths were caused by disease progression ([redacted]).

Fatal TEAEs occurred in [redacted] with LBCL and included COVID-19, COVID-19 pneumonia, progressive multifocal leukoencephalopathy, ICANS, myocardial infarction, general physical health deterioration, hepatotoxicity, pulmonary embolism. COVID-19 and COVID-19 pneumonia, which occurred in [redacted] and [redacted] with LBCL respectively, were the only fatal TEAEs reported in more than [redacted]. This is shown below in Table 36. An overview of fatal TEAEs among patients with other LBCL subtypes is provided in Appendix F.

[redacted] fatal TEAE was reported that was considered related to epcoritamab by the investigator; [redacted].

Table 36: Summary of fatal TEAEs by PT (SAF; [redacted] data cut-off)

Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Progressive multifocal leukoencephalopathy	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]

[a] Adverse events are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 14.3.2.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[21]

B.2.10 *Ongoing studies*

This submission presents results from the EPCORE™ NHL-1 trial (NCT03625037) for the [redacted] data cut-off. The EPCORE™ NHL-1 trial is ongoing and as per the protocol for EPCORE™

NHL-1, there are upcoming [redacted][21]

As described in Section B.2.2, EPCORE™ DLBCL-1 (NCT04628494) is an ongoing, Phase 3, randomised, open-label, trial of epcoritamab versus Investigator's choice chemotherapy in patients with R/R DLBCL. [redacted].

B.2.11 *Interpretation of clinical effectiveness and safety evidence*

B.2.11.1 Principal findings from the clinical evidence base

Findings from EPCORE™ NHI-1

The clinical efficacy and safety evidence base for epcoritamab as a treatment for adult patients with R/R LBCL after two or more lines of systemic therapy is informed by the EPCORE™ NHL-1 trial. In the trial, a total of 157 patients with LBCL (including 139 patients with DLBCL, nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL) were included, representing a broad range of LBCL patients. UK clinical experts confirmed that the population included in EPCORE™ NHL-1 is reflective of patients with R/R LBCL that they would see in UK clinical practice.[4]

The clinical efficacy results from EPCORE™ NHL-1 demonstrate that epcoritamab drives clinically meaningful, deep and durable responses in patients with DLBCL and LBCL. Results were consistent across the aNHL subtypes groups presented in this submission based on data from the [redacted] data cut-off (median study follow-up of [redacted] for DLBCL patients). Results of the primary endpoint, ORR based on IRC assessment (Lugano criteria), demonstrate that epcoritamab is associated with a clinically meaningful ORR, with ORR in patients with DLBCL being [redacted] (95% CI: [redacted]); furthermore, [redacted] and [redacted] achieved a best response of CR and PR, respectively. Results for ORR were consistent for patients with other LBCL subtypes. In addition, the median DOR in all responders was [redacted]

The secondary endpoints from EPCORE™ NHL-1 provide further evidence of the clinically meaningful treatment benefit provided by epcoritamab. At the [redacted] data cut-off, among patients with DLBCL, median PFS based on IRC assessment (Lugano criteria) was [redacted], and the estimated percentage of patients remaining progression-free at six and nine months was [redacted] and [redacted], respectively. At the [redacted] data cut-off, in patients with DLBCL, among patients in CR, median PFS was [redacted] months [redacted] Among patients in PR, median PFS was [redacted] when compared with non-responders ([redacted] versus [redacted]).[65] These results were consistent again across the different subtypes of LBCL. Median OS was [redacted], at which time [redacted] had died and [redacted] were still alive.

The cohort of patients included in EPCORE™ NHL-1 represents a heavily pre-treated population, with a median number of [redacted] prior lines of therapy (range: [redacted]), which aligns with the population of interest in this submission: patients with R/R LBCL following two or more prior lines of therapy. In this heavily pre-treated patient population, effective treatment options are currently

limited. As such, epcoritamab would be a valuable addition to the treatment pathway for these hard-to-treat patients.

Findings from the ITCs

As EPCORE™ NHL-1 is a single-arm trial, ITCs, in the form of MAICs, were conducted to provide comparative efficacy evidence on epcoritamab versus the relevant comparators in this evaluation (axi-cel and R-based CIT) in patients with R/R LBCL after two or more prior therapies as per the decision problem. MAICs versus Pola + BR were also conducted for use in scenario analyses.

In the MAIC informing base case analysis A (patients who are ineligible for, or choose not to receive, intensive treatments; epcoritamab versus R-based CIT), the epcoritamab DLBCL population is adjusted to match the Sehn *et al.* 3L+ population after two or more prior lines of therapy and then compared to R-based CIT. In the MAIC informing base case analysis B (patients who are eligible for intensive therapy; epcoritamab versus axi-cel), the epcoritamab DLBCL, no prior CAR-T, eligible for CAR-T population is unadjusted to match the axi-cel population from ZUMA-1.

For the comparisons of epcoritamab versus R-based CIT for the adjusted outcomes, the results of the MAIC demonstrate that epcoritamab is associated with a [redacted] treatment benefit in terms of the OS HR ([redacted]), difference in CR rate ([redacted]) and difference in ORR ([redacted]). No PFS data were available for R-based CIT from SCHOLAR-1 (Section B.3.3). For the comparison of epcoritamab versus axi-cel, the results of the MAIC using the unadjusted epcoritamab population demonstrate that there is [redacted] treatment benefit for patients receiving epcoritamab versus axi-cel in terms of the OS HR ([redacted] and PFS HR [redacted]). [redacted] was also observed for CR rate and ORR for epcoritamab versus axi-cel, with the difference in CR rate of [redacted] and a difference in ORR of [redacted]. Results of additional sensitivity analyses conducted are presented in **Appendix N**.

Safety data on epcoritamab

Overall, the safety profile of epcoritamab is consistent across the DLBCL, LBCL and other subtype populations included in the trial. Among patients with LBCL, serious TEAEs were reported in [redacted] and only [redacted] experienced at least one TEAE leading to treatment discontinuation. In general, AEs were considered manageable with appropriate monitoring and mitigation measures, including dose delays and/or supportive care.

B.2.11.2 Strengths and limitations of the clinical evidence base

Internal validity

The clinical evidence presented as part of the submission has been derived from an SLR that was conducted according to the principles of systematic reviewing published in the Cochrane handbook. The clinical SLR identified the pivotal clinical trial, EPCORE™ NHL-1, as the primary evidence source for epcoritamab in the population of interest. The results of the quality assessment of EPCORE™ NHL-1 demonstrated that it is a methodologically robust and well-reported trial (Table 13).

External validity

The EPCORE™ NHL-1 trial and its results are relevant to the decision problem outlined in the NICE scope, specifically the population of interest which is adult patients with R/R LBCL after two or more lines of systemic therapy and UK clinical experts confirmed the generalisability of data from EPCORE™ NHL-1 to patients in UK clinical practice.

- **Population** – EPCORE™ NHL-1 provides evidence on the efficacy and safety of epcoritamab as a treatment for adult patients with R/R LBCL after two or more lines of systemic therapies. The population included in the trial is aligned with the expected marketing authorisation for epcoritamab in this indication and the population listed in the NICE final scope. Furthermore, a high proportion of patients enrolled in the EPCORE™ NHL-1 trial were from European countries ([redacted] [redacted]), with [redacted] from the UK, and UK clinical experts confirmed that the population included in EPCORE™ NHL-1 is reflective of patients in the population of interest in UK clinical practice.
    - Efficacy data from the DLBCL population of EPCORE™ NHL-1 were used in the ITCs and therefore are primarily presented within this submission. This population was selected in the ITCs as UK clinical experts suggested that adjustment of the epcoritamab population to match the Sehn *et al.* 3L+ population was appropriate, as the Sehn *et al.* 3L+ baseline characteristics are reflective of the population of interest in this submission. It is assumed that 100% of patients had DLBCL in the Sehn *et al.* 3L+ population and so the DLBCL population from EPCORE™ NHL-1 was selected to reduce heterogeneity. Efficacy data on the whole LBCL population and for patients with other LBCL subtypes are presented in Appendix M, and demonstrate that results were consistent among the LBCL subtypes.
- **Intervention** – Epcoritamab was administered in EPCORE™ NHL-1 in line with the expected marketing authorisation and as it would be used in UK clinical practice.
- **Comparator** – As EPCORE™ NHL-1 is a single arm-trial, MAICs were used to generate comparative efficacy evidence versus the relevant comparators to epcoritamab (R-based CIT and axi-cel). These comparators are consistent with the treatments currently used in UK clinical practice, based on feedback from UK-based clinicians, as well as feedback from clinical experts and National Health Service England and National Health Service Improvement (NHSEI) during NICE evaluations in the same indication (such as ID3795).[14, 17, 89] Although Pola + BR is recommended by NICE as a treatment for R/R DLBCL, UK clinical experts stated that the majority of patients would no longer receive Pola + BR at 3L+ following the NICE recommendation of Pola + R-CHP as a treatment for first-line DLBCL in February 2023.[10, 13, 44]
- **Outcomes** – A range of endpoints were evaluated in EPCORE™ NHL-1, including those outlined in the NICE scope, that are relevant to patients and clinicians. Where relevant, outcomes were assessed by IRC (Lugano criteria) as well as by investigator assessment. Results assessed by IRC are generally considered to be more robust, but IRC-assessed and investigator-assessed results were consistent.

Limitations

The single-arm, open-label nature of EPCORE™ NHL-1 represents a necessary limitation of the trial. EPCORE™ DLBCL-1, a Phase 3, randomised controlled trial assessing the efficacy and safety of epcoritamab versus Investigator's choice chemotherapy in patients with R/R DLBCL, is

currently ongoing; however, data from this Phase 3 trial are not yet available. Given the high unmet need for additional effective treatment options that are readily available for a broad range of patients with R/R LBCL at 3L+, AbbVie considers that the NHS and patients would benefit from epcoritamab being prioritised for evaluation based on the available data from the Phase Ib/II trial, EPCORE™ NHL-1.

As a result of the single-arm nature of the trial, ITCs were required to determine the comparative efficacy of epcoritamab versus relevant comparators. Although the analyses provide robust evidence for the comparative efficacy of epcoritamab, there is some uncertainty associated with the results, as with any ITC. Despite the comparative analyses being adjusted for clinically important variables, bias due to residual confounding and unaccounted unobserved residual bias cannot be excluded; it is important to note that differences remaining following adjustment are understood to bias against epcoritamab, so the derived estimates can be considered to be conservative.

For the ITC informing base case analysis A (ineligible for intensive therapies; epcoritamab versus R-based CIT), the epcoritamab DLBCL population is adjusted to match Sehn *et al.* 3L+ and then compared to R-based CIT. It is important to note that adjustment to one core comparator population will introduce some uncertainty in the comparative efficacy estimates as the epcoritamab population is not fully adjusted to match R-based CIT. The same uncertainty will apply to the comparison of epcoritamab versus axi-cel, in which the unadjusted epcoritamab population is used.

A number of supportive analyses have also been conducted, whereby different epcoritamab populations and/or alternative sources of comparator efficacy data are used. The adjusted HRs generated by the supportive pairwise analyses demonstrate that the base case ITC is likely underestimating the treatment benefit associated with epcoritamab; despite the uncertainty in the base case ITC, it can be considered to be conservative and bias against epcoritamab.

Despite a heavily pre-treated population including CAR-T therapy, treating LBCL with epcoritamab led to a median [redacted]). Compared with other data sets, such as those included in the ITCs and real-world data from Northend *et al.* (2021), this demonstrates a survival benefit associated with epcoritamab.[45] Furthermore, improvements in PFS would be expected to translate into improvements in OS with longer follow-up, so PFS results from EPCORE™ NHL-1 can be used to support the existence of an OS benefit from epcoritamab.

B.2.11.3 Conclusions

EPCORE™ NHL-1 is a methodologically robust and well-reported trial and the results demonstrate that epcoritamab drives clinically meaningful, deep and durable responses in patients with R/R LBCL after two or more systemic therapies. Furthermore, epcoritamab has a tolerable and manageable safety profile, whilst driving improvements in HRQoL. The comparative efficacy data demonstrates that epcoritamab provides a [redacted] benefit versus R-based CIT, and improvements [redacted] were detected for the comparison of epcoritamab with axi-cel.

In summary, epcoritamab adds a novel mechanism of action to the existing R/R LBCL treatment pathway and is expected to provide a significant benefit by offering a clinically meaningful benefit for both patients and clinicians compared with currently available therapies. Moreover,

epcoritamab represents a treatment option that would be available to a broad range of patients, regardless of eligibility for intensive therapies and proximity to specialist centres.

B.3 Cost effectiveness

A de novo cost-utility analysis was undertaken based on a partitioned survival model (PSM), similar to those used in previous NICE appraisals for R/R LBCL[3, 14, 44]

- The objective of this analysis was to evaluate the cost-effectiveness of epcoritamab as a new treatment option versus existing UK standard of care for [redacted] The comparators considered are R-based CIT and axi-cel. For completeness, Pola + BR is considered in a scenario analysis since this is increasingly used in earlier lines of therapy as confirmed by UK clinical experts.
- In this submission, economic analyses are presented separately for two separate patient populations due to differing clinical pathways of care and differing levels of patient fitness, as supported by feedback from UK clinical experts:
    - Base case analysis A: Patients who are ineligible for, or choose not to receive, intensive therapies (epcoritamab versus R-based CIT).
    - Base case analysis B: Patients who are eligible to receive intensive therapies (epcoritamab versus axi-cel).
- A PSM was developed, which included three health states:
    - PFS: patients that are alive and haven't progressed.
    - Post-progression survival (PPS): patients that are alive but have progressed.
    - Death: patients that have died.
- In line with prior NICE submissions in R/R LBCL and based on feedback from UK clinical experts, it was assumed that patients remaining in the pre-progression survival state for 24 months would be considered as survivors with long-term remission.[3, 13, 63, 90] These patients would have improved outcomes in terms of mortality, HRQoL, and disease management cost.
- The analysis was undertaken from a UK NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a time horizon of 45 years was used, which represents a lifetime horizon.
- The key efficacy inputs in the model are OS, PFS and time to treatment discontinuation (TTD). As EPCORE™ NHL-1 is a single-arm trial, comparative efficacy evidence for the economic analyses was informed by MAICs.

Survival analyses

- For epcoritamab, the long-term time-to-event outcomes were extrapolated based on EPCORE™ NHL-1 [redacted] data-cut IPD. For the comparator arms, the long-term time-to-event outcomes were derived by applying HRs from the MAICs to the extrapolated outcomes of epcoritamab for PFS and OS. This approach was validated by UK clinical and health economic experts.[4, 13] For the comparators, TTD was assumed to be equal to PFS based feedback from clinical experts.
- In accordance with NICE DSU TSD 14,[80] the range of parametric distributions fitted to the EPCORE™ NHL-1 trial were: exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma.
- The parametric distributions for epcoritamab were selected based on a rigorous process to avoid bias and to reflect clinical plausibility, based on statistical fit and visual fit to the observed data and feedback from UK clinicians.
- The following extrapolations were selected for use in the base case analyses:
    - In base case analysis A, the generalised gamma extrapolation was selected to model OS, PFS and TTD for epcoritamab.
    - In base case analysis B, the generalised gamma, Gompertz and log-logistic extrapolations were selected to model OS, PFS and TTD for epcoritamab, respectively.

Cost-effectiveness results

Base case analysis A:

- For base case analysis A, the total costs associated with R-based CIT and epcoritamab (PAS price) are £89,183 and [redacted], respectively. The total QALYs associated with R-based CIT and epcoritamab are 1.325 and [redacted] (with a [redacted] severity modifier applied).
- The resulting ICER for epcoritamab versus R-based CIT is £24,682, which demonstrates that epcoritamab is a cost-effective use of NHS resources when compared with R-based CIT, for patients who are ineligible for, or choose not to receive, intensive therapies.

Base case analysis B:

- For base case analysis B, the total costs associated with axi-cel and epcoritamab (PAS price) are £391,116 and[redacted], respectively. The total QALYs associated with axi-cel and epcoritamab are 3.442 and [redacted], respectively.
- Epcoritamab was therefore found to be dominant versus axi-cel, demonstrating that it to be cost-saving whilst also incurring greater health benefits over the model time horizon.
- The NHB for epcoritamab versus axi-cel at £20,000 and £30,000 respectively is [redacted] and [redacted] (at epcoritamab PAS price).

Sensitivity analyses

- Parameter uncertainty was explored through probabilistic sensitivity analysis while structural uncertainty and key assumptions were explored through extensive scenario analyses and deterministic one-way sensitivity analyses.
- The results of the sensitivity and scenario analyses demonstrate that there is minimal uncertainty that epcoritamab represents a cost-effective use of NHS resources.

Conclusions

- The results of the economic analyses presented in this submission demonstrate that epcoritamab represents a cost-effective use of NHS resources for patients with R/R LBCL following two or more prior lines of therapy.

B.3.1 *Published cost-effectiveness studies*

An economic SLR was conducted on 10th October 2022, and subsequently updated on 21st November 2022 to identify published cost-effectiveness studies, health state utility values (HSUVs) and cost and healthcare resource use data in the LBCL population (including DLBCL) after two or more lines of systemic therapies. Overall, the searches identified 26 relevant economic evaluations (16 LBCL and ten DLBCL economic evaluations), reported in 29 publications. Full details of the economic SLR methods and results are presented in Appendix G.

Of the 16 LBCL evaluations, 11 were partitioned survival models, four were decision tree models, and one budget impact model. A summary of the key features of all studies identified in the economic SLR is provided in Appendix G.

B.3.2 *Economic analysis*

The objective of this economic evaluation was to assess the cost-effectiveness of epcoritamab as a new treatment option versus existing UK standard of care in adult patients with R/R LBCL after two or more lines of systemic therapies in UK clinical practice. The population included in the base case economic analysis is considered to be relevant to clinical practice within the NHS and reflects the anticipated positioning of epcoritamab in the treatment pathway, as confirmed by UK clinical experts.

A *de novo* cost-utility analysis of epcoritamab versus R-based CIT and axi-cel relevant to the decision problem for this submission was performed. In line with the NICE reference case, the

analysis was conducted from the perspective of the NHS and PSS over a lifetime time horizon.[91] Sections B.3.2.1, B.3.2.2, and B.3.2.3 present the patient population, the model structure, and the included interventions and comparators, respectively.

B.3.2.1 Patient population

The analysis evaluated the cost-effectiveness of epcoritamab for the treatment of adult patients with R/R LBCL [redacted] after two or more lines of systemic therapies. The population of interest in this submission is aligned with the expected licensed indication (Section B.1.1). Data on the patient population were informed by the EPCORE™ NHL-1 trial ([redacted] data cut; [redacted] of median follow-up), in line with the final scope (Section B.1),[21] with the baseline characteristics used in the cost-effectiveness model being presented in Section B.3.3.1.

In this submission, economic analyses are presented separately for two separate patient populations due to differing clinical pathways of care and differing levels of patient fitness, as supported by feedback from UK clinical and economic experts:

- Base case analysis A: Patients who are ineligible for, or choose not to receive, intensive therapies.
- Base case analysis B: Patients who are eligible to receive intensive therapies

B.3.2.2 Model structure

A *de novo* economic model was developed to conduct a cost-effectiveness analysis of epcoritamab versus the relevant comparators for the target population. The model structure was based on previous NICE submissions in this indication, the treatment pathway of patients with R/R LBCL, data availability from EPCORE™ NHL-1 and feedback from UK clinical and health economics experts. A PSM was developed, which included three health states:

- PFS: patients who are alive and have not progressed
- PPS: patients who are alive but have progressed
- Death: patients who have died

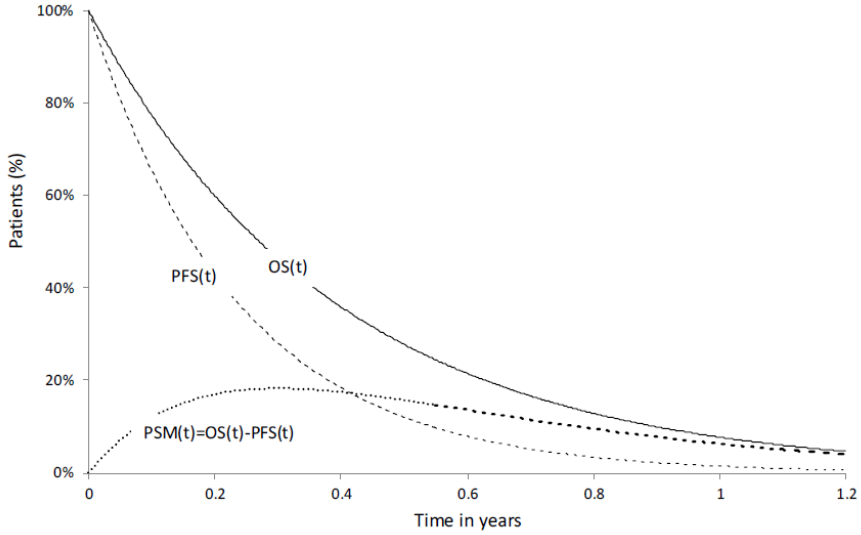
Partitioned survival model

The PSM approach was selected given that it permits the use of outcome data from the ITCs, presented in Section B.2.8, and allows the clinical benefits of epcoritamab, in terms of improved disease control and delayed progression, to be captured by reflecting the increased proportion of patients expected to be alive and/or progression-free over time. Moreover, the PSM can be used regardless of the availability of IPD for both the intervention and comparator arms. The use of a PSM aligns with previous NICE evaluations in R/R LBCL and is the most widely accepted model in oncology by HTA bodies.[3, 14, 44, 63, 76] Furthermore, the PSM appropriately captures disease progression and long-term extrapolations in a way that allows them to be validated by clinical experts, thereby ensuring the external validity of the outputs of the model.

The proportion of patients within each health state was determined by OS and PFS curves via an area-under-the-curve approach (Figure 16). The PFS curve (*PFS(t)*) determined the proportion of

patients remaining alive and progression-free, and the OS curve (*OS(t)*) determined the proportion of patients remaining alive (regardless of progression status). The difference between the PFS and OS curves (*PSM(t)*) determined the proportion of patients remaining alive post progression.

Figure 16: Determination of state membership in a standard three-state PSM



Abbreviations: OS: overall survival; PFS: progression-free survival; PSM: partitioned survival model.

In addition, in line with prior NICE submissions in R/R LBCL and based on feedback from UK clinical experts, it was assumed that patients remaining in the pre-progression survival state for a certain period of time would be considered as survivors with long-term remission.[3, 13, 63, 90] These patients would have improved outcomes in terms of mortality, and disease management cost. Based on feedback from UK clinical experts, a 24-month time point was used in the base case, which aligns with prior NICE appraisals in R/R LBCL.[89]

In the model, as stated above, patients who are progression-free after 24 months are considered to be in long-term remission. Patients in long-term remission after 24 months no longer follow the extrapolated PFS curve and instead experience an adjusted background mortality rate; a standardised mortality ratio of 1.41 is applied, based on a US study that was accepted by the External Assessment Group [EAG] in TA649),[90] which represents an increased relative risk of mortality when compared with the general population, due to long-term complications arising from cancer and cancer treatment. They are also assumed to use no healthcare resources beyond those required for treatment administration after 24 months. For patients who progress prior to 24 months, their mortality continues to be informed by the OS curve; this assumes that the OS curve is primarily informed by patients who have progressed.

Features of the economic analysis

The current evaluation was compared to previous NICE evaluations in R/R LBCL: TA559 (axi-cel for treating DLBCL and PMBCL after two or more systemic therapies), TA649 (Pola + BR for treating R/R DLBCL), and ID3795 (tafasitamab with lenalidomide for treating R/R DLBCL).[3, 14, 44] All of the evaluations considered used a three-state PSM and adopted a lifetime horizon. However, some appraisals applied mixture-cure-models. A summary of the key features of the economic analysis is presented in Table 37.

Perspective

In line with the NICE reference case, the analysis was undertaken from a UK NHS and PSS perspective.[92]

Cycle length

A 28-day cycle length was adopted in the model, as it provides the appropriate level of detail and was consistent with the epcoritamab dose schedules. Previous models used in NICE evaluations in R/R LBCL have used cycle lengths of one month, four weeks or one week.[3, 14, 44]

Time horizon and discounting

The costs and outcomes in the model were calculated over a lifetime horizon. Considering a mean age at model entry of [redacted] years, a time horizon of 45 years was used in the base case to represent a lifetime horizon; 0% of patients are expected to be alive in the model at the end of the time horizon. This is in line with the NICE reference case and based on the NICE guideline's recommendation that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies that are being compared.[92] This is also consistent with the approach taken in previous models used in NICE evaluations in R/R LBCL.[3, 14, 44]

Both costs and effects were discounted at 3.5% per annum in accordance with the NICE reference case.[92]

Table 37: Features of the economic analysis compared to previous NICE evaluations in the population of interest[a]

Factor	Previous evaluations			Current evaluation	
	TA559[3]	TA649[44]	ID3795[14]	Chosen values	Justification
Model design	Three-state PSM	Three-state PSM	Three-state PSM	Three-state PSM	Captures the clinical benefits of epcoritamab and is aligned with previous NICE evaluations in similar indications
Time horizon	Lifetime (44 years)	Lifetime (45 years)	Lifetime (45 years)	Lifetime (45 years)	In line with NICE reference case[91]
Cycle length	1 month	1 week	4 weeks	4 weeks	In line with the dosing regimens for epcoritamab and expected to be sufficiently short enough to capture time-to-event outcomes and any differences in clinical outcomes between treatments
Discount	3.5%	3.5%	3.5%	3.5%	In line with NICE reference case[91]
Health effects measure	QALYs	QALYs	QALYs	QALYs	In line with NICE reference case[91]
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS/PSS	In line with NICE reference case[91]
Treatment waning effect	No treatment waning applied	No treatment waning applied	No treatment waning applied	No treatment waning applied	Patients with R/R LBCL after two or more lines of systemic therapy have a poor prognosis, and any treatment effect waning is assumed to be implicitly captured in the selected extrapolations.
Source of health state utilities	ZUMA-1 trial	Based on data from TA559 (ZUMA-1 trial)	Based on data from TA559 (ZUMA-1 trial)	Based on data from EPCORE™ NHL-1 (DLBCL, no prior CAR-T population)	EQ-5D-3L data were collected in EPCORE™ NHL-1 and utility values were derived from these data. These utility values were deemed to be the most appropriate for use in the cost-effectiveness model, as per the NICE reference case.[91] In order to align with the efficacy data informing the base case cost-effectiveness analysis, the utility values are based on the DLBCL, no prior CAR-T population from EPCORE™ NHL-1.

					Scenario analyses have also been conducted using utility values from ZUMA-1.
Source of costs	• NHS National Reference costs • PSSRU • eMIT • BNF	• NHS National Reference costs • PSSRU • eMIT • BNF	• NHS National Reference costs • PSSRU • eMIT • BNF	• NHS National Reference costs • PSSRU • eMIT • BNF	In line with NICE reference case[91] Costs were sourced from 2019–2020 and inflated to 2021.

[a] TA559 and TA649 were selected as they represent NICE evaluations of the relevant comparators and ID3795 represents the most recent NICE evaluation in the indication of interest.[3, 14, 44]

Abbreviations: BNF: British National Formulary; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; eMIT: electronic market information tool; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; ID: identification; LBCL: large B-cell lymphoma; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSM: partitioned survival model; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; R/R: relapsed and/or refractory; TA: technology appraisal.

Source: NICE TA559;[3] NICE TA649;[44] NICE ID3795.[14]

B.3.2.3 Intervention technology and comparators

Intervention

The intervention included in the model is epcoritamab, which is administered via a SC injection, following the dosing regimen presented in Table 38. Epcoritamab was modelled as being administered until disease progression or unacceptable toxicity, in four-week (i.e., 28-day) cycles. This is line with the regimen administered in the EPCORE™ NHL-1 trial and the anticipated marketing authorisation.[21]

Table 38: Epcoritamab dosing schedule

Cycle	1				2 and 3				4–9		10+
Day of cycle	1	8	15	22	1	8	15	22	1	15	1
Dose (mg)[a]	0.16	0.8	48	48	48	48	48	48	48	48	48

[a] 0.16 mg is a priming dose, 0.8 mg is an intermediate dose and 48 mg is a full dose.
Source: AbbVie, epcoritamab draft SmPC 2022.[5]

Comparators

In line with current standard of care in UK clinical practice, the comparators included in the model are dependent on eligibility for intensive therapies. For patients not eligible for, or choose not to receive, intensive therapies, the comparator is R-based CIT. For patients eligible for intensive treatments, the comparator is axi-cel. Feedback from UK clinical experts gathered during advisory boards in July 2022 and February 2023 confirmed that these represent the most relevant comparators for epcoritamab in this indication.[4] As EPCORE™ NHL-1 is a single-arm trial, data informing comparative efficacy for the above comparators are derived from ITCs, using MAIC methodology (Section B.2.8).

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics of the cohorts included in the cost-effectiveness model are based on the aNHL cohort of EPCORE™ NHL-1, and are presented in Table 39.[21] As outlined in Section B.3.2.1, the economic analyses in this submission are presented for patients who are ineligible for, or choose not to receive, intensive therapies (base case analysis A: epcoritamab versus R-based CIT), and patients who are eligible to receive intensive therapies (base case analysis B: epcoritamab versus axi-cel), separately. As such, Table 39 presents the two sets of modelled baseline characteristics that are used for the base case analyses.

As outlined in Section B.2.8, a number of supportive ITCs were conducted in which alternative populations from the EPCORE™ NHL-1 trial were selected for inclusion, namely the LBCL population, and alternative sources of comparator efficacy data are explored. The alternative patient characteristics included in the model for these scenario analyses are presented in Appendix P.

Baseline mean age and female proportion were used to inform mortality rates and utilities of the general population. Mean bodyweight and body surface area (BSA) were used to inform weight or BSA-based dosing of treatments.

Table 39: Baseline patient characteristics applied in the cost-effectiveness model, base case approach

Parameter	Base case analysis A: Ineligible for, or choose not to receive, intensive therapies (epcoritamab versus R-based CIT)	Base case analysis B: Eligible for intensive therapies (epcoritamab versus axi-cel)
	DLBCL population adjusted to Sehn *et al.* 3L+ (N=[redacted])	DLBCL, no prior CAR-T and CAR-T eligible, unadjusted to match ZUMA-1 (N=[redacted])
Mean age (SE), year	[redacted]	[redacted]
Female proportion (SE)	[redacted]	[redacted]
Bodyweight (SE), kg[a]	[redacted]	[redacted]
BSA (SE), kg/m^{2}[a]	[redacted]	[redacted]

[a] Bodyweight and BSA inputs used for each population were consistently obtained from the unadjusted overall LBCL population from EPCORE™ NHL-1 (N=157), since these two variables were not included as matching variables in the MAIC.
Abbreviations: BSA: body surface area; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; R: rituximab; SE: standard error.

Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

For the ITC informing base case analysis A (ineligible for intensive therapies), an approach was taken that allows for one PFS and OS reference curve across multiple comparisons, thereby allowing fully incremental cost-effectiveness analysis, if required. NICE have previously criticised comparisons where each individual adjusted comparison leads to a change in the reference survival curve, such as during ID3795, and this approach addresses that concern.[14]

In order to do so, UK clinical experts were consulted on which comparator population represents the population that is most generalisable to patients with R/R LBCL in the UK. After consultation with UK clinical experts during an AbbVie-organised advisory board which took place in July 2022, clinical and economic experts suggested that adjustment of the epcoritamab population to match the Sehn *et al.* 3L+ population was appropriate, as the Sehn *et al.* 3L+ baseline characteristics are reflective of the population in the decision problem: patients with R/R LBCL after two or more prior lines of therapy in UK clinical practice.[4] Therefore, in the ITC informing base case analysis A, the epcoritamab population was adjusted to match the Sehn *et al.* 3L+ population and then compared to R-based CIT based on data from SCHOLAR-1.[70]

The EPCORE™ NHL-1 trial included a population of heavily pre-treated patients. However, as outlined in Section B.2.8 and Appendix N, the Pola + BR trial included 11 patients (27.5%) who had received fewer than two prior lines of systemic therapy. As such, synthetic OS and PFS KM curves for a population who had received two or more prior lines of therapy were derived from the data published on Pola + BR by Sehn *et al.* (2019), referred to as the Sehn *et al.* 3L+ population.[72] In addition, the EPCORE™ NHL-1 trial included patients who had received prior CAR-T therapies, as well as patients with different subtypes of LBCL (including DLBCL, HGBCL, PMBCL and FL Gr 3B). In the Sehn *et al.* trial, as well as the SCHOLAR -1 trial, no patients had received prior CAR-T therapy and the Sehn *et al.* trial included patients with DLBCL only. Therefore, to reduce heterogeneity between the trial populations, the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 was selected for inclusion in the ITC and adjusted to the

Sehn *et al.* 3L+ population. As such, in the base case, the modelled baseline characteristics are those of the DLBCL, no prior CAR-T epcoritamab population adjusted to the Sehn *et al.* 3L+ population.[72] This population is referred to as the 'DLBCL population adjusted to Sehn *et al.* 3L+'.

The clinical characteristics and disease pathways of DLBCL and other subtypes of LBCL are largely similar (Section B.1); as such, the comparative efficacy evidence of treatments for DLBCL provided by this ITC is considered to be generalisable to other subtypes of LBCL. This is further supported by the additional ITCs of epcoritamab versus axi-cel and Pola + BR in which the LBCL population from EPCORE™ NHL-1 was used (Appendix N).

Base case analysis B: Patients eligible for intensive therapies

In the ITC informing the base case analysis B (patients that are eligible for intensive therapies), the epcoritamab population was compared to the axi-cel population from ZUMA-1. To ensure the comparison is reflective of the expected epcoritamab population in UK clinical practice, the DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 was included in the ITC. The unadjusted epcoritamab population was used to compare to axi-cel from ZUMA-1; as outlined in Section B.2.8, this is a conservative approach that biases against epcoritamab when compared to the adjusted population however maintains the maximum sample size.

B.3.3.2 Survival inputs and assumptions

The key efficacy inputs in the model are OS, PFS and ToT. As EPCORE™ NHL-1 is a single-arm trial, comparative efficacy evidence for the economic analyses was informed by MAICs (Section B.2.8).

For epcoritamab, the long-term time-to-event outcomes were extrapolated based on EPCORE™ NHL-1 [redacted] data-cut IPD. For the comparator arms, the long-term time-to-event outcomes were derived by applying HRs from the MAICs to the extrapolated outcomes of epcoritamab. This approach was taken to allow the use of one reference curve per population for epcoritamab rather than yielding different survival estimates for epcoritamab in each pair-wise comparison conducted (which has been previously criticised by NICE during the appraisal of tafasitamab with lenalidomide [ID3795]).[14] This approach was also validated by UK clinical and health economic experts and is commonly accepted as a modelling method to derive comparator data in cost-effectiveness modelling.[4, 13]

In line with NICE DSU TSD14, parametric models for PFS, OS and ToT were fitted to the KM curves from the EPCORE™ NHL-1 trial (Section B.2.8).[72] The parametric distributions for epcoritamab were selected based on a rigorous process to avoid bias and to reflect clinical plausibility, based on statistical goodness of visual fit to the observed data, feedback form UK clinicians and comparison with long-term OS data in the published literature. The parametric model fitting was conducted according to the following steps recommended in the NICE DSU TSD 14:[80]

1) Tests for the proportional hazards (PH) assumption between treatment arms were conducted, which inferred the choice of fitting independent or dependent models. If the PH assumption held, a single dependent model for each survival curve was estimated, with treatment modelled as a single covariate. If violated, the same distribution was selected for all arms and fitted independently.
2) An initial selection of extrapolation models was performed based on visual inspection and statistical fit of the models to the trial data, based on Akaike Information Criterion (AIC)

and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival and smoothed hazard curves.

3) The best fitting models from step 2 were further evaluated against additional evidence from data in the published literature. For outcomes where no additional evidence was available, model selection was based on the outcomes of step 2.

Once a number of plausible curves had been determined based on the above steps, feedback from UK clinical experts and comparison with long-term OS data identified in the clinical SLR was used to determine the most clinically plausible curves for selection in the base case. Feedback from UK clinical experts was gathered during teleconference interviews on survival estimates by timepoint and treatment, the clinical validity of parametric distributions for epcoritamab and the clinical plausibility of MAIC results used to generate the comparator models (Section B.2.8.2). In addition, long-term OS data identified by the clinical SLR were used to assess the clinical plausibility of the OS extrapolations. However, most RCTs in the SLR did not report landmark survival data for DLBCL at 24 months or later, which is expected given the historically poor survival outcomes.

In accordance with NICE DSU TSD 14,[80] the range of parametric distributions fitted to the EPCORE™ NHL-1 trial were: exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma. Mixture cure models were also explored within the PSM framework, but were deemed to be less appropriate than the standard parametric models. Further details for the interpretation of AIC and BIC differences is provided in Appendix N.

B.3.3.3 Time-to-event analyses: Patients ineligible for, or chose not to receive, intensive therapies

Epcoritamab efficacy – Base case approach

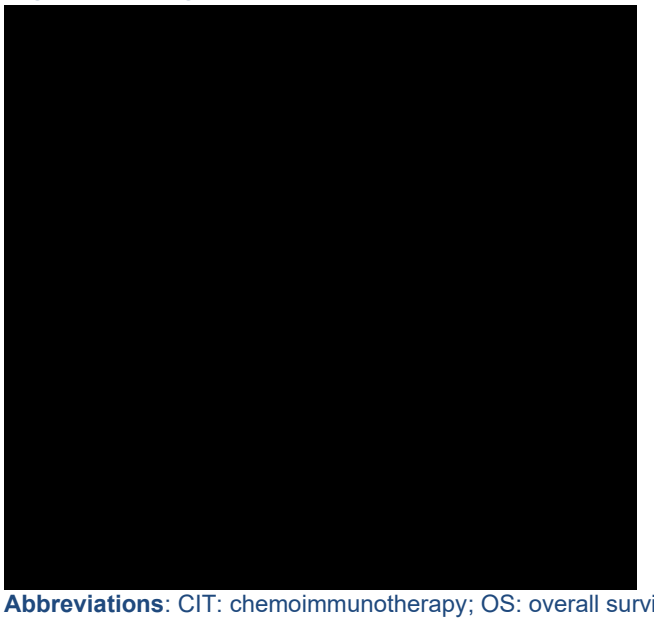
Overall survival

Assessment of the PH assumption

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus R-based CIT are presented in Figure 17 and Figure 18. The log-cumulative hazard curve demonstrates that both of the treatment arms intersect at around 1.3 months (~0.2 months on the natural log scale), and around 1.6 months (~0.5 months on the natural log scale) and around two months (~0.7 months on the natural log scale). After two months, the cumulative hazards appear to move parallel over time, suggesting proportionality for the hazard curves for OS.

The Schoenfeld residual curve exhibits an almost zero slope except towards the end of the trial, suggesting the covariate is time independent for most of the time after Month 2. This suggests that the proportional hazards assumption may not be violated. This is also consistent with the Grambsch and Therneau test of OS, as the p-value of [redacted] indicates that the proportional hazards cannot be rejected.

Figure 17: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT)



Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 18: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Extrapolation selection

The same seven parametric distributions were also fitted to the OS KM data of the EPCORE™ NHL-1 trial, and evaluated based on AIC and BIC values, which are presented in Table 40.

Based on AIC and BIC, the log-normal model provides the best statistical fit. However, there is minimal difference in AIC between the log-logistic, Gompertz, generalised gamma and Weibull extrapolations; there is a difference of ≤2 which indicates substantial support for the statistical fit of the models being equal (Appendix P). In terms of BIC, the log-normal, exponential, log-logistic and Gompertz models all demonstrate a good statistical fit, and the difference in BIC between these four best-fitting extrapolations suggests that there is weak support for one model being preferred over the other.

Table 40: Goodness of fit statistics for OS (AIC and BIC): base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	AIC	Distribution	BIC
Log-normal	[redacted]	Log-normal	[redacted]
Log-logistic	[redacted]	Exponential	[redacted]
Gompertz	[redacted]	Log-logistic	[redacted]
Generalised gamma	[redacted]	Gompertz	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Gamma	[redacted]
Exponential	[redacted]	**Generalised gamma**	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 19. The corresponding survival estimates at several landmarks are presented in Table 41.

Figure 19: Long-term OS extrapolations for epcoritamab: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Abbreviations: OS: overall survival.

During interviews with UK clinical experts, all clinical experts commented that the generalised gamma represents the most clinically plausible extrapolation to model OS. Furthermore, the clinical experts provided estimates of the percentage of patients with R/R LBCL receiving treatment with epcoritamab after two or more lines of prior therapy expected to be alive at one, two and five years. The clinicians estimated a plausible range of 10–50% alive at two years and 5–45% alive at five years; considering the most likely value only, the clinicians estimated a range of 30–46% and 20–37% of patients alive at two and five years, respectively. Based on these

estimates, both the generalised gamma and Gompertz extrapolations could be considered clinically plausible; the generalised gamma extrapolation provides survival estimates towards the lower end of the clinicians estimated range and the Gompertz extrapolation provides estimates towards the upper end of the clinicians estimated range.

Further validation of the selected extrapolations was conducted through comparison with published long-term OS data identified in the clinical SLR. Most RCTs identified in the clinical SLR did not report DLBCL landmark survival data at 24 months or later. The only study that reported a 24-month OS estimate was the CORAL trial (median follow-up of 30.1 months), which reported OS estimates at 12 and 24 months of 23% and 15.7%, respectively.[93] However, patients in the CORAL trial received R-based CIT regimens (R-ICE or R-DHAP) so this study has limited validity in validating the extrapolation of OS for the epcoritamab arm.[93]

Overall, the generalised gamma extrapolation was selected to model OS for epcoritamab in base case analysis A, as it demonstrates reasonable statistical and visual fit to the observed trial data. Furthermore, it was consistently selected as the most clinically plausible by all clinical experts which is important to ensure the model is projecting realistic outcomes in the long-term. When compared with the other clinically plausible extrapolation identified by UK clinical experts (Gompertz), the generalised gamma extrapolation represents a conservative assumption.

Table 41: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in base case analysis A.
[a] Landmark survival estimates are excluding the durable remission assumption.
Abbreviations: CI: confidence intervals; NR: not reported; OS: overall survival.

Progression-free survival

Assessment of proportional hazards

As PFS results were not reported in SCHOLAR-1, the results of the assessment of the PH assumption for OS for epcoritamab versus R-based CIT are assumed to apply to PFS for epcoritamab versus R-based CIT also as per TA559 and TA872.[3, 94]

Extrapolation selection

As described in Section B.3.3.2 seven parametric distributions were fitted to the PFS KM data of the EPCORE™ NHL-1 trial. These were evaluated based on AIC and BIC values, which are presented in Table 42.

The log-normal, generalised gamma, log-logistic, and Gompertz were considered to be the best fitting models compared with the other models (i.e., Weibull, exponential, and gamma) based on AIC and BIC. The best statistical fit is provided by the log-normal model in terms of both AIC and BIC.

Table 42: Goodness of fit statistics for PFS (AIC and BIC): base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	AIC	Distribution	BIC
Log-normal	[redacted]	Log-normal	[redacted]
Generalised gamma	[redacted]	Log-logistic	[redacted]
Log-logistic	[redacted]	Gompertz	[redacted]
Gompertz	[redacted]	**Generalised gamma**	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Exponential	[redacted]
Exponential	[redacted]	Gamma	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 20.[21] The corresponding survival estimates at several landmarks are presented in Table 43.

Figure 20: Long-term PFS extrapolations for epcoritamab: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Abbreviations: PFS: progression-free survival.

Table 43: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in base case analysis A.
[a] Landmark survival estimates are excluding the durable remission assumption.
Abbreviations: CI: confidence intervals; NR: not reported; PFS: progression-free survival.

During interviews with UK clinical experts, two clinical experts commented that the Gompertz extrapolation represents the most clinically plausible extrapolation to model PFS; a third clinician stated that the generalised gamma extrapolation was the most plausible to model PFS. Furthermore, the clinical experts provided estimates of the percentage of patients with R/R LBCL

receiving treatment with epcoritamab after two or more lines of prior therapy they would expect to be progression-free at one, two and five years. The clinicians estimated a plausible range of 10–40% progression-free at two years and 5–35% progression-free at five years; considering the most likely value only, the clinicians estimated a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively. Based on these estimates, the Gompertz and generalised gamma extrapolations appear to represent the most clinically plausible extrapolation. However, the long-term estimates of the Gompertz extrapolation demonstrates a plateau at a level that is currently only partially supported by the available PFS data from complete responders.

As such, the generalised gamma extrapolation was selected to model PFS for epcoritamab in base case analysis A, as it demonstrates reasonable statistical and visual fit to the observed data. Furthermore, it can be considered clinically plausible based on feedback from UK clinical experts and the available data on epcoritamab. The survival estimates provided by the generalised gamma extrapolation underestimate the predicted PFS of epcoritamab when compared to estimates provided by UK clinicians; as such, the selection of the generalised gamma extrapolation can be considered to be a conservative assumption.

Time on treatment

The AIC and BIC values based on the seven parametric distributions fitted to the ToT KM data from EPCORE™ NHL-1 are presented in Table 44.

The log-normal model is the best fitting model in terms of both BIC and AIC. The log-logistic, Gompertz and potentially exponential distributions also provide a relatively good statistical fit to the observed data.

Table 44: Goodness of fit statistics for ToT (AIC and BIC): base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	AIC	Distribution	BIC
Log-normal	[redacted]	Log-normal	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Exponential	[redacted]	Gompertz	[redacted]
Gompertz	[redacted]	Exponential	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Gamma	[redacted]
Generalised gamma	[redacted]	**Generalised gamma**	[redacted]

The generalised gamma extrapolation was chosen to model ToT for epcoritamab in base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ToT: time on treatment.

The long-term extrapolations for ToT, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 21. The corresponding ToT estimates at several landmarks are presented in Table 45.

Figure 21: Long-term ToT extrapolations for epcoritamab: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Abbreviations: ToT: time on treatment.

Table 45: Predicted and observed ToT for epcoritamab at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model ToT for epcoritamab in base case analysis A.
[a] Landmark survival estimates are excluding the durable remission assumption.
Abbreviations: CI: confidence intervals; NR: not reported; ToT: time on treatment.

Considering the feedback from UK clinical experts, the clinicians provided varied responses; two clinicians concluded that the generalised gamma extrapolation can be considered to be one of the most clinically plausible extrapolation, whilst one clinician concluded that the log-normal or

log-logistic extrapolations are the most clinically plausible. Two clinicians stated that the Gompertz extrapolation was clinically implausible due to the high plateau.

In addition, the UK clinical experts stated that they would expect the TTD curve to be similar in shape but repressed compared to PFS curves, as patients would be likely to remain on treatment until they progress; the clinical experts stated that it was possible for patients to discontinue treatment due to toxicity rather than progression, but the available data suggests that epcoritamab is well-tolerated with only [redacted] of patients with DLBCL from EPCORE™ NHL-1 discontinuing due to AEs. As such, the generalised gamma extrapolation was selected to model TTD for epcoritamab in base case analysis A in order to align with the extrapolation choice for PFS. The estimated proportion of patients remaining on treatment at two and five years predicted by the generalised gamma model also aligns with the estimates provided by the UK clinicians.

Comparator efficacy – Base case analysis A

As outlined in Section B.3.3.2 the long-term time-to-event outcomes for the comparator arms were derived by applying HRs to the extrapolated outcomes of epcoritamab. The HRs were derived using the ITC, as outlined in Section B.2.8. An overview of the HRs and CIs that were applied to the epcoritamab curves to derive the time-to-event outcomes for the comparators arms in the cost-effectiveness model is provided in Table 46, including both the base case approach and the scenario analyses explored.

HRs for OS and PFS only are presented in Table 46. As R-based CIT is administered for a fixed number of doses or cycles, a different approach is taken for the ToT of R-based CIT than for epcoritamab. Feedback from UK clinical experts stated that patients would primarily only discontinue treatment with R-based CIT upon progression. As such, ToT for R-based CIT is assumed equal to PFS. For the R-based CIT arm, the HR for PFS was assumed to be the same as the HR derived for OS, as no PFS KM data are reported from SCHOLAR-1. This is consistent with the approach taken in TA559 and feedback from UK clinical and health economic experts supported the plausibility of this assumption.[3]

An overview of the HRs and CIs that were applied to the epcoritamab curves to derive the time-to-event outcomes for the comparators arms in the cost-effectiveness model is provided in Table 46, including both the base case approach and the scenario analyses explored.

Table 46: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (base case analysis A)

Outcome	Hazard ratio (95% CI)
Base case analysis A (modelled population: DLBCL population adjusted to Sehn *et al.* 3L+)	
OS	[redacted]
PFS	[redacted][a]
ToT	N/A[b]*
Source of comparator efficacy	SCHOLAR-1

[a] The R-based CIT PFS HR is assumed equal to the derived OS HR. [b] As R-based CIT is administered for a fixed number of doses or cycles and based on feedback from UK clinical experts, ToT for R-based CIT is assumed equal to PFS.
Abbreviations: CI: confidence interval; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; N/A: not applicable; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab; RW: real world; 3L+: third-line and beyond; ToT: time on treatment.

B.3.3.4 Time-to-event analyses: Patients eligible for intensive therapies

Epcoritamab efficacy – Base case approach

In this analysis, IPD from the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 were the source of the long-term time-to-event outcomes for the epcoritamab arm. A KM plot of PFS, OS and ToT for the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 is provided in Figure 22.

Figure 22: KM plot of PFS, OS and ToT in the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population (N=[redacted]) from EPCORE™ NHL-1 ([redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS IRC: progression-free survival-Independent Review Committee; ToT: time on treatment; TTD: time to treatment discontinuation.

Overall survival

Assessment of PH assumption

The log-cumulative hazard plot and the Schoenfeld residual curve for OS for epcoritamab versus axi-cel are presented in Figure 23 and Figure 24, respectively.

The log-cumulative hazard plot demonstrates that both of the treatment arms intersect at around 2.7 months (~1 month on the natural log scale) and around 7.4 months (~2 months on the natural log scale). This therefore suggests non-proportionality for the hazard curves for OS. The Schoenfeld residual curve demonstrates a patter which suggests that the covariate is not time independent, thereby suggesting that the proportional hazards assumption may be violated. This is consistent with the results of the Grambsch and Therneau test, as the p-value of [redacted] indicates that the proportional hazards assumption is rejected.

Despite the proportional hazards assumption being rejected, HRs were applied to the epcoritamab curves to derive the time-to-event outcomes for axi-cel in the cost-effectiveness

model for the base case analysis B. This represents a conservative approach as it is anticipated that alternative approaches would produce more favourable outcomes for epcoritamab.

Figure 23. Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)

Abbreviations: Axi-cel: axicabtagene ciloleucel; OS: overall survival.

Figure 24. Schoenfeld residual curve – OS (epcoritamab versus axi-cel)

Abbreviations: Axi-cel: axicabtagene ciloleucel; OS: overall survival.

Extrapolation selection

The same seven parametric distributions were also fitted to the OS KM data of the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 trial, and evaluated based on AIC and BIC values, which are presented in Table 47 and Table 40.

Based on AIC and BIC, the generalised gamma model provides the best statistical fit. Due to small differences in the AIC and BIC when compared with the generalised gamma model, the log-normal and exponential models can also be considered to provide a good statistical fit.

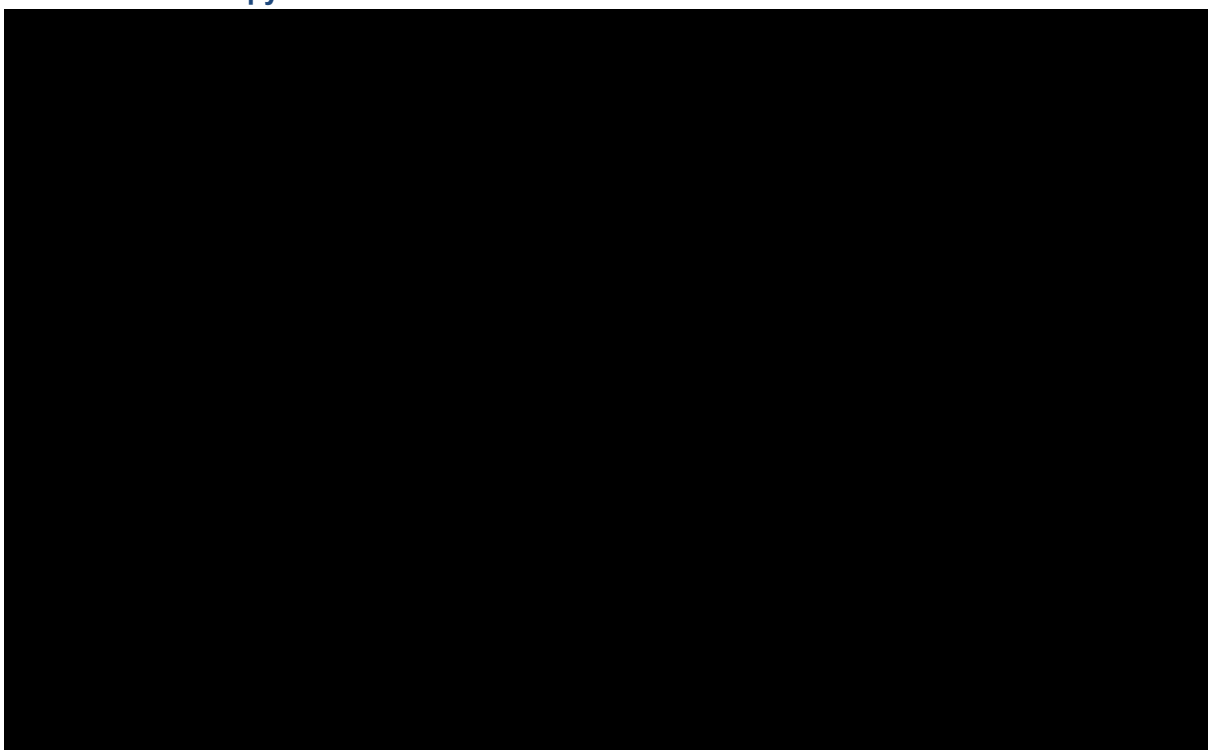
Table 47: Goodness of fit statistics for OS (AIC and BIC): base case analysis B – eligible for intensive therapy

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 25. The corresponding survival estimates at several landmarks are presented in Table 48.

Figure 25: Long-term OS extrapolations for epcoritamab: base case analysis B – eligible for intensive therapy



Abbreviations: OS: overall survival.

Table 48: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in base case analysis B.
[a] Landmark survival estimates are excluding the durable remission assumption.
Abbreviations: CI: confidence intervals; N/A: not applicable; OS: overall survival.

During interviews with UK clinical experts, the clinicians estimated a plausible range of 10–50% alive at two years and 5–45% alive at five years for patients receiving epcoritamab; considering the most likely value only, the clinicians estimated a range of 30–46% and 20–37% of patients alive at two and five years, respectively. Based on the estimates provided by clinical experts only, the log-logistic and log-normal extrapolations appear to be the most appropriate to model

OS for epcoritamab. Considering the generalised gamma model which provides the best statistical fit, this model appears to slightly overestimate OS for epcoritamab when compared with the clinicians' estimates.

However, the plausibility of the OS estimates produced by each extrapolation for axi-cel (after application of the HR derived from the MAIC [Section B.2.8.2]) must also be considered. Through comparison with the OS estimates for axi-cel in R/R LBCL (TA842), it is apparent that the log-logistic and log-normal extrapolations would produce implausibly low OS estimates for axi-cel. In the base case cost-effectiveness analysis of axi-cel in R/R LBCL, approximately 50% of patients were estimated to be alive at 60 months.

As such, in order to produce clinically plausible results for both epcoritamab and axi-cel, the generalised gamma extrapolation was selected to model OS for epcoritamab in base case analysis B. The log-normal and log-logistic extrapolations are explored in scenario analyses.

Progression-free survival

Assessment of the PH assumption

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus axi-cel are presented in Figure 26 and Figure 27.

The log-cumulative hazard curve demonstrates that both of the treatment arms cross at multiple time points, around 1.1 months (~0.1 months on the natural log scale, around 2.7 months (~1 month on the natural log scale) and around 20.1 months (~3 months on the natural log scale). This therefore suggests non-proportionality for the hazard curves for PFS. The Schoenfeld residual curve demonstrates a patter which indicates that the covariate is not time independent, thereby suggesting that the proportional hazards assumptions is violated. However, the Grambsch and Therneau test of PFS produced a p-value of [redacted], which suggests that the proportional hazards assumption cannot be rejected, as the p-value is higher than 0.05.

Figure 26. Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)

Abbreviations: Axi-cel: axicabtagene ciloleucel; PFS: progression-free survival.

Figure 27. Schoenfeld residual curve – PFS (epcoritamab versus axi-cel)

Abbreviations: Axi-cel: axicabtagene ciloleucel; PFS: progression-free survival.

Extrapolation selection

As described in Section B.3.3.2, seven parametric distributions were fitted to the PFS KM data of the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 trial. These were evaluated based on AIC and BIC values, which are presented in Table 40 and Table 42.

The best statistical fit based on both AIC and BIC is provided by the generalised gamma model. However, the generalised gamma model did not converge well and should therefore be disregarded. Of the remaining models, the log-normal, log-logistic and exponential models provide the best statistical fit in terms of both AIC and BIC.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 28. The corresponding survival estimates at several landmarks are presented in Table 50. All extrapolations slightly underestimate the observed median survival.

Table 49: Goodness of fit statistics for PFS (AIC and BIC): base case analysis B – eligible for intensive therapy

Distribution	AIC	Distribution	BIC
Generalised gamma	[redacted]	Generalised gamma	[redacted]
Log-normal	[redacted]	Exponential	[redacted]
Exponential	[redacted]	**Log-normal**	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]

Distribution	AIC	Distribution	BIC
Gompertz	[redacted]	Gompertz	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Gamma	[redacted]

The log-normal extrapolation was selected to model PFS for epcoritamab in base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 28: Long-term PFS extrapolations for epcoritamab: base case analysis B – eligible for intensive therapy

Abbreviations: PFS: progression-free survival.

Table 50: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Month[a]					
	12	24	48	60	120	180
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The log-normal extrapolation was selected to model PFS for epcoritamab in base case analysis B. [a] Landmark survival excluding the durable remission assumption.
Abbreviations: CI: confidence intervals; N/A: not applicable; PFS: progression-free survival.

Considering feedback from UK clinical experts, the clinicians estimated a plausible range of 10–40% of patients are progression-free at two years and 5–35% progression-free at five years; considering the most likely value only, the clinicians estimated a range of 30–35% and 20–30% of patients are progression-free at two and five years, respectively. Considering these estimates, all extrapolations appear to underestimate PFS for epcoritamab, with the log-logistic, log-normal and Gompertz extrapolations providing the closest estimates; there are minimal differences in the estimates provided by these three extrapolations.

As such, of the extrapolations that produce the closest estimates to those provided by the clinicians, the extrapolation which provided the best statistical fit to the EPCORE™ NHL-1 data, the lognormal extrapolation, was selected to model PFS for epcoritamab in base case analysis B. The Gompertz extrapolation was selected to model PFS for epcoritamab in a scenario analysis.

Time on treatment

The AIC and BIC values based on the seven parametric distributions fitted to the ToT KM data from the unadjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 are presented in Table 51 and Table 44.

Based on AIC and BIC criteria, the log-normal, generalised gamma, Gompertz and log-logistic model all provide a good statistical fit. The log-normal model provides the best statistical fit in terms of BIC, whilst the generalised gamma model provides the best statistical fit in terms of AIC.

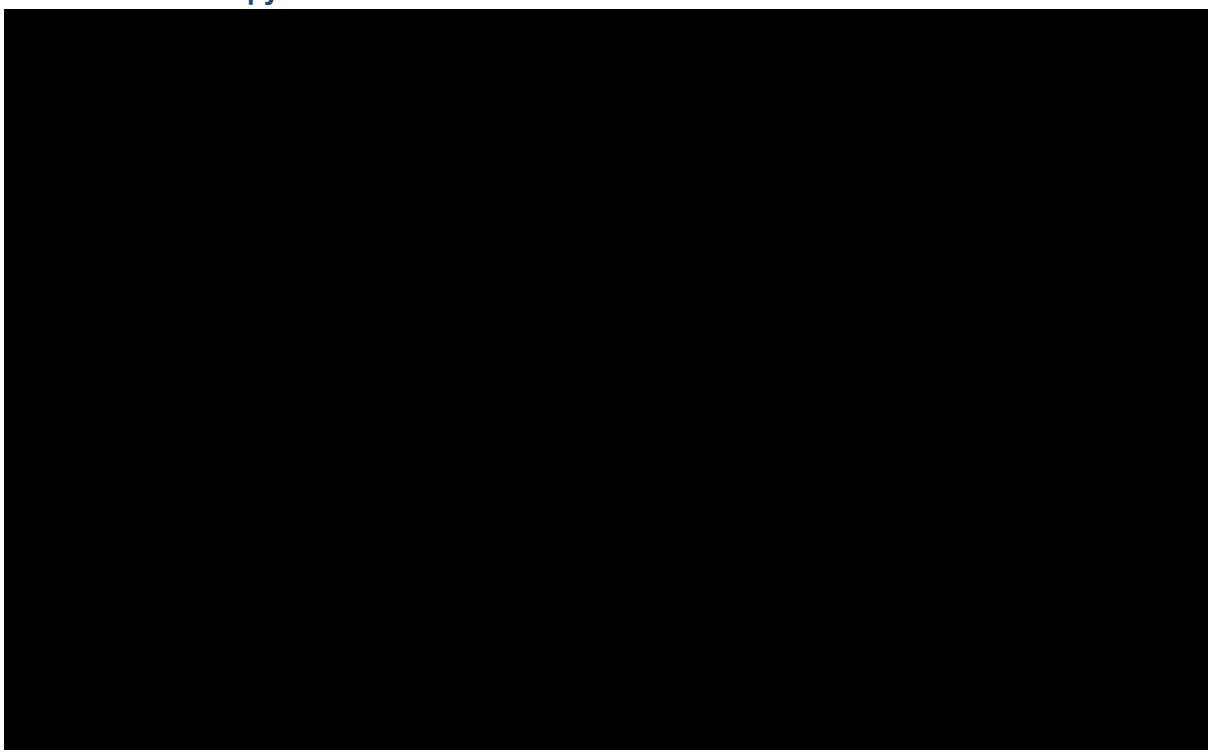
The long-term extrapolations for ToT, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 29. The corresponding ToT estimates at several landmarks are presented in Table 52. All distributions slightly overestimate the observed median survival.

Table 51: Goodness of fit statistics for ToT (AIC and BIC): base case analysis B – eligible for intensive therapy

Distribution	AIC		BIC
Log-normal	[redacted]	Log-normal	[redacted]
Generalised gamma	[redacted]	Gompertz	[redacted]
Gompertz	[redacted]	Generalised gamma	[redacted]
Log-logistic	[redacted]	**Log-logistic**	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Gamma	[redacted]
Exponential	[redacted]	Exponential	[redacted]

The log-logistic extrapolation was selected to model ToT for epcoritamab in base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ToT: time on treatment.

Figure 29: Long-term ToT extrapolations for epcoritamab: base case analysis B – eligible for intensive therapy



Abbreviations: ToT: time on treatment.

Table 52: Predicted and observed ToT for epcoritamab at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The log-logistic extrapolation was [redacted] selected to model ToT for epcoritamab in base case analysis B. [a] Landmark survival excluding the durable remission assumption.
Abbreviations: CI: confidence intervals; NR: not reported; ToT: time on treatment.

Considering feedback received by UK clinical experts, the clinicians estimated a plausible range of 20–40% of patients remain on treatment at two years and 15–35% remain on treatment at five years; considering the most likely value only, the clinicians estimated a range of 27–30% and 20–25% of patients remain on treatment at two and five years, respectively. Considering the estimated proportion of patients remaining on treatment at these landmarks predicted by each of

the extrapolations, the log-logistic extrapolation most closely aligns with the estimates provided by the clinicians. Considering the best statistically fitting curves, the generalised gamma and Gompertz extrapolations overestimate ToT, whilst the log-normal extrapolation underestimates ToT at later timepoints.

As such, considering statistical fit and clinical plausibility, the log-logistic extrapolation was selected to model ToT for epcoritamab in base case analysis B.

Epcoritamab efficacy – Scenario analyses

As outlined in Section B.2.8, an additional supportive ITC was conducted to support the ITC that informs the epcoritamab and comparative efficacy estimates base case analysis B. An overview of all ITCs conducted for population B is presented in Section B.2.8.2.

In the ITC informing base case analysis B, the DLBCL population from EPCORE™ NHL-1 was selected for inclusion in the ITC. However, a scenario analysis in which the LBCL population from EPCORE™ NHL-1 was included in the ITC informing the comparative efficacy estimates was conducted. In this scenario analysis, the modelled baseline characteristics are informed by the LBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1.

For the scenario analysis, the long-term time-to-event outcomes for epcoritamab were extrapolated based on EPCORE™ NHL-1 IPD, following the same methods as outlined in Section B.2.8.1. Full details of the survival analysis for the different epcoritamab populations included in the scenario analyses is provided in Appendix P. Details of the patient characteristics included in the model for these scenario analyses are also presented in Appendix P.

Table 53: Epcoritamab populations included in scenario analyses: Patients eligible for intensive therapies

	Comparison conducted	Epcoritamab population	Source of comparator efficacy data
Base case analysis B	Epcoritamab versus axi-cel	DLBCL, no prior CAR-T, CAR-T eligible, unadjusted (n=[redacted])	ZUMA-1[71]
Scenario analysis B.1	Epcoritamab versus axi-cel	LBCL, no prior CAR-T, CAR-T eligible, unadjusted (n=[redacted])	ZUMA-1[71]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma.

Comparator efficacy (axi-cel)

Base case analysis B

As outlined in Section B.3.3.2, the long-term time-to-event outcomes for the comparator arms were derived by applying HRs to the extrapolated outcomes of epcoritamab. The HRs were derived using the ITC, as outlined in Section B.2.8. For the economic analysis of patients who are eligible for treatment with intensive therapies, the HRs were derived using the MAIC in which the DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 was unadjusted to match the axi-cel population from ZUMA-1.

Scenario analysis B.1

In the ITC informing base case analysis B, the DLBCL population from EPCORE™ NHL-1 was selected for inclusion in the ITC. As outlined in Section B.1.3, data on DLBCL are expected to be generalisable to all LBCL subtypes, and this is supported by data from EPCORE™ NHL-1. However, to explore any uncertainty associated with this assumption, a scenario analysis in which the LBCL population from EPCORE™ NHL-1 was included in the ITC informing the comparative efficacy estimates was conducted. In this scenario analysis, the modelled baseline characteristics are informed by the LBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1.

Summary

An overview of the HRs and CIs that were applied to the epcoritamab curves to derive the time-to-event outcomes for axi-cel in the cost-effectiveness model for the base case analysis B and scenario analysis B.1 is provided in Table 54. HRs for OS and PFS only are presented in Table 54, as ToT is not applicable for axi-cel as it is administered as a single-dose.

Table 54: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – Patients eligible for intensive therapies

Outcome	Hazard ratio (95% CI)
Base case analysis B – modelled population: DLBCL, no prior CAR-T, CAR-T eligible, unadjusted	
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	ZUMA-1[71]
Scenario analysis B.1 – modelled population: LBCL, no prior CAR-T, CAR-T eligible, unadjusted	
OS	[redacted]
PFS	[redacted]
Source of comparator efficacy	ZUMA-1[71]

[a] ToT is not applicable for axi-cel as it is administered as a single-dose.
Abbreviations: CAR-T therapy: chimeric antigen receptor T-cell therapy; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; LBCL: large B-cell lymphoma; N/A: not applicable; OS: overall survival; PFS: progression-free survival.

B.3.3.5 Adverse events

TEAEs of grade 3 or above that occurred in ≥5% of the patients in any of the studies (either EPCORE™ NHL-1 or the relevant comparator trials) were included in the cost-effectiveness model and were associated with a disutility and cost. This is consistent with the approach commonly adopted in oncology economic models and prior NICE appraisals.[3, 14, 63, 90] Grade 1 or 2 AEs were also considered if those AEs are expected to lead to hospitalisation and costly

treatments. Specifically, grade 1 and grade 2 B-cell aplasia that may occur in patients receiving axi-cel were included.

An overview of all AEs included in the model with the incidence per treatment arm and the duration of the AE in days is provided in Table 55, alongside the sources. The duration of AE was informed by previous NICE appraisals in R/R LBCL, as indicated in Table 55.[3, 14, 62, 90]

Table 55: AEs incidence and duration inputs applied in the cost-effectiveness model

Adverse event	Incidence per treatment arm			Duration	
	Epcoritamab	R-based CIT	Axi-cel	Days	Source
Anaemia	[redacted]	17.90%	0.00%	16	NICE TA649[90]
B-cell aplasia[a]	[redacted]	0.00%	11.00%	365	NICE TA559[3]
CRS	[redacted]	0.00%	13.00%[c]	4	NICE TA559[3]
Febrile neutropenia	[redacted]	12.80%	0.00%	6	NICE TA559[3]
Hypokalaemia	[redacted]	2.60%	0.00%	72	NICE ID3795[14]
ICAN	[redacted]	0.00%	28.00%	17	NICE TA559[3]
Leukopenia	[redacted]	7.70%	0.00%	14	NICE TA306[62]
Lymphopenia	[redacted]	0.00%	0.00%	34	NICE ID3795[14]
Neutropenia	[redacted]	33.30%	0.00%	15	NICE TA306[62]
Neutrophil count decreased	[redacted]	0.00%	0.00%	15	Assumed to be the same as neutropenia
Pneumonia	[redacted]	2.60%	0.00%	15	NICE ID3795[14]
Rash	[redacted]	7.70%	0.00%	16	Assumed to be the same as anaemia
Thrombocytopenia	[redacted]	23.10%	0.00%	23	NICE TA306[62]
Source	Epcoritamab CSR[21]	NICE TA649[90]	NICE TA559[3]	-	-

[a] B-cell aplasia includes only grade 1 and 2 AEs; [b] The incidence of CRS in the epcoritamab treatment arm is based on the proportion of patients experiencing SAEs of CRS in the EPCORE™ NHL-1 trial; this approach was taken to best represent the cost of CRS associated with epcoritamab; [c] The incidence of CRS in the axi-cel arm is based on the proportion of patients experiencing grade 3 or higher CRS events in line with TA559; this approach was taken to reflect the impact of CRS associated with axi-cel on quality of life.
Abbreviations: axi-cel: axicabtagene ciloleucel; CRS: cytokine release syndrome; CSR: clinical study report; ICAN: immune effector cell-associated neurotoxicity syndrome; ID: identification.

B.3.3.6 Background mortality

The cost-effectiveness model includes Office for National Statistics (ONS) 2021 life tables pooled from 2018 to 2020 to estimate background mortality (i.e., mortality not related to the disease) to reflect the UK population's general mortality.[95] These were adjusted by the baseline mean age and sex ratio of the EPCORE™ NHL-1 population.

The final mortality rates used in the model were based on the maximum between the hazard of the extrapolated OS and the hazard of the general population to ensure that mortality hazards for the modelled population could not be lower than the mortality hazard observed in the general population at any point in time.

In addition, patients who are progression-free and alive after 24 months are considered to be in long-term remission (Section B.3.2.2). Therefore, for these patients, background mortality is applied after the 24-month timepoint. An additional risk of death is applied as 1.41 times the hazard of background mortality, due to long-term complications arising from cancer and cancer treatment; this is based on a US study and was accepted by the EAG in TA649.[90]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-3L data were collected in EPCORE™ NHL-1 and linear mixed models (LLM) for repeated measures were used to analyse the EQ-5D-3L data obtained in the trial. In addition, adjusted limited dependent variable mixture models (ALDVMM) were explored. The UK specific value set by Dolan was used to derive UK utility values.[89] Full details on the derivation of utility values are provided in Appendix O.

For the analysis of the EQ-5D-3L data from EPCORE™ NHL-1 using LLM, three models were fitted that used one, two or three components as covariates (health state; health state and treatment status; or health state, treatment status and interaction between health state and treatment status). All models were conducted using the random intercept model, accounting for differences in utilities between patients. The utility values derived using the LLM model with one covariate was deemed to be the most appropriate as this model demonstrated the best statistical fit in terms of AIC and BIC, and it aligns with NICE's preference to pool health state utility values across treatment arms with AEs included separately.

Utilities estimated using ALDVMM were deemed to be less appropriate than those estimated using LLM, and the ALDVMM with two components had convergence issues which meant that standard errors could not be calculated.

The utility values derived from the DLBCL, no prior CAR-T population and the overall LBCL population of the EPCORE™ NHL-1 trial are provided in Table 56. Utility values derived from the LBCL, no prior CAR-T population from EPCORE™ NHL-1 were deemed to be the most suitable for inclusion in the base case, in order to ensure consistency with the efficacy data used in the base case, with the utility values derived from the LBCL population used in the appropriate scenario analyses (Scenario analyses A.3 and B.1).

Table 56: Summary of utility values derived from EPCORE™ NHL-1 – linear mixed models

Health state	Utility value	SE
DLBCL, no prior CAR-T		
Pre-progression	[redacted]	[redacted]
Post progression	[redacted]	[redacted]
LBCL (overall population)		
Pre-progression	[redacted]	[redacted]
Post progression	[redacted]	[redacted]

Abbreviations: CAR-T therapy: chimeric antigen receptor T-cell therapy; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; SE: standard error.

B.3.4.2 Mapping

No mapping methods were required to be implemented as part of this submission.

B.3.4.3 Health-related quality-of-life studies

As described in Section B.3.1, a *de novo* economic SLR was conducted to identify cost-effectiveness, health state utility values, and cost and healthcare resource use data to include in the cost-effectiveness model, where appropriate. An overview of the HRQoL data identified in the economic SLR is provided in Appendix H.

As stated in Section B.3.4.1, utility values derived from EPCORE™ NHL-1 were deemed to be the most appropriate for inclusion in the base case. However, other plausible utility values were identified in the published literature. Recent NICE evaluations in LBCL (TA649 and ID3695) have utilised the same health state utility values as used in TA559, a previous NICE appraisal in DLBCL and PMBCL.[3, 14, 44] In TA559, the utility values were derived from the ZUMA-1 trial.[3] For consistency with prior appraisals, a scenario analysis has been conducted using the utility estimates from ZUMA-1 (see Section 0).

Table 57: Summary of utility values from ZUMA-1 used in prior NICE evaluations[3, 14, 44]

Health state	Utility value	SE
Pre-progression	0.720	0.030
Post-progression	0.650	0.060

Abbreviations: NICE: National Institute for Health and Care Excellence; SE: standard error.
Source: NICE TA559.[3]

B.3.4.4 Age-related utility deterioration

To account for the deterioration in HRQoL associated with ageing, the utility values used in the cost-effectiveness model were age-adjusted based on published decrements as recommended by the NICE DSU TSD 12.[96] The data used to inform the adjustment was taken from the study by Ara and Brazier , which pooled data from four consecutive health surveys for England (2003–2006).[97]

The age-related utility deterioration was included in the model by applying a natural utility decrement to account for people having a lower utility value as they become older. This relative decrement was applied to the health state specific utility values presented in Section B.3.4.4.

B.3.4.5 Adverse reactions

Total QALY losses due to AEs were applied during the first model cycle, estimated as a sum of product of event disutility and duration across all the AEs. This is consistent with the approach taken in TA559.[3] AE disutility values were obtained from previous NICE submissions whenever available. An overview of the AE disutility values used in the cost-effectiveness model is presented in Table 58. AE incidence and duration are presented in Section B.3.3.5 and the associated costs are provided in Section B.3.5.3.

Table 58: Adverse event-related utility decrements applied in the cost-effectiveness model

Adverse event	Utility decrement	SE	Source
Anaemia	0.250	0.025	NICE TA649[90] and NICE TA306[62]
B-cell aplasia	0.370	0.037	NICE ID3795[14]
CRS	0.772	0.077	Assumed equal to the utility associated with the progression-free health state, in line with NICE TA559[3]
Febrile neutropenia	0.150	0.015	NICE TA559[3]
Hypokalaemia	0.090	0.009	NICE ID3795[14]
ICAN	0.772	0.077	Assumed to be the same as CRS
Leukopenia	0.090	0.009	NICE TA649[90]
Lymphopenia	0.090	0.009	NICE ID3795[14]
Neutropenia	0.090	0.009	NICE TA649[90]
Neutrophil count decreased	0.090	0.009	Assumed to be the same as neutropenia
Pneumonia	0.200	0.020	NICE TA649[90] and NICE TA559[3]
Rash	0.250	0.025	Assumed to be the same as anaemia
Thrombocytopenia	0.110	0.011	NICE TA649[90]

Abbreviations: CRS: cytokine release syndrome; ICAN: immune effector cell-associated neurotoxicity syndrome; ID: identification; NICE: National Institute for Health and Care Excellence; SE: standard error; TA: technology appraisal.

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the health state utility values applied in the cost-effectiveness model, sourced from EPCORE™ NHL-1 derived using LLM, is presented in Table 59.[3]

Table 59: Summary of utility values for the cost-effectiveness analysis

Health state	Utility value	95% CI	Reference in submission	Source
Pre-progression (first 24 months)	[redacted]	[redacted]	Section B.3.4.1	EPCORE™ NHL-1
Pre-progression (after 24 months)	[redacted]	[redacted]	Section B.3.2.2	EPCORE™ NHL-1
Post-progression	[redacted]	[redacted]	Section B.3.4.1	EPCORE™ NHL-1

Abbreviations: CI: confidence interval.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An economic SLR was conducted to identify any relevant cost or resource use data that could be incorporated into the model. Full details of the economic SLR search strategy, study selection process and results are presented in Appendix G.

The cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England and therefore only included costs that would be incurred by the health system.

The model includes several cost categories to reflect the key cost components related to treatments, disease management, and monitoring of R/R LBCL. The following cost types were included in the model: drug acquisition and administration costs, disease management costs, AE costs and subsequent treatment costs. These were aligned with previous NICE appraisals in R/R LBCL.[14, 44]

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs were calculated by combining dosing regimens with relative dose intensity adjustments derived from appropriate sources, including the EPCORE™ NHL-1 trial, NICE submissions, and published literature.[3, 67, 90, 98] Table 60 presents the drug dosage-related inputs used in the model.

The drug acquisition costs are presented in Table 60. The drug acquisition costs were sourced from the electronic market information tool (eMIT) where available, and the British National Formulary (BNF) or AbbVie data on file in other instances.[99] For drugs with more than one formulation and prices, the least expensive option was used in the economic evaluation. For axi-cel, the drug acquisition costs are captured as a one-time drug acquisition cost, as treatment with axi-cel only requires one administration (Table 62). For drugs based on body weight or BSA, costs of drug wastage were included.

For costing of R-based CIT, R-GemOx was used as a proxy for all R-based chemotherapies (from SCHOLAR-1);[70] this only influenced the drug acquisition and administration costs. R-GemOx was considered an appropriate proxy for all R-based chemotherapies as UK based clinical and economic experts stated that R-GemOx is an appropriate surrogate during an advisory board (July 2022) organised by AbbVie for this evaluation. R-GemOX represents one of the least costly R-based CIT regimens, thereby making it a conservation option.[100] Furthermore, R-GemOX was identified as a clinically relevant comparator in prior NICE evaluations, ID3795

and TA649, and the drug dosage inputs used align with previous NICE evaluations in DLBCL.[10, 14, 21]

Table 60: Drug dosage inputs applied in the cost-effectiveness model

Treatment	Admin route	Admin frequency	Dose intensity	Vial sharing	Reference
Epcoritamab	SC	Cycle 1: 0.16 mg day 1, 0.8 mg day 8, 48 mg day 15 and 22 Cycle 2 and 3: 48 mg day 1, 8, 15, and 22 Cycle 6-9: 48 mg day 1 and 15 Cycle 10+: 48 mg day 1	[redacted]	No	EPCORE™-NHL 1 CSR[21]
R-based CIT					
Rituximab	IV	375 mg/m^2 day 1 up to 8 cycles	100%	No	Mounier N, et al. 2013
Gemcitabine	IV	1,000 mg/m^2 day 1 up to 8 cycles	100%	No	
Oxaliplatin	IV	100 mg day 1 up to 8 cycles	100%	No	
Axi-cel	IV	One time administration	NA	NA	NICE TA559[3]

Abbreviations: admin: administration; axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; CSR: clinical study report; IV: intravenous; N/A: not applicable; NICE: National Institute for Health and Care Excellence; SC: subcutaneous; TA: technology appraisal.

Table 61: Drug acquisition costs for intervention and comparators

Treatment	Dose	Cost per package	Cost per mg	Reference
Epcoritamab	1 x 4 mg	[redacted] PAS price: [redacted]	[redacted] PAS price: [redacted]	AbbVie data on file
	1 x 48 mg	[redacted] PAS price: [redacted]	[redacted] PAS price: [redacted]	AbbVie data on file
Rituximab	2 x 100 mg	£314.33	£1.57	BNF
	2 x 500 mg	£1,571.67	£1.57	BNF
Axicabtagene ciloleucel[a]	-	-	-	-
Gemcitabine	1 x 200 mg	£3.42	£0.02	eMIT 2022
	1 x 1000 mg	£8.59	£0.01	eMIT 2022
Oxaliplatin	1 x 50 mg	£20.45	£0.41	eMIT 2022
	1 x 200 mg	£60.29	£0.30	eMIT 2022

[a] Drug acquisition costs are captured in the one-time drug acquisition costs instead (Table 62).

Abbreviation: BNF: British National Formulary; eMIT: Electronic market information tool; PAS: patient access scheme.
Source: NICE. BNF. Updated September 2022.

One-time drug acquisition, administration and monitoring costs

One-time treatment-related costs were included in the model whenever applicable; these are provided in Table 62. For R-based CIT, the one-time costs were used to account for the difference in the costs for the first and subsequent administrations (SB13Z and SB15Z from the National Schedule of Reference Costs 2019–2020, respectively).[101]

As treatment with axi-cel only requires one administration, all costs for this treatment were applied as one-time costs. The drug acquisition costs were based on the axi-cel list price. The administration and monitoring costs were based on the costs included in the NICE TA559,[3] which were further inflated to 2021.

Table 62: One-time drug acquisition, administration, or monitoring cost inputs applied in the cost-effectiveness model

Treatment	Drug acquisition	Administration and/or monitoring	Reference
R-based CIT	-	£5,660.02	NICE TA559[3] (axi-cel) inflated to 2021 cost year
Axi-cel	£294,684.42	Administration cost: £37,540.60 Monitoring cost: £1,489.18 Total: £39,029.78[a]	Drug acquisition cost: Yescarta 40million–200million cells/68ml dispersion for infusion bags (Gilead Sciences Ltd). NHS AMP One-time administration cost: NICE TA872[94] One-time monitoring cost: NICE TA559[3], inflated to 2021 cost year[b]

[a] The full one-time administration and monitoring cost sourced from TA872 is £41,101. The cost of CRS has been removed from the administration cost to prevent double counting, as the management of CRS is captured within the one-time administration cost. [b] The one-time monitoring cost accounts for excess bed days which accrue due to the AEs associated with the treatment of axi-cel, in line with TA599.
Abbreviations: AE: adverse event; axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; CRS: cytokine release syndrome; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab; TA: technology appraisal.

The drug administration cost inputs that were applied in the cost-effectiveness model were obtained from the National Schedule of Reference Costs 2019–2020 and are summarised in Table 63.[101]

Table 63: Drug administration cost inputs applied in the cost-effectiveness model

Administration route	Costs	Reference
IV	£358.62	SB15Z (National Schedule of Reference Costs 2019-20) inflated to 2021 cost year[101]
SC	£298.46	SB12Z (National Schedule of Reference Costs 2019-20) inflated to 2021 cost year [101]
Oral	£221.52	SB11Z (National Schedule of Reference Costs 2019-20) inflated to 2021 cost year [101]

Abbreviation: IV: intravenous; SC: subcutaneous.

Subsequent treatment costs

Following progression in the model, patients were assumed to receive subsequent treatments and incur the costs associated with these treatments. In order to align with UK clinical practice, the proportion of patients receiving subsequent treatments and the distribution of subsequent treatments received for all treatment arms was informed by feedback from UK clinical experts based on their experiences and expectations in UK clinical practice.[17]

Table 64 presents the proportion of patients receiving subsequent treatment, and the distribution of subsequent treatments received for each treatment arm in the model. Table 65 presents the costs associated with each subsequent treatment and the time on treatment inputs used. For base case analysis B, the proportions of subsequent treatments used will overestimate costs compared with the benefits observed in the respective trials. As such, this represents a conservative assumption.

Table 64: Proportion of patients receiving subsequent treatments and the distribution of subsequent treatments used in the cost-effectiveness model

Treatment at entry	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	No active treatment
Epcoritamab	52.5%	5%	25%	0.5%	3%	13.5%
R-based CIT	46%	10%	26%	1.5%	1.5%	15%
Axi-cel	52%	0%	32%	1%	5%	10%
Reference	AbbVie. Clinical Expert Interviews[17]					

Abbreviations: allo: allogenic; auto: autologous; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; CSR: clinical study report; NICE: National Institute for Health and Care Excellence; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab; SCT: stem cell transplant.

Table 65: Subsequent treatment cost inputs applied in the cost-effectiveness model

Subsequent treatment	Cost per administration	Number of administrations per model cycle	Mean time on treatment (months)	Reference
R-based CIT	£1,254.99	1.00	8.00	Mounier N, et al. 2013
CAR-T therapy	£332,225.02	1.00	1.00	NICE TA559 and axi-cel list price
Radiotherapy	£3,673.17	10.00	1.00	NICE submission (ID3795)[14]
Autologous SCT	£28,398.07	1.00	1.00	NICE submission (ID3795)[14]
Allogenic SCT	£81,718.44	1.00	1.00	NICE submission (ID3795)[14]

Abbreviations: axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; ID: identification; NICE: National Institute for Health and Care Excellence; R: rituximab; SCT, stem cell transplant; TA: technology appraisal.

B.3.5.2 Health-state unit costs and resource use

Disease management costs

The costs associated with routine monitoring visits and procedures which occur during the treatment pathway of a patient with R/R LBCL were captured under the disease management costs category. An overview of disease-management related resource use by health state, and the associated costs, is provided in Table 66. The disease progression-related resource use and associated costs applied to patients in the PD health state in the cost-effectiveness model are also provided in Table 67. The terminal care-related resource use and associated costs are provided in Table 68.

For patients in the progression-free health state, resource use differed based on whether a patient is on-treatment or off-treatment. As outlined in the SmPC, patients receive epcoritamab continuously until progression or unacceptable toxicity; as such, patients in the epcoritamab arm will always be on-treatment whilst progression-free. However, the resource use of patients receiving epcoritamab is anticipated to decrease over time. In order to reflect the fact that the resource use of patients would decrease whilst still on treatment with epcoritamab, patients in the epcoritamab treatment arm are assumed to switch from the 'PF on-treatment' resource use estimates to the 'PF off-treatment' resource use estimates after [redacted]; this is the median PFS for patients with DLBCL in partial response based on EPCORE™ NHL-1.

The unit costs were sourced from the National Schedule of Reference Costs whenever available or published literature, with costs inflated to 2021.[101] The frequency of resource use in both the PFS and PD health states was taken from NICE TA649, NICE TA559 and NICE TA306, which all used the same recourse use inputs.[3, 44, 62] These resource use inputs were subsequently validated by UK clinical experts who commented that for the PFS off-treatment resource use, GP, oncologist and hospice care should be set to zero, and for diagnostic tests during disease progression, bone marrow biopsies should be set to zero. Further feedback from the clinical experts is explored in scenario analyses.

Table 66: Disease management-related resource use by health state and cost inputs applied in the cost-effectiveness model

Resource	Cost per event		Resource use by health state, per model cycle		
	Value	Reference	PF on-treatment	PF off-treatment	PD
Residential care	£155.00	Jones, K. & Burns, A. (2021)	2.99	0.75	-
Day care	£66.00	Jones, K. & Burns, A. (2021)	1.12	0.28	1.87
Home care	£35.82	NICE TA649[90] [a]	4.67	1.17	9.33
Hospice	£168.86	NICE TA649[90] [a]	0.05	-	0.93
Oncologist	£210.36	WF01A 370 – Medical oncology[a]	1.67	-	0.33
Haematologist	£179.86	WF01A 303 – Clinical haematology[a]	0.78	0.19	1.00
Radiologist	£161.19	WF01A 811 – Interventional Radiology[a]	1.33	0.33	-
Nurse	£45.66	N02AF – District nurse, Adult, face to face[a]	4.00	1.00	-
Palliative care team	£157.13	SD03A – Hospital specialist Palliative care 19 years and over[a]	-	-	1.33
Specialist nurse	£45.66	N02AF – District nurse, Adult, face to face[a]	0.67	0.17	2.50
GP	£33.19	Per patient contact lasting 9.22 minutes, unit costs of Health and Social Care 2021	2.00	-	3.33
District nurse	£45.66	N02AF – District nurse, Adult, face to face[a]	1.50	0.38	4.00
CT scan	£111.11	Average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z[a]	0.31	0.31	0.03
Full blood count	£2.66	DAPS05 – Haematology[a]	3.33	3.33	1.00

LDH	£2.66	DAPS05 – Haematology[a]	2.00	2.00	0.33
Liver function	£2.66	DAPS05 – Haematology[a]	3.33	3.33	1.00
Renal function	£2.66	DAPS05 – Haematology[a]	3.33	3.33	0.33
Immunoglobulin	£2.66	DAPS05 – Haematology[a]	0.67	0.67	0.33
Calcium phosphate	£2.66	DAPS05 – Haematology[a]	0.67	0.67	1.00

[a] Inflated to 2021 cost year
Abbreviations: CT: computerised tomography; GP: general practitioner; LDH: lactate dehydrogenase; N/A: not applicable; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free.

Table 67: Disease progression-related resource use and cost inputs applied in the cost-effectiveness model

Resource	Costs per patient	Reference	Use (% of patients)
ECG	£147.66	RD51A diagnostic imaging outpatient[a]	67%
MUGA	£511.56	RN03A Nuclear medicine outpatient[a]	33%
CT-scan	£111.11	Average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z[a]	17%
MRI	£151.01	RD01A diagnostic imaging outpatient[a]	7%
PET-CT	£511.56	RN03A Nuclear medicine outpatient[a]	57%
Bone marrow biopsy	£624.12	SA33Z day case[a]	0%

[a] Inflated to 2021 cost year
Abbreviations: CT: computed topography; ECG: electrocardiogram; MUGA: multigated acquisition; MRI: magnetic resonance imaging; PET: positron emission tomography.

Table 68: Terminal care-related resource use and cost inputs applied in the cost-effectiveness model

Resource	Costs per patient	Reference	Use (% of patients)
CT-scan	£111.11	Average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z[a]	33%
MRI	£151.01	RD01A diagnostic imaging outpatient[a]	7%

[a] inflated to 2021 cost year
Abbreviations: CT: computed topography; ECG: electrocardiogram; MUGA: multigated acquisition; MRI: magnetic resonance imaging; PET: positron emission tomography.

B.3.5.3 Adverse reaction unit costs and resource use

As outlined in Section B.3.3.5 AE probabilities for each treatment arm were informed by the EPCORE™ NHL-1 trial and published literature. A summary of the AE rates for each treatment and the associated sources is provided in Table 55.

AEs are assumed to occur within the first cycle of the model for patients receiving each treatment. AEs are associated with a one-off cost, as presented in Table 69. In addition, AEs are associated with a decrement to utility, as presented in Section B.3.4.5 (Table 58).

Table 69: AE cost inputs applied in the cost-effectiveness model

Adverse event	Cost per event	SE	Reference
Anaemia	£328.40	£32.84	SA04K day case (National Schedule of Reference Costs 2019–20)[101] [a]
B-cell aplasia	£2,600.02	£260.00	NICE TA559[3] [a]
CRS	£3,560.40	£356.04	XC01Z critical care (National Schedule of Reference Costs 2019–20) and XD31Z from NHS 2015–16 costs
Febrile neutropenia	£1,884.72	£188.47	NICE TA306[a]
Hypokalaemia	£1,456.44	£145.64	NICE ID3795[14]
ICAN	£3,560.40	£356.04	Assumed the same as CRS
Leukopenia	£476.74	£47.67	WH07F day case (National Schedule of Reference Costs 2019–20)[a]
Lymphopenia	£1,533.37	£153.34	NICE ID3795[14]
Neutropenia	£384.55	£38.46	SA35C day case (National Schedule of Reference Costs 2019–20)[a]
Neutrophil count decreased	£384.55	£38.46	Assumed the same as neutropenia
Pneumonia	£904.16	£90.42	DZ11S non-elective short stay (National Schedule of Reference Costs 2019–20)[a]
Rash	£384.55	£38.46	Assumed the same as neutropenia
Thrombocytopenia	£381.86	£38.19	SA12K day case (National Schedule of Reference Costs 2019–20)[a]

[a] Inflated to 2021 cost year
Abbreviations: AE: adverse event; CRS: cytokine release syndrome; ICAN: immune effector cell-associated neurotoxicity syndrome; ID: identification; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

B.3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous unit costs and resource use were included in the model. Therefore, this section is not relevant to this submission.

B.3.6 *Severity*

The expected quality-adjusted life expectancy for the general population was calculated in line with the methods provided by Schneider *et al.* (2022).[102] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2017–2019.[95] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernandez Alava et al. (2022) through the NICE DSU.[103]

The total QALYs for the current UK population of patients with R/R LBCL following two or more prior lines of therapy was considered separately for the two base case populations. For patients who are ineligible for, or choose not to receive, intensive therapy, the total QALYs was set equal to the QALYs associated with R-based CIT in the base case economic analysis population A. For patients who are eligible for intensive therapy, the total QALYs was set equal to the QALYs associated with axi-cel in the base case economic analysis population B.

Based on the QALY shortfall analysis summarised across Table 70–Table 72, the proportional QALY shortfall for base case population A meets the threshold for applying a severity modifier of 1.2 to the incremental QALYs. As such, this modifier is applied in the base case results for analyses considering the population of patients who are ineligible for, and choose not to receive, intensive therapy.

Table 70: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)		Reference to section in submission
	Base case population A	Base case population B	
Sex distribution (% female)	[redacted]	[redacted]	Table 39, Section B.3.2.1
Starting age	[redacted]	[redacted]	Table 39, Section B.3.2.1

Abbreviations: QALY: quality-adjusted life year.

Table 71: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (SE)	Undiscounted life years	
		Base case population A	Base case population B
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year; SE: standard error.

Table 72: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Base case population A: ineligible for, or choose not to receive, intensive therapy			
[redacted]	1.06	[redacted]	90.86%
Base case population B: eligible for intensive therapy			
[redacted]	4.41	[redacted]	60.87%

Abbreviations: QALY: quality-adjusted life year

B.3.7 *Uncertainty*

LBCL is a heterogenous disease that is comprised of numerous subtypes, some of which are rare subtypes, such as PMBCL. As a result, it was not feasible to conduct subgroup analyses using data on each of the individual subtypes of LBCL (expect for DLBCL) due to the small sample sizes from the EPCORE™ NHL-1 trial. To reduce heterogeneity with data from the comparator trials, the economic analysis in this submission is presented using data on the DLBCL population from the EPCORE™ NHL-1 trial.

This represents a source of uncertainty in this appraisal that is inherent to this disease area; however, data from the DLBCL population of EPCORE™ NHL-1 can be considered to represent a suitable proxy for the overall LBCL population and, as discussed in Section B.1.3, the subtypes of LBCL are similar in their disease course and treatment pathway. While small patient numbers make interpretation challenging, visual inspection of the subgroup KM outcomes indicate these are comparable irrespective of the population (DLBCL, LBCL or other subgroup), which is also supported by response data; the data from EPCORE™ NHL-1 demonstrate that the outcomes for the overall LBCL cohort are highly similar to those for patients with DLBCL and other subtypes (Section B.2.6 and Appendix M). As such, this is not expected to be a significant source of uncertainty in this economic analysis, and considering the higher unmet need and innovative potential of epcoritamab in the wider LBCL population, should not represent a barrier to approval.

B.3.8 *Managed access proposal*

Epcoritamab data available at the time of submission, and therefore presented within this dossier are sourced from the [redacted] data cut-off of the Phase 2 EPCORE™ NHL-1 trial and indirectly compared to current NHS standard of care. These data are anticipated to provide sufficient evidence for the clinical and cost-effectiveness of epcoritamab as a treatment for R/R LBCL following two or more systemic therapies to support the single technology appraisal.

As per the protocol for EPCORE™ NHL-1, additional data cuts will continue to be conducted; therefore, [redacted]. Furthermore, EPCORE™ DLBCL-1 is an ongoing, Phase 3, randomised, open-label trial of epcoritamab versus Investigator's choice chemotherapy in patients with R/R DLBCL. [redacted].

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

A summary of the base case model inputs and settings are presented in Table 73.

Table 73: Summary of variables applied in the economic model

Variable	Value		Measurement of uncertainty and distribution	Reference to section in submission
Model settings				
Discount rate, %	3.5%		NA	Section B.3.2.2
Time horizon	45 years			
Perspective	NHS/PPS			
Cycle length	28 days			
Clinical parameters				
OS extrapolation	Base case analysis A: generalised gamma Base case analysis B: generalised gamma		Varied in scenario analyses	Section B.3.3.3 Section B.3.3.4
PFS extrapolation	Base case analysis A: generalised gamma Base case analysis B: Log-normal			
TTD extrapolation	Base case analysis A: generalised gamma Base case analysis B: Log-logistic			
Utility inputs				
PFS	[redacted]		Beta	Section B.3.4.1
PD	[redacted]			Section B.3.4.1
PFS after 24 months	[redacted]			Section B.3.2.2
Cost parameters				
Drug acquisition costs				
Epcoritamab	1 x 4 mg	[redacted]	N/A	Section B.3.5.1
		PAS price: [redacted]		
	1 x 48 mg	[redacted]		
		PAS price: [redacted]		
Rituximab	2 x 100 mg	£314.33		
	2 x 500 mg	£1,571.67		
Gemcitabine	1 x 200 mg	£3.42		
	1 x 1000 mg	£8.59		
Oxalipatin	1 x 50 mg	£20.45		
	1 x 200 mg	£60.29		
Axi-cel	£280,451.00			
Heath state resource use				
Residential care	£155.00		Gamma	

Day care	£66.00		Section B.3.5.2
Home care	£35.82		
Hospice	£168.86		
Oncologist	£210.36		
Haematologist	£179.86		
Radiologist	£161.19		
Nurse	£45.66		
Palliative care team	£157.13		
Specialist nurse	£45.66		
GP	£33.19		
District nurse	£45.66		
CT scan	£111.11		
Full blood count	£2.66		
LDH	£2.66		
Liver function	£2.66		
Renal function	£2.66		
Immunoglobulin	£2.66		
Calcium phosphate	£2.66		
Disease progression-related resource use			
ECG	£147.66	Gamma	Section B.3.5.2
MUGA	£511.56		
CT-scan	£111.11		
MRI	£151.01		
PET-CT	£511.56		
Bone marrow biopsy	£624.12		
Terminal care-related resource use			
CT-scan	£111.11	Gamma	Section B.3.5.2
MRI	£151.01		
Subsequent treatments			
R-based CIT	£1,254.99	Beta	Section B.3.5.1
CAR-T therapy	£332,225.02		
Radiotherapy	£3,673.17		
Autologous SCT	£28,398.07		
Allogenic SCT	£81,718.44		
Adverse Events			
AEs	Grade III/IV AEs and unit costs were included based on prior NICE appraisals in R/R LBCL. Where relevant, unit costs were also sourced from the National Schedule of NHS Costs 2019/20[a]	Beta	Section B.3.5.3

Abbreviations: AE: adverse events; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CT: computed topography; ECG: electrocardiogram; GP: General Practitioner; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; MUGA: multigated acquisition; N/A: not applicable; NHS: National Health Service; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PET: positron emission tomography; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy; SCT: stem cell treatment; TTD: time to treatment discontinuation..

B.3.9.2 Assumptions

The key assumptions adopted in the base case of the cost-effectiveness model are presented in Table 74.

Table 74: Key model assumptions for the base case cost-effectiveness analysis

Category	Assumption in the base case	Justification	Addressed in scenario analysis
Survival models			
PFS curves	Base case analysis A: Generalised gamma Base case analysis B: Log-normal	As outlined in Section B.3.3.3, IPD from EPCORE™ NHL-1 were used to extrapolate long-term PFS outcomes. EPCORE™ NHL-1 provides direct clinical evidence for the efficacy of epcoritamab in the population of interest in this submission. The selection of extrapolation for PFS was based on statistical fit, visual inspection and long-term clinical plausibility, as validated by UK clinical experts.	Scenario analyses have been conducted for both populations in which the Gompertz extrapolation was selected to model PFS for epcoritamab.
OS curves	Base case analysis A: Generalised gamma Base case analysis B: Generalised gamma	As outlined in Section B.3.3.3, IPD from EPCORE™ NHL-1 were used to extrapolate long-term OS outcomes. EPCORE™ NHL-1 provides direct clinical evidence for the efficacy of epcoritamab in the population of interest in this submission. The selection of extrapolation for OS was based on statistical fit, visual inspection and long-term clinical plausibility, as validated by UK clinical experts.	Scenario analyses have been conducted for both populations in which the log-normal extrapolation was selected to model OS for epcoritamab. For case base analysis B, an additional scenario analysis has been conducted in which the log-logistic extrapolation was selected to model OS for epcoritamab.
	Patients in long-term remission after 24 months have an increased relative risk of mortality when compared	As outlined in Section B.3.2.2 patients remaining in the PFS health state after 24 months are considered survivors with long-term remission. However, these patients have	No scenario analyses have been conducted varying this assumption.

Category	Assumption in the base case	Justification	Addressed in scenario analysis
	with the general population (standardised mortality ratio of 1.41)	an increased relative risk of mortality when compared with the general population due to long-term complications associated with cancer and cancer treatment (standardised mortality ratio of 1.41 based on a recent US study accepted by the EAG in TA649).[90] For patients who progressed prior to 24 months, their mortality rate is continued to be informed by the OS curve.	
ToT curves	Base case analysis A: Generalised gamma Base case analysis B: Log-logistic	As outlined in Section B.3.3.3, IPD from EPCORE™ NHL-1 were used to extrapolate ToT. EPCORE™ NHL-1 provides direct clinical evidence for epcoritamab in the population of interest in this submission. The selection of extrapolation for ToT was based on statistical fit, visual inspection and long-term clinical plausibility and based on UK clinical experts feedback.	No scenario analyses have been conducted in which the extrapolation for epcoritamab ToT is varied. This is because other parametric models produced results that were inconsistent with clinical feedback and demonstrate poor visual fit to the observed trial data.
	ToT for R-based CIT in base case analysis A is assumed to be equal to PFS	Feedback from UK clinicians stated that patients would primarily discontinue treatment with R-based CIT upon progression. As such, ToT for R-based CIT is assumed to be equal to PFS.	No scenario analyses have been conducted varying the ToT for R-based CIT in base case analysis A.
Indirect treatment comparison			
Comparative efficacy estimates	**Base case analysis A:** Comparative efficacy estimates are based on the DLBCL, no prior CAR-T population from EPCORE™ NHL-1, adjusted to Sehn *et al.* 3L+ and matched to SCHOLAR-1	The DLBCL, no prior CAR-T population ([redacted]) from EPCORE™ NHL-1 was selected for inclusion in the ITCs following feedback from UK clinical experts, to reduce heterogeneity between the epcoritamab population and the Sehn *et al.* 3L+ population.	No scenario analyses have been conducted varying the epcoritamab population used to inform comparative efficacy estimates for base case analysis A.

Category	Assumption in the base case	Justification	Addressed in scenario analysis
		Supportive ITCs were conducted for the comparison of epcoritamab versus Pola + BR in which the overall LBCL population from EPCORE™ NHL-1 was used as the source of efficacy data for epcoritamab.	
	Base case analysis B: Comparative efficacy estimates are based on the DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 unadjusted to match ZUMA-1	The DLBCL, no prior CAR-T, CAR-T eligible population ([redacted]) from EPCORE™ NHL-1 was selected to reduce heterogeneity between the epcoritamab population and the axi-cel population. A supportive ITC was conducted in which the LBCL population from EPCORE™ NHL-1 was used as the source of efficacy data for epcoritamab in the ITC.	A scenario analysis has been conducted in which the comparative efficacy estimates are informed by the MAIC in which the LBCL, no prior CAR-T, CAR-T eligible population ([redacted]) from EPCORE™ NHL-1 is used
PFS HR for R-based CIT	The PFS HR for R-based CIT is assumed equal to the derived OS HR for R-based CIT.	No PFS KM data are reported in SCHOLAR-1, so it was not possible to derive a PFS HR for R-based CIT using the MAIC methodology. As such, the PFS HR was assumed to be equal to the derived OS HR; this is aligned with one of the approaches taken in TA559 and was validated as an appropriate assumption by UK clinical experts during the clinical validation interviews.[3]	No scenario analyses have been conducted varying this assumption.
Costs			
Drug acquisition cost	Costs of drug wastage were included for drugs dosed based on body weight or BSA.	This is a common approach for intravenously administered products that are dosed based on body weight or BSA.	No scenario analyses have been conducted varying this assumption as vial sharing is not conducted in UK clinical practice.
Drug acquisition cost	For costing purpose, R-GemOx was assumed to be	UK based clinicians stated that R-GemOx is an appropriate surrogate for all R-based CIT during an advisory board (July 2022) and R-	No scenario analyses have been conducted varying this assumption as R-GemOx is

Category	Assumption in the base case	Justification	Addressed in scenario analysis
	representative of R-based CIT (from SCHOLAR-1).	GemOX represents one of the least costly R-based CIT regimens, thereby making it a conservation option.[100] Furthermore, R-GemOX was identified as a clinically relevant comparator in ID3795 and TA649.[14, 21]	considered to be the most appropriate surrogate for all R-based CIT.
Axi-cel administration cost	The costs associated with administration of axi-cel therapy are aligned with TA872.	In line with TA872, a one-off administration cost for axi-cel of £41,101 has been included. This one-off administration cost is assumed to include axi-cel leukapheresis costs, hospitalisation costs for conditional chemotherapy, weighted average cost of CRS, hospitalisation costs for axi-cel administration, axi-cel costs for weighted average cost of alloSCT, training costs, medical resource use costs for the first 100 days, hypogammaglobulinemia costs for the first 100 days	A scenario analysis has been conducted in which the one-off administration cost for axi-cel is £65,415, in line with the original tariff suggested by NHS England in TA872.
Durable Remission	Patients in the progression-free health state after 24 months are considered to be in long-term remission and are assumed to use no healthcare resources after 24 months.	This approach was adopted based on feedback from UK clinical experts and in line with prior NICE appraisals in R/R LBCL.[3, 17, 63, 90] This is further supported by data from EPCORE™ NHL-1 on the PFS for patients in CR	No scenario analyses have been conducted varying this assumption as this is line with previous NICE appraisals in R/R LBCL.
Utility values			
Utility values	Utility values were sourced from EPCORE™ NHL-1, using the LLM model.	EQ-5D-3L data were collected in EPCORE™ NHL-1 and utility values derived from these data were deemed to be the most appropriate for inclusion in the cost-effectiveness model, in line with the NICE reference case.	Scenario analyses have been conducted using alternative utility values identified in the published literature, such as those from ZUMA-1 which were used in TA559, TA649 and ID3795.
Durable Remission	Patients in the progression-free health state after 24	This approach was adopted based on feedback from UK clinical experts and in line	A scenario analysis was conducted to explore this assumption in which patients that are alive

Category	Assumption in the base case	Justification	Addressed in scenario analysis
	months are considered to be in long-term remission. The utility for these patients is informed by the PFS utility value based on EPCORE™ NHL-1 ([redacted])	with prior NICE appraisals in R/R LBCL.[3, 17, 63, 90] This is further supported by data from EPCORE™ NHL-1 on the PFS for patients in CR	and progression-free after 24 months are assigned a health state utility value that is 5% higher than the base case value ([redacted]). These patients are assumed to be complete responders
Age-related disutility	Utility values used in the cost-effectiveness model were age-adjusted based on published decrements from the study by Ara and Brazier.[97]	This approach was adopted to account for the deterioration in HRQoL associated with ageing. This approach is consistent with recommendations by NICE DSU TSD 12.[96]	No scenario analyses have been conducted varying this assumption.
Subsequent treatments			
Subsequent treatments	The proportion of patients receiving subsequent treatments and the distribution of subsequent treatments received were informed by estimates from UK clinical experts.	Data on subsequent treatments were collected in EPCORE™ NHL-1, however, these data were not deemed appropriate to inform the subsequent treatments in the model, based on applicability to UK clinical practice and feedback from UK clinical experts. Estimates from UK clinical experts represent the most appropriate source to inform the distribution of subsequent treatments received in all treatment arms. The subsequent treatment proportions used in the base case were an average of the estimates provided by all clinicians during clinical validation interviews.	During the clinical validation interviews, two clinical experts provided estimates for the proportion of patients receiving each subsequent treatment which were broadly aligned. However, one clinician provided estimates that were considerably different. As such, scenario analyses have been conducted using an average of the first two clinicians' estimates and a second scenario analysis has been conducted using the third clinicians estimates.
AEs			
Adverse event proportions	TEAEs of grade 3 or above that occurred in ≥5% of the patients in any of the studies (either EPCORE™ NHL-1 or	This is consistent with the approach commonly adopted in oncology economic models and prior NICE appraisals.[3, 14, 63, 90]	No scenario analyses varying this assumption have been conducted.

Category	Assumption in the base case	Justification	Addressed in scenario analysis
	the relevant comparator trials) were included in the cost-effectiveness model. Grade 1 or 2 AEs were also considered if those AEs are expected to lead to hospitalisation, costly treatments or substantial impact on health state utility values.		
Adverse event disutility	Total QALY losses associated with AEs were applied during the first model cycle.	This is consistent with the approach taken in TA559, as AEs associated with treatment are likely to occur in the short-term following administration.[3]	No scenario analyses have been conducted varying this assumption.

Abbreviations: axi-cel: axicabtagene ciloleucel; BSA: body surface area; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; CR: complete response; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; EAG: External Assessment Group; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; HR: hazard ratio; HRQoL: health-related quality of life; HTA: health technology appraisal; ID: identification; ITC: indirect treatment comparison; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; LLM: linear mixed models; MAIC: matching adjusted indirect comparisons; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; QALY: quality-adjusted life year; R: rituximab; R/R: relapsed and/or refractory; TA: technology appraisal; TEAE: treatment-emergent adverse events; ToT: time on treatment; UK: United Kingdom; US: United States; 3L+: third-line and beyond..

B.3.10 *Base-case results*

B.3.10.1 Base-case cost-effectiveness analysis results

Probabilistic base-case results

Base case analysis A: Patients ineligible for, or chose not to receive, intensive therapies

As outlined in Section B.3.6, the shortfall for base case population A meets the threshold for applying a severity modifier of 1.2 to the incremental QALYs. As such, this modifier is applied in the base case results for analyses considering the population of patients who are ineligible for, and choose not to receive, intensive therapy. Results of the base case analysis A without a severity modifier applied, and subsequently with the 1.2 severity modifier applied to the QALYs, are presented in the following sections.

No severity modifier

For patients ineligible for, or choose not to receive, intensive therapies, the results of the probabilistic fully incremental analysis are presented in Table 75 (at epcoritamab PAS price) and Table 76 (at epcoritamab list price). The probabilistic net health benefit (NHB) associated with epcoritamab is presented in Table 77 (at epcoritamab PAS price) and Table 78 (at epcoritamab list price). The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Table 75: Base-case probabilistic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£89,183 (£70,675, £128,089)	[redacted]	1.325 (0.772, 2.591)	[redacted]	[redacted]	[redacted]	£29,618

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 76: Base-case probabilistic results (no severity modifier; epcoritamab list price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£88,618 (£71,532, £121,108)	[redacted]	1.296 (0.770, 2.389)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; R: rituximab; QALYs: quality-adjusted life years.

Table 77: Net health benefit (probabilistic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£89,183	1.325	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 78: Net health benefit (probabilistic; no severity modifier; at epcoritamab list price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£88,618	1.296	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Severity modifier applied

Equivalent probabilistic and deterministic results cost-effectiveness results and NHB are presented in Table 79–Table 82. Deterministic base case results with the severity modifier applied are presented in Appendix J.

Table 79: Base-case probabilistic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£89,183 (£70,675, £128,089)	[redacted]	1.325 (0.772, 2.591)	[redacted]	[redacted]	[redacted]	£24,682

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 80: Base-case probabilistic results (epcoritamab list price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£88,618 (£71,532, £121,108)	[redacted]	1.296 (0.770, 2.389)	[redacted]	[redacted]	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; R: rituximab; QALYs: quality-adjusted life years.

Table 81: Net health benefit (probabilistic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£89,183	1.325	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 82: Net health benefit (probabilistic; at epcoritamab list price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£88,618	1.296	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Base case analysis B: Patients eligible for intensive therapies

For patients eligible for intensive therapies, the results of the probabilistic analysis are presented in Table 83 (at epcoritamab PAS price) and Table 84 (at epcoritamab list price). The probabilistic net health benefit (NHB) associated with epcoritamab is presented in Table 85 (at epcoritamab PAS price) and Table 86 (at epcoritamab list price). The PSA was run for 1000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Table 83: Base-case probabilistic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£391,116 (£352,792, £453,905)	[redacted]	3.442 (0.717, 5.466)	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 84: Base-case probabilistic results (epcoritamab list price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£393,502 (£351,674, £458,333)	[redacted]	3.490 (0.658, 5.620)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 85: Net health benefit (probabilistic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
Axi-cel	£391,116	3.442	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 86: Net health benefit (probabilistic; at epcoritamab list price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
Axi-cel	£393,502	3.490	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; QALYs: quality-adjusted life years; NHB: net health benefit. .

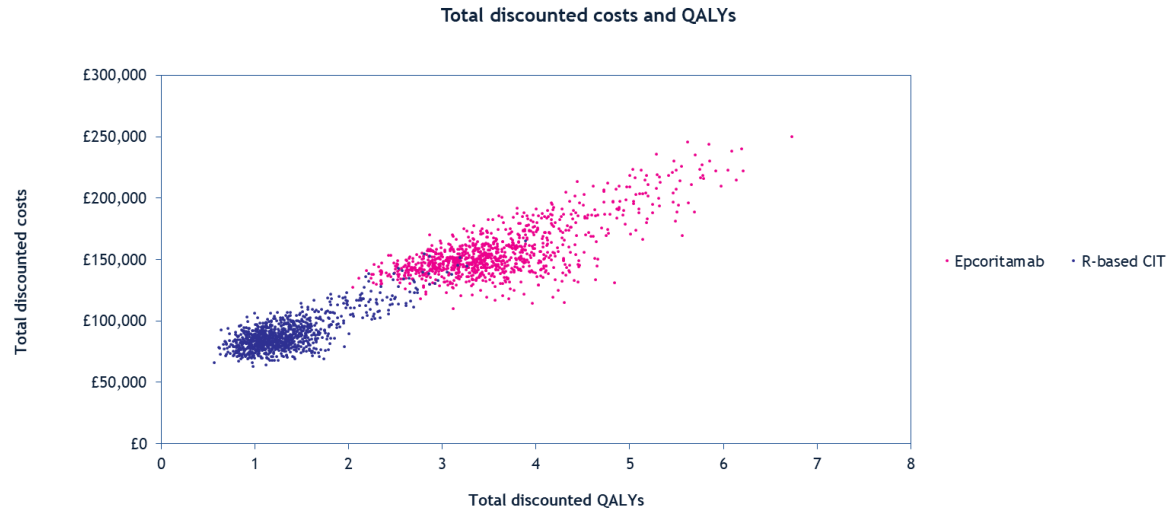
B.3.11 *Exploring uncertainty*

B.3.11.1 Probabilistic sensitivity analysis

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for epcoritamab versus R-based CIT for patients who are ineligible for, or choose not to receive, intensive therapies are presented in Figure 30 and Figure 31, respectively. The equivalent figures for epcoritamab versus axi-cel for patients eligible for intensive therapies are presented in Figure 32 and Figure 33.

Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

Figure 30: Cost-effectiveness scatter plot for epcoritamab versus R-based CIT (epcoritamab PAS price)



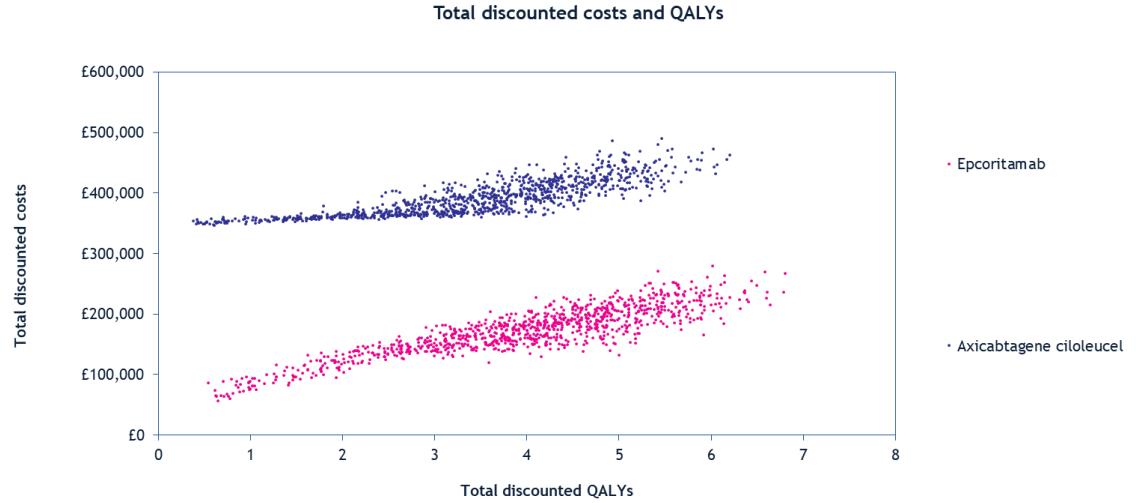
Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

Figure 31: Cost-effectiveness acceptability curve for epcoritamab versus R-based CIT (epcoritamab PAS price)

Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

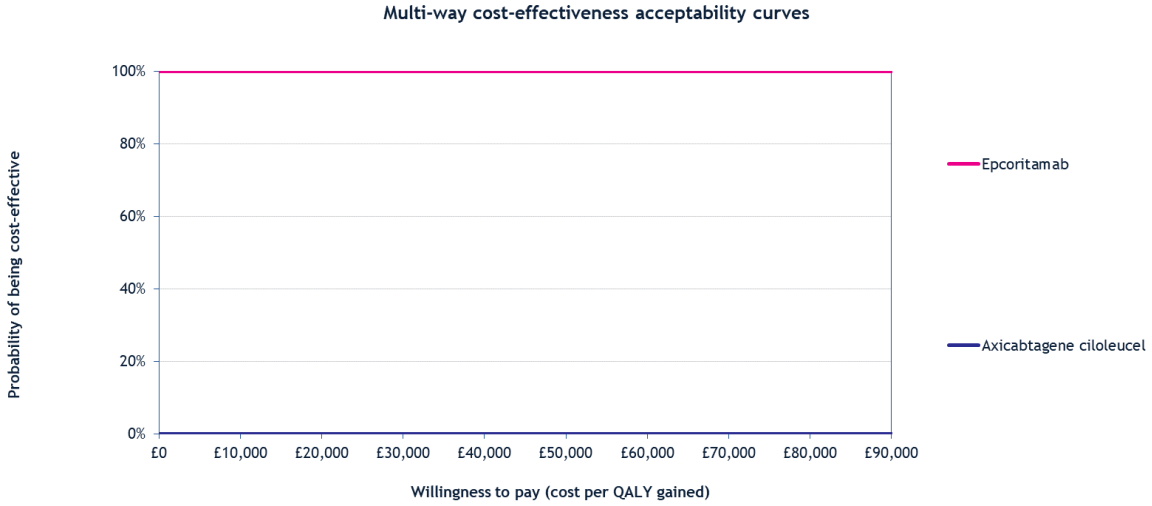
Base case analysis B: Patients eligible for intensive therapies

Figure 32: Cost-effectiveness scatter plot for epcoritamab versus axi-cel (epcoritamab PAS price)



Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 33: Cost-effectiveness acceptability curve for epcoritamab versus axi-cel (epcoritamab PAS price)



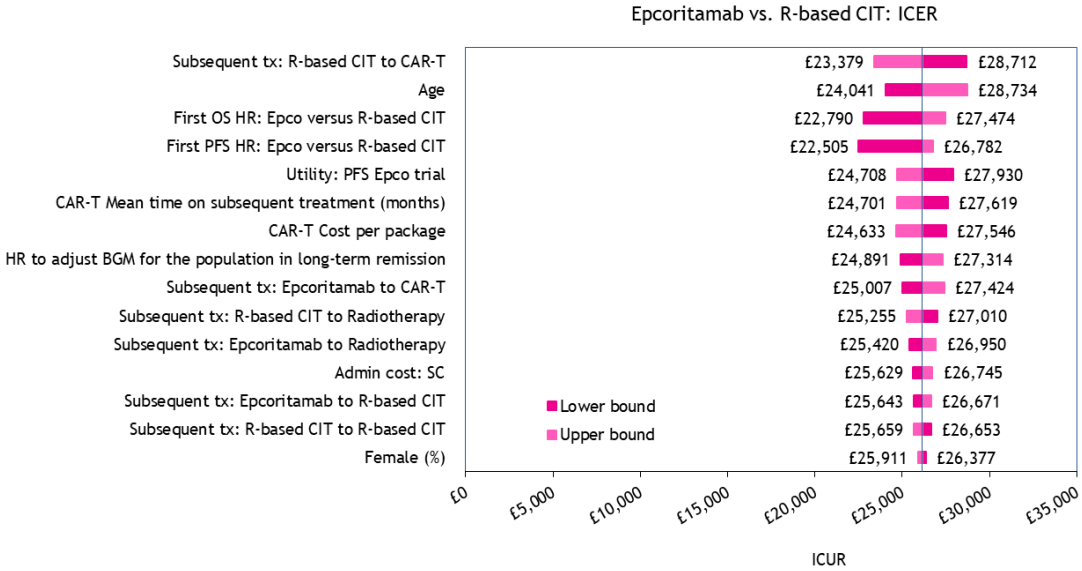
Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

B.3.11.2 Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis (DSA) was conducted. Where available, each parameter was varied by 95% CIs. For parameters where CIs were not available the input was varied by ±10% of their mean value.

Patients ineligible for, or choose not to receive, intensive therapies

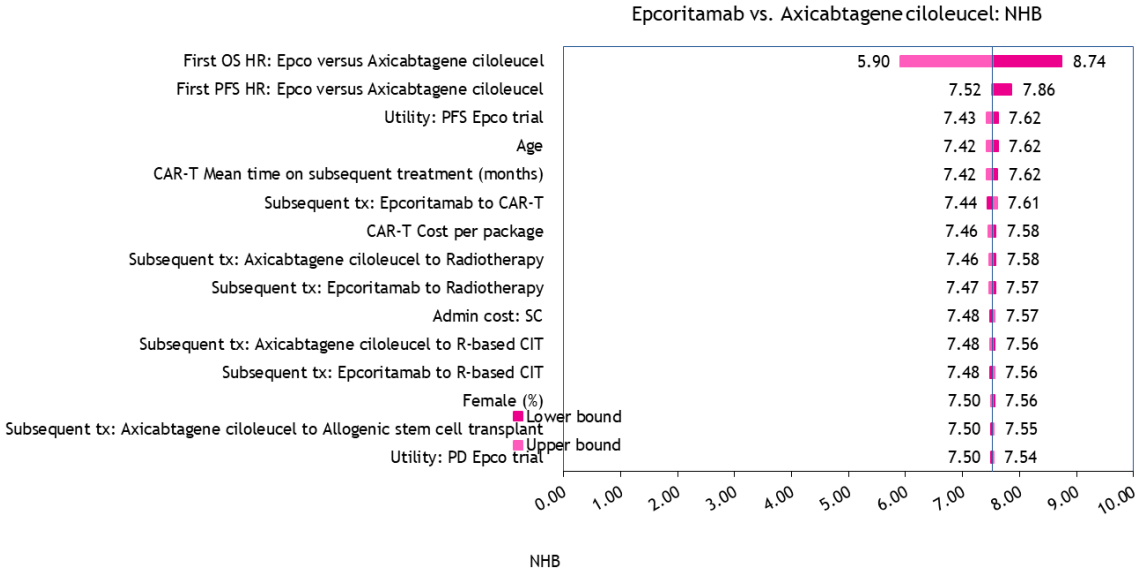
Figure 34: DSA tornado plot for epcoritamab versus R-based CIT (epcoritamab PAS price)



Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

Patients eligible for intensive therapies

Figure 35: DSA tornado plot for epcoritamab versus axi-cel (epcoritamab PAS price)



Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; DSA: deterministic sensitivity analysis; epco: epcoritamab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy; SC: subcutaneous.

B.3.11.3 Scenario analysis

In addition to the DSA, a number of scenario analyses were conducted to explore the impact of certain assumptions and alternative inputs on the results of the economic analysis. Each scenario analysis is described in turn below and full results of the scenario analyses are presented in Table 89.

Patients ineligible for, or choose not to receive, intensive therapy (base case analysis A)

Details regarding scenario analyses conducted in which Pola + BR is considered as a comparator are presented in Appendix P.

PFS extrapolation

- Base case: The generalised gamma extrapolation was used to model PFS
    - Scenario analysis: The Gompertz extrapolation was used to model PFS

OS extrapolation

- Base case: The generalised gamma extrapolation was used to model OS
    - Scenario analysis: The log-normal extrapolation was used to model OS

Patients eligible for intensive therapy (base case analysis B)

Scenario analysis B.1: Pairwise comparison of epcoritamab versus axi-cel, based on ZUMA-1 (LBCL population, no prior CAR-T, CAR-T eligible, unadjusted)

In the ITC informing base case analysis B, the DLBCL population from EPCORE™ NHL-1 was selected for inclusion in the ITC. As outlined in Section B.1.3, data on DLBCL are expected to be generalisable to all LBCL subtypes, and this is supported by data from EPCORE™ NHL-1. However, to explore any uncertainty associated with this assumption, a scenario analysis in which the LBCL population from EPCORE™ NHL-1 was included in the ITC informing the comparative efficacy estimates was conducted. The resulting HRs were used to estimate the time-to-event outcomes for axi-cel. The HRs used in this scenario analysis are presented in Table 87. In this scenario analysis, utility values based on data from the LBCL population of EPCORE™ NHL-1 were used for consistency with the efficacy data.

Table 87: Scenario analysis B.1– HRs applied to the epcoritamab curves to derive the time-to-event outcomes for axi-cel

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
Source of comparator efficacy	ZUMA-1[71]

Abbreviations: axi-cel: axicabtagene ciloleucel; CI: confidence interval; OS: overall survival; PFS: progression-free survival.

PFS extrapolation

- Base case: The log-normal extrapolation was used to model PFS
    - Scenario analysis: The Gompertz extrapolation was used to model PFS

OS extrapolation

- Base case: The generalised gamma extrapolation was used to model OS
    - Scenario analysis: The log-normal extrapolation was used to model OS
    - Scenario analysis: The log-logistic extrapolation was used to model OS

Additional scenario analyses (base case analysis A and base case analysis B)

Health state utility values

- Base case: Utility values sourced from EPCORE™ NHL-1, using the LLM model, were used
    - Scenario analysis: Utility values based on ZUMA-1 are used
- Base case: Patients in the progression-free health state after 24 months are assigned the PFS utility value derived from EPCORE™ NHL-1 ([redacted])
    - Scenario analysis: Patients in the progression-free health state after 24 months are assigned a health state utility value that is 5% higher than the base case value ([redacted]

Axi-cel administration cost

- Base case: The costs associated with administration of axi-cel are aligned with those accepted by the EAG in TA872 (£41,101)
    - Scenario analysis: The costs associated with administration of axi-cel are based on the initial tariff suggested by NHS England in TA872 (£65,415)

Resource use - PD

Resource use in the PD health state in the base case is informed by previous NICE appraisals in R/R LBCL.[44, 62] Scenario analyses were conducted in which additional feedback from UK clinical experts were considered.[17] The resource use estimates applied in this scenario analysis are presented in Table 88.

Table 88: Resource use estimates applied to the PD health state based on previous NICE appraisals in R/R LBCL and clinical expert feedback

Resource use category	Resource use for PD health state, per model cycle		Source for scenario analysis
	Base case	Scenario	
Day care	1.87	1.25	NICE TA306 and Clinical Expert Opinion
Home care	9.33	9.33	NICE TA306
Hospice	0.93	0.93	NICE TA306
Oncologist	0.33	0.22	NICE TA306 and Clinical Expert Opinion
Haematologist	1.00	0.66	NICE TA306 and Clinical Expert Opinion
Palliative care team	1.33	1.33	NICE TA306
Specialist nurse	2.50	2.50	NICE TA306
GP	3.33	3.11	NICE TA306 and Clinical Expert Opinion
District nurse	4.00	2.67	NICE TA306 and Clinical Expert Opinion
CT scan	0.03	0.03	NICE TA306

Full blood count	1.00	0.66	NICE TA306 and Clinical Expert Opinion
LDH	0.33	0.33	NICE TA306
Liver function	1.00	1.00	NICE TA306
Renal function	0.33	0.55	NICE TA306
Immunoglobulin	0.33	0.31	NICE TA306 and Clinical Expert Opinion
Calcium phosphate	1.00	0.93	NICE TA306 and Clinical Expert Opinion

Abbreviations: CT: computed topography; GP: general practitioner; LDH: lactate dehydrogenase; NICE: National Institute for Health and Care Excellence; PD: progressed disease; TA: technology appraisal.

Resource use – diagnostic tests

- Base case: 57% of patients receive a PET-CT scan, based on previous NICE appraisals in R/R LBCL[44, 62]
    - Scenario analysis: 100% of patients receive a PET-CT scan, based on feedback from UK clinical experts[17]

Scenario analyses results

The results of all scenario analyses at epcoritamab PAS price are presented in Table 89. The results of the scenario analyses demonstrate that there is minimal uncertainty that epcoritamab is a cost-effective use of NHS resources when compared to axi-cel and R-based CIT. For the comparison of epcoritamab and axi-cel, epcoritamab is associated with cost-savings in all scenario analyses conducted.

Table 89: Scenario analyses results (epcoritamab PAS price)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A vs CIT			[redacted]	[redacted]	£24,682	[redacted]	[redacted]
PFS extrapolation	Generalised gamma	Gompertz	[redacted]	[redacted]	£25,268	[redacted]	[redacted]
OS extrapolation	Generalised gamma	Log-normal	[redacted]	[redacted]	£24,793	[redacted]	[redacted]
Health state utility values	Derived from EPCORE™ NHL-1	Derived from ZUMA-1	[redacted]	[redacted]	£25,164	[redacted]	[redacted]
	Utility value for patients in the PFS health state after 24 months is equal to the PFS utility value from EPCORE™ NHL-1	Utility value for patients in the PFS health state after 24 months is 5% higher than the PFS utility value from EPCORE™ NHL-1	[redacted]	[redacted]	£23,645	[redacted]	[redacted]
Axi-cel administration cost	Aligned with those accepted in TA872	Aligned with the original tariff suggested by NHS England in TA872	[redacted]	[redacted]	£24,170	[redacted]	[redacted]
Resource use – PD	Resource use based on previous NICE appraisals	Resource use based on previous NICE appraisals and feedback from UK clinical experts	[redacted]	[redacted]	£24,413	[redacted]	[redacted]
Resource use – diagnostic tests	57% of patients receive PET-CT	100% of patients receive PET-CT	[redacted]	[redacted]	£24,576	[redacted]	[redacted]
Base case population B vs Axicel			[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis B.1	Efficacy data from DLBCL, no prior CAR-T, CAR-T eligible population	Efficacy data from LBCL, no prior CAR-T, CAR-T eligible population	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
PFS extrapolation	Log-normal	Gompertz	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
OS extrapolation	Generalised gamma	Log-normal	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
Health state utility values	Derived from EPCORE™ NHL-1	Derived from ZUMA-1	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
	Utility value for patients in the PFS health state after 24 months is equal to the PFS utility value from EPCORE™ NHL-1	Utility value for patients in the PFS health state after 24 months is 5% higher than the PFS utility value from EPCORE™ NHL-1	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
Axi-cel administration cost	Aligned with those accepted in TA872	Aligned with the original tariff suggested by NHS England in TA872	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
Resource use – PD	Resource use based on previous NICE appraisals	Resource use based on previous NICE appraisals and feedback from UK clinical experts	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Resource use – diagnostic tests	57% of patients receive PET-CT	100% of patients receive PET-CT	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: AE: adverse event; axi-cel: axicabtagene ciloleucel; CT: computed topography; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; NHB: net health benefit; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PET: positron emission tomography; PFS: progression-free survival; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy; TA: technology appraisal.

B.3.12 *Subgroup analysis*

No economic subgroup analyses were conducted as part of this appraisal.

B.3.13 *Benefits not captured in the QALY calculation*

As mentioned in Section B.1.3.3, epcoritamab is the first and only SC bispecific antibody for the treatment of R/R LBCL in adult patients after two or more lines of systemic therapy. The SC administration enables quick administration across different practice settings, and greater flexibility and convenience for both clinicians and patients. Whilst the cost-savings associated with SC administration compared to IV administration will be captured in the economic analyses, the benefits of greater flexibility and convenience for patients, as well as the reduced capacity burden for the NHS and opportunity to optimise infrastructure with reduced numbers of IV infusions, will not be captured in the analysis.

Feedback from UK clinical experts highlighted that the introduction of epcoritamab would enhance equity in accessing effective treatments for R/R LBCL.[17] Currently, there is regional variation in access to CAR-T therapies, due to a limited number of CAR-T centres and apheresis slots, which results in some patients being unable to access treatment with CAR-T therapies. As access to epcoritamab would not be constrained by factors such as the number of centres of requirement for apheresis, the introduction of epcoritamab would help to resolve this inequity in access to effective treatments. The benefits associated with decreased inequity itself and the positive impact of this on patients and their families will not be included in the QALY calculation.

Furthermore, the potential positive impact on carers and/or relatives associated with the improved outcomes of patients that receive treatments with epcoritamab is not considered in the economic analysis. The impact of improved outcomes on the productivity of patients, carers and/or relatives is also not considered.

Lastly, epcoritamab represents an innovative option for the management of R/R LBCL in UK clinical practice, [redacted]. The value of innovative additions to UK clinical practice is not captured in the cost-effectiveness model.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

Clinical expert opinion

Expert clinical input was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Feedback from clinical and economic experts was obtained at an advisory board and during subsequent interviews with UK clinical experts. As detailed throughout the submission, the approaches and key assumptions used in the economic analyses were validated by UK clinical experts and relevant details of the clinical validation are provided in the reference pack accompanying this submission.

Advisory boards

In order to obtain clinical expert opinion in advance of this submission, AbbVie organised an advisory board that was attended by four clinical experts (oncologists) and two health economics experts. The objective of the advisory board was to obtain clinical and health economic expert opinion on the following model assumptions and/or inputs:

- The clinical positioning and proposed use of epcoritamab in UK clinical practice
- The relevant comparators to epcoritamab
- The approach to estimating comparative clinical efficacy
- The economic model, including its inputs, structure and suitability for submission to NICE

Ahead of the advisory board, the expert advisors were sent pre-read materials covering the LBCL disease background, clinical data from the EPCORE™ NHL-1 trial, and AbbVie's proposed ITC and economic modelling approaches. The advisory board meeting was held in person on [redacted].

In addition, AbbVie organised a second medical advisory board that was attended by eight clinical experts. The objectives of the advisory board were to:

- Discuss the current data and knowledge gaps applicable to AbbVie's clinical development programme in LBCL
- Understand treatment management for bispecific antibodies in LBCL, including relevant challenges and patient treatment journey
- Discuss current educational resources and needs in LBCL, including potential solutions for gaps identified

Ahead of the advisory board, the clinical experts were sent pre-read materials covering LBCL disease background, clinical data from EPCORE™ NHL-1, an overview of the R/R LBCL treatment landscape and AbbVie's proposed positioning of epcoritamab in R/R LBCL after two or more treatments. The advisory board was held in person on [redacted].

Clinical validation interviews

Following the advisory board, additional clinical and health economic expert opinion was gathered to further validate key model assumptions and inputs. The expert opinion was gathered through teleconference calls that were attended by a maximum of two AbbVie representatives, one external consultancy representative and one clinical or health economic expert. The interviews were conducted virtually across December 2022–March 2023, with the clinical validation interviews lasting between 40 minutes and 2.5 hours.[17]

Technical validation

In alignment with best practice, validation of the economic model structure was conducted by an independent health economist prior to submission. The model quality control was conducted using the published TECH-VER checklist.[104]

Furthermore, a number of technical and 'sanity' checklists were completed by an independent team of health economists to ensure that the model functioned as intended and generated accurate results which were consistent with input data and robust to extreme analyses. The

validation process also aimed to ensure that a high degree of transparency was maintained throughout the model and so adaptations were carried out where necessary to ensure the validity of the cost-effectiveness model.

B.3.15 *Interpretation and conclusions of economic evidence*

B.3.15.1 Generalisability of the analysis

The economic evaluation is based on the patient population from the EPCORE™ NHL-1 trial adjusted to Sehn *et al*. 3L+, which can be considered to be representative of patients with R/R LBCL after two or more systemic therapies in UK clinical practice, based on feedback from UK clinical experts. As outlined previously (Section B.1.3.4), data from Northend et al. (2021) may be more reflective of UK clinical practice but it was not feasible to conduct a MAIC versus these data as sufficient details to derive a 3L+ population are not available.

The comparators included in this analysis (R-based CIT and axi-cel) represent the key comparators for epcoritamab in UK clinical practice, and this was validated by UK-based clinical experts. Economic analyses are presented separately for patients who are ineligible for, or choose not to receive, intensive therapies (base case analysis A) or those who are eligible to receive intensive therapies (base case analysis B) due to differing clinical pathways of care and differing levels of fitness, as supported by feedback from UK clinical experts. Furthermore, the analysis was conducted from an NHS and PSS perspective. As such, the results of this analysis can be considered to be generalisable to UK clinical practice.

B.3.15.2 Strengths and limitations of the analysis

The structure of the model was deemed appropriate for this decision problem as it captures the clinical benefits associated with epcoritamab and also aligns with previous NICE evaluations in R/R LBCL.[3, 14, 21] The treatment pathways included in the model were based on the treatments available for patients in UK clinical practice at third-line and beyond.

A number of parameters for the economic analyses were sourced from EPCORE™ NHL-1, which is a methodologically robust clinical trial in the exact patient population of interest to this submission. Where inputs were not available from EPCORE™ NHL-1, inputs and assumptions from previous cost-effectiveness analyses and NICE evaluations in R/R LBCL were used. The use of inputs and assumptions from other published sources for this economic evaluation was validated as appropriate by UK clinical experts.

While EPCORE™ NHL-1 provides evidence for the efficacy and safety of epcoritamab as a treatment for patients with R/R LBCL after two or more lines of systemic therapy, it is a single-arm trial, so it does not provide comparative efficacy evidence for epcoritamab versus current standard of care in the UK. As a result, ITCs were required to generate comparative efficacy evidence and the results of these ITCs were used to inform comparative efficacy in the cost-effectiveness model. The ITCs conducted took the form of unanchored MAICs and were conducted in accordance with NICE DSU TSD 14.[80] Although the ITC used robust methodologies that adjusted for observed differences in the patient populations, bias due to residual confounding cannot be excluded.

B.3.15.3 Summary of the economic evidence for epcoritamab

The innovative benefits of epcoritamab for patients with R/R LBCL after two or more prior therapies is reflected in the cost-effectiveness results where epcoritamab is cost-effective at a WTP threshold of £30,000 per QALY in the relevant patient population.

For base case analysis A, the results of the probabilistic cost-effectiveness analysis demonstrate that the total costs associated with R-based CIT and epcoritamab (PAS price) are £89,183 and [redacted], respectively. The total QALYs associated with R-based CIT and epcoritamab are 1.325 and [redacted] (with a 1.2 severity modifier applied). The resulting ICER for epcoritamab versus R-based CIT is £24,682, which demonstrates that epcoritamab is a cost-effective use of NHS resources when compared with R-based CIT, for patients who are ineligible for, or choose not to receive, intensive therapies.

For base case analysis B, the results of the cost-effectiveness analysis demonstrate that the total costs associated with axi-cel and epcoritamab (PAS price) are £391,116 and [redacted], respectively. The total QALYs associated with axi-cel and epcoritamab are 3.442 and [redacted], respectively. Epcoritamab was therefore found to be dominant versus axi-cel, demonstrating it to be cost-saving whilst also potentially incurring greater health benefits over the model time horizon. The NHB for epcoritamab versus axi-cel at £20,000 and £30,000 respectively is [redacted] and [redacted] (at epcoritamab PAS price).

The PSA analyses demonstrated that the probability that epcoritamab is the most cost-effective treatment option is estimated to be [redacted]% and [redacted]% with PAS at a WTP threshold of £30,000 per QALY for base case populations A and B, respectively.

The DSA results identified a small number of key influential parameters – namely the OS and PFS HRs – with the model being robust to variation, supporting the conclusions of the base case economic analyses, that epcoritamab is a cost-effective use of NHS resources.

Scenario analyses were conducted to explore the uncertainty relating to key assumptions used in the base case economic analyses. The results of the scenario analyses demonstrated minimal variation in the resulting ICERs and NHBs, further demonstrating the uncertainty surrounding the cost-effectiveness of epcoritamab versus axi-cel and R-based CIT is minimal.

B.3.15.4 Conclusions

For patients with R/R LBCL after two or more lines of systemic therapy, epcoritamab would present an innovative treatment option that drives deep and durable responses, thereby prolonging progression and survival in patients with R/R LBCL after two or more lines of systemic therapy. The results of the economic analyses presented in this submission demonstrate that epcoritamab represents a cost-effective use of NHS resources for these patients.

References

1. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med 2021;384:842-858.
2. The Haematological Malignancy Research Network. Prevalence. Estimated UK prevalence. Available at: https://hmrn.org/statistics/prevalence [Accessed: 18 January 2023].
3. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. Final appraisal document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document [Accessed: 1 November 2022].
4. AbbVie Advisory Board. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). 14 July 2022.
5. AbbVie Data on File. Epcoritamab Draft SmPC. 8 November 2022.
6. Stewart D, Aucoin JS, Crosbie T, et al. Update on the subcutaneous administration of rituximab in Canadian cancer centres. Curr Oncol 2020;27:113-116.
7. Cwynarski K, Marzolini MAV, Barrington SF, et al. The management of primary mediastinal B-cell lymphoma: a British Society for Haematology Good Practice Paper. Br J Haematol 2019;185:402-409.
8. Lymphoma Action. Diffuse Large B-Cell Lymphoma. Available at: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma [Accessed: 10 October 2022]
9. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol 2016;174:43-56.
10. NICE. Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [TA874]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10785/documents [Accessed: 17 Feb 2023].
11. NICE. Non-Hodgkin's lymphoma: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng52/resources/nonhodgkins-lymphoma-diagnosis-and-management-pdf-1837509936325 [Accessed: 18 November 2022].
12. Kantar. CancerMPact® Treatment Architecture Non-Hodgkin Lymphoma, EU5. Published May 2020.
13. AbbVie Data on File. Epcoritamab for Treating Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL). UK Medical Advisory Board – Meeting Report. 22 February 2023.
14. NICE. Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10645/documents [Accessed: 25 November 2022].
15. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-18.
16. MOFFITT Cancer Center. Differences Between Hodgkin & Non-Hodgkin Lymphoma. Available at: https://moffitt.org/cancers/lymphomas-hodgkin-and-non-hodgkin/faqs/hodgkin-lymphoma-vs-non-hodgkin-lymphoma/#:~:text=In%20non-Hodgkin%20lymphoma%2C%20these%20cells%20are%20not%20present.,Non-Hodgkin%20lymphoma%20is%20more%20common%20than%20Hodgkin%20lymphoma [Accessed: 13 February 2023].
17. AbbVie Data on File. Epcoritamab in Large B-Cell Lymphoma: Clinical Validation Interviews. December 2022–March 2023.
18. The Haematological Malignancy Research Network. Prevalence. Estimated UK incidence. Available at: https://hmrn.org/statistics/incidence [Accessed: 9 March 2023].
19. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
20. Lymphoma. Diffuse Large B-Cell Lymphoma: Relapsed/Refractory. Available at: https://lymphoma.org/understanding-lymphoma/aboutlymphoma/nhl/dlbcl/relapseddlbcl/#:~:text=Diffuse%20Large%20B-Cell%20Lymphoma%3A%20Relapsed%2FRefractory%20The%20term%20%E2%80%9Crelapsed%E2%80%9D,response%20to%20treatment%20does%20not%20last%20very%20long [Accessed: 16 January 2023]
21. AbbVie Data on File. EPCORE™ NHL-1 CSR. January 2022. .

22. Blood cancer UK. Diffuse large B-cell lymphoma (DLBCL) treatment and side effects. Available at: https://bloodcancer.org.uk/understanding-blood-cancer/lymphoma/diffuse-large-b-cell-lymphoma/dlbcl-treatment-side-effects/treatment-transformed-non-hodgkin-lymphoma/ [Accessed: 26 January 2023]
23. Yang X, Laliberté F, Germain G, et al. Real-World Characteristics, Treatment Patterns, Health Care Resource Use, and Costs of Patients with Diffuse Large B-Cell Lymphoma in the U.S. Oncologist 2021;26:e817-e826.
24. Thunberg U, Enblad G, Berglund M. Classification of diffuse large B-cell lymphoma by immunohistochemistry demonstrates that elderly patients are more common in the non-GC subgroup and younger patients in the GC subgroup. Haematologica 2012;97:e3; author reply e4.
25. Gurbuxani S, Anastasi J, Hyjek E. Diffuse large B-cell lymphoma--more than a diffuse collection of large B cells: an entity in search of a meaningful classification. Arch Pathol Lab Med 2009;133:1121-34.
26. Deng M, Xu-Monette ZY, Pham LV, et al. Aggressive B-cell Lymphoma with MYC/TP53 Dual Alterations Displays Distinct Clinicopathobiological Features and Response to Novel Targeted Agents. Mol Cancer Res 2021;19:249-260.
27. Lymphoma Research Foundation. High grade B-cell lymphoma. Available at: https://lymphoma.org/understanding-lymphoma/aboutlymphoma/nhl/hgbcl/ [Accessed: 1 November 2022].
28. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. Blood Rev 2017;31:37-42.
29. Friedberg JW. How I treat double-hit lymphoma. Blood 2017;130:590-596.
30. Falini B, Martino G, Lazzi S. A comparison of the International Consensus and 5th World Health Organization classifications of mature B-cell lymphomas. Leukemia 2023;37:18-34.
31. Lymphoma Research Foundation. Understanding Lymphoma High-Grade B-Cell Lymphoma. Available at: https://lymphoma.org/wp-content/uploads/2022/07/LRF_High_Grade_B_Cell_Lymphoma_Fact_Sheet.pdf [Accessed: 18 January 2023].
32. Dabrowska-Iwanicka A, Walewski JA. Primary mediastinal large B-cell lymphoma. Curr Hematol Malig Rep 2014;9:273-83.
33. Yu Y, Dong X, Tu M, et al. Primary mediastinal large B cell lymphoma. Thorac Cancer 2021;12:2831-2837.
34. Macmillan Cancer Support. Primary mediastinal large B-cell lymphoma (PMBCL). Available at: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/primary-mediastinal-large-b-cell [Accessed: 19 January 2023].
35. Lymphoma action. Follicular lymphoma. Available at: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/follicular-lymphoma. [Accessed: 14 November 2022].
36. Galaznik A, Huelin R, Stokes M, et al. Systematic review of therapy used in relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. Future Sci OA 2018;4:Fso322.
37. Salaverria I, Siebert R. Follicular lymphoma grade 3B. Best Pract Res Clin Haematol 2011;24:111-9.
38. Barraclough A, Bishton M, Cheah CY, et al. The diagnostic and therapeutic challenges of Grade 3B follicular lymphoma. Br J Haematol 2021;195:15-24.
39. Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008;26:5165-9.
40. Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol 2015;33:2516-22.
41. Macmillan Cancer Support. Follicular lymphoma (FL). Available at: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/follicular [Accessed: 14 Nov 2022].
42. Cancer Research UK. Survival. Available at: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/survival [Accessed: 26 September 2022]

43. Ernst M, Oeser A, Besiroglu B, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev 2021;9:Cd013365.
44. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Available at: https://www.nice.org.uk/guidance/ta649/resources/polatuzumab-vedotin-with-rituximab-and-bendamustine-for-treating-relapsed-or-refractory-diffuse-large-bcell-lymphoma-pdf-82609146587077 [Accessed: 10 October 2022].
45. Northend M, Wilson W, Osborne W, et al. Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. Blood Adv 2022;6:2920-2926.
46. Ahmed Z, Afridi SS, Shahid Z, et al. Primary Mediastinal B-Cell Lymphoma: A 2021 Update on Genetics, Diagnosis, and Novel Therapeutics. Clin Lymphoma Myeloma Leuk 2021;21:e865-e875.
47. Al-Juhaishi T, McKay J, Sindel A, et al. Perspectives on chemotherapy for the management of double-hit lymphoma. Expert Opin Pharmacother 2020;21:653-661.
48. Cancer Research UK. Diffuse Large B-Cell Lymphoma. Available at: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma [Accessed: 1 November 2022].
49. Macmillan. R-CHOP. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/r-chop [Accessed: 14 November 2022].
50. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531-2544.
51. MHRA. Yescarta (axicabtagene ciloleucel) SmPC. Available at: https://mhraproducts4853.blob.core.windows.net/docs/13ac3d92fcf9878c0e2b86407a2c1883cdd980fc [Accessed: 10 March 2023].
52. MHRA. Polivy (polatuzumab vedotin bendamustine rituximab) SmPC. Available at: https://mhraproducts4853.blob.core.windows.net/docs/13ac3d92fcf9878c0e2b86407a2c1883cdd980fc [Accessed: 10 March 2023].
53. Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). Ann Oncol 2017;28:836-842.
54. Gye A, Goodall S, De Abreu Lourenco R. A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared With Older Patients. Value Health 2022;25:47-58.
55. NICE. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10580 [Accessed: 26 January 2023]
56. AbbVie Data on File. SLR for burden of illness for R/R DLBCL. .
57. Engelberts PJ, Hiemstra IH, de Jong B, et al. DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing. EBioMedicine 2020;52:102625.
58. Sachdeva M, Dhingra S. Obinutuzumab: A FDA approved monoclonal antibody in the treatment of untreated chronic lymphocytic leukemia. International Journal of Applied and Basic Medical Research 2015;5:54.
59. Cerny T, Borisch B, Introna M, et al. Mechanism of action of rituximab. Anticancer Drugs 2002;13 Suppl 2:S3-10.
60. AbbVie Oncology. Investigational Drugs for Cancer. Available at: https://abbviescience.com/oncology/pipeline [Accessed: 24 November].
61. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015;26:v116-v125.
62. NICE. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma [TA306]. Available at: https://www.nice.org.uk/guidance/ta306 [Accessed: 18 November 2022].
63. NICE. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. Available at: https://www.nice.org.uk/guidance/TA567 [Accessed: 18 November 2022].

64. Kuhnl A, Roddie C, Kirkwood AA, et al. A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience. Br J Haematol 2022;198:492-502.
65. Thieblemont C, Phillips T, Ghesquieres H, et al. ABCL-422 Subcutaneous Epcoritamab in Patients With Relapsed or Refractory Large B-Cell Lymphoma (EPCORE NHL-1): Pivotal Results from a Phase 2 Study. Clinical Lymphoma Myeloma and Leukemia 2022;22:S379.
66. Belada D, Christensen JH, Drott K, et al. Subcutaneous epcoritamab in combination with R-CHOP in patients with previously untreated high-risk diffuse large B-Cell lymphoma: preliminary results from a phase 1/2 trial. Blood 2021;138:1413.
67. clinicaltrials.gov. A Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in R/R DLBCL (EPCORE™DLBCL-1). Available at: https://clinicaltrials.gov/ct2/show/NCT04628494 [Accessed: 16 December 2022].
68. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. The Lancet 2021;398:1157-1169.
69. David M. Phillippo, A. E. Ades, Safia Dias, et al. NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. Report by the Decision Support Unit., 2016.
70. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood advances 2021;5:4149-4155.
71. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
72. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-165.
73. Liebers N, Duell J, Fitzgerald D, et al. Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas. Blood Adv 2021;5:2707-2716.
74. EUnetHTA. PTJA06 – Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. Available at: https://www.eunethta.eu/ptja06/ [Accessed: 09 December 2022].
75. Sehn LH, Hertzberg M, Opat S, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood advances 2022;6:533-543.
76. NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. Report by the Decision Support Unit. Available at: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD19-Partitioned-Survival-Analysis-final-report.pdf [Accessed: 14 February 2023].
77. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935-45.
78. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value in Health 2012;15:940-947.
79. Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. PloS one 2011;6:e18174.
80. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data: NICE Decision Support Unit, 2011.
81. Rutherford M.J. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. 2020, NICE Decision Support Unit.
82. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2015.
83. Lumley T. Package 'survey'. Available at the following link: https://cran. r-project. org 2020.
84. Lumley T. Analysis of complex survey samples. Journal of statistical software 2004;9:1-19.
85. Maloney DG, Kuruvilla J, Liu FF, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol 2021;14:140.
86. Avivi I, Perry C, Segman Y, et al. Polatuzumab-based regimen or CAR T cell for patients with refractory/relapsed DLBCL-a matched cohort analysis. Ann Hematol 2022;101:755-762.

87. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-638.
88. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-78.
89. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
90. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Available at: https://www.nice.org.uk/guidance/ta649 [Accessed: 31 Mar23].
91. NICE. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#discounting [Accessed: 6 Jan 2023].
92. National Institute of Health and Care Excellence. NICE health technology evaluations: the manual. www.nice.org.uk/process/pmg36: National Institute of Health and Care Excellence,, 2022:181.
93. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant 2016;51:51-7.
94. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA872]. Available at: https://www.nice.org.uk/guidance/ta872 [Accessed: 31 March 2023].
95. Office for National Statistics. National life tables UK 2018-2020. In: Office for National Statistics, ed. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables, 2021.
96. Ara R, Wailoo A. NICE DSU Technical Support Document 12: the use of health state utility values in decision models. 2017.
97. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value in Health 2011;14:539-545.
98. Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica 2013;98:1726.
99. National Institute of Health and Care Excellence. British National Formulary (BNF). Volume 2022. https://bnf.nice.org.uk/, 2022.
100. AbbVie. Epcoritamab in DLBCL Advisory Board. .
101. NHS England. 2019/20 National Cost Collection Data Publication. 27 July 2022 ed. https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/, 2022.
102. York. QALY Shortfall Calculator. Available at: https://shiny.york.ac.uk/shortfall/ [Accessed: 10 March 2023].
103. NICE. Report by the Decision Support Unit. Estimating EQ-5D by age and sex for the UK. Available at: https://www.sheffield.ac.uk/sites/default/files/2022-02/DSU%20Age%20based%20utility%20-%20Final%20for%20website.pdf [Accessed: 10 March 2023].
104. Büyükkaramikli NC, Rutten-van Mölken MP, Severens JL, et al. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics 2019;37:1391-1408.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments

[ID4045]

Summary of Information for Patients (SIP)

April 2023

File name	Version	Contains confidential information	Date
ID4045_Epcoritamab_NICE_SIP_Final_09June23 [ACIC]	Final	No	09 June 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Epcoritamab

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is adults who have **relapsed** or **refractory** (R/R) **large B-cell lymphoma** (LBCL) after having already received two previous **cancer** treatments. Relapsed or refractory disease is when a disease becomes worse after a period of improvement or shows resistance to treatment. LBCL is a type of cancer that affects the **lymphatic system** which forms part of the **immune system**. There are multiple types of LBCL such as **diffuse large B-cell lymphoma** (DLBCL), **high grade B-cell lymphoma** (HGBCL), **primary mediastinal B-cell lymphoma** (PMBCL), and **follicular lymphoma grade 3B** (FL Gr 3B) which are considered within this appraisal.[a]

[a] Please note that further explanations for the phrases highlighted in **black** at first instance are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **green**.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence that sets out the conditions for the use of a treatment based on evidence for its safety and effectiveness. Epcoritamab is anticipated to receive marketing authorisation for use in adult patients with R/R LBCL (including DLBCL, PMBCL, and FL Gr 3B) after two or more different treatment regimens. This marketing authorisation is pending approval by the relevant regulatory body.

Further details on the anticipated dates for approval can be found in **Document B**, **Section B.1.2** of the submission

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates with a range of stakeholders with an interest in R/R LBCL.

This includes collaboration with patient groups to support improvements in health and care for individuals with R/R LBCL.

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: https://www.abbvie.co.uk/our-company/policies-disclosures.html

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The main condition that epcoritamab is intended to treat is R/R LBCL that has been treated with at least two previous cancer treatments

What is large B-cell lymphoma (LBCL)?

Lymphoma is a blood cancer that forms **tumours** in the lymphatic system. Lymphoma is divided into two main types called **Hodgkin lymphoma** and **Non-Hodgkin lymphoma** (NHL).[1] LBCL is a type of NHL and almost 30% of all people with NHL have LBCL.[2] An estimated 8.3 people are diagnosed with LBCL per 100,000 people each year in the UK, which equates to approximately 5,420 new diagnoses of LBCL each year.

Patients with LBCL typically have swollen **lymph nodes** in the neck, abdomen, testicles, armpit or groin and can experience a range of symptoms such as:[3]

- Fever
- Night sweats
- Unexplained weight loss
- Fatigue
- Pain
- Severe itching

Numerous types of LBCL exist. The diagnosis of these subtypes is based on a number of factors including the type of lymphoma and the **stage** of the disease. The subtypes of disease included within this submission are DLBCL, HGBCL, PMBCL and FL Gr 3B. Although FL Gr 3B is not technically a subtype of LBCL, it has been included in the clinical trials for epcoritamab because it is treated in the same way as the subtypes of LBCL. All of these subtypes are discussed further in the following paragraphs.

The population of interest in this submission is adult patients with R/R LBCL who have already received two or more previous treatment regimens. When the disease is controlled (has improved or is no longer detected), this is called **remission.** The term 'relapsed' refers to disease that returns or worsens following a period of remission. Refractory refers to disease that does not respond to treatment, either at the beginning of treatment or during treatment.[4]

In addition, LBCL can be either ***de novo*** (diagnosed from the original site that the cancer developed in) or transformed. Transformed disease occurs when a less severe type of lymphoma develops into a different type of lymphoma. This transformed disease is commonly DLBCL.[5]

What is diffuse large B-cell lymphoma (DLBCL)?

DLBCL is a type of large B-cell lymphoma which has abnormal and enlarged **B-cells** (a type of **white blood cell**). These cancer **cells** also appear in a spread-out pattern, called a **diffuse** pattern. Approximately 90% of patients with LBCL in the UK are diagnosed with DLBCL, making it the most common subtype of LBCL. An estimated 7.4 people are diagnosed with DLBCL per 100,000 people in the UK each year, which equates to approximately 4,860 new diagnoses of DLBCL in the UK each year.[6, 7] It affects slightly

more men than women. It is also most commonly diagnosed in older adults (people aged 65–74 years).[8] In most cases, the causes of DLBCL are unknown.[9] However, occasionally, it is associated with **autoimmune conditions,** infections and prior **organ** transplantation.[9] Patients with DLBCL often experience the same symptoms as those with LBCL.

What is high grade B-cell lymphoma (HGBCL)?

Particularly aggressive, **high-grade** (fast growing) lymphomas such as HGBCL are recognised as a different type of disease than DLBCL. These patients with HGBCL make up approximately 5% of DLBCL diagnoses.[10] HGBCL also has some distinct features when compared with DLBCL. For example, it is associated with reduced survival rates for patients and increased risk of tumours in the brain and spinal cord.[11] With that said, the symptoms of HGBCL are largely similar to those of DLBCL and LBCL more generally.[12] Therefore HGBCL is commonly treated in the same way as DLBCL.[12, 13]

What is primary mediastinal B-cell lymphoma (PMBCL)?

PMBCL is an aggressive type of LBCL that predominately affects the area behind the breastbone and between the lungs (**mediastinum**). It is another relatively rare subtype of LBCL making up roughly 3% of LBCL diagnoses in the UK.[6] An estimated 0.2 people are diagnosed with PMBCL per 100,000 people every year in the UK. PMBCL mainly affects young adults (aged 20–40 years) and is more common in women than men.[13] [14]

As PMBCL primarily develops within the area of the mediastinum, the symptoms associated with PMBCL are caused by the pressure of the tumours on the chest. This leads to specific symptoms such as:[15]

- Coughing
- Pain or aching in the chest
- Changes to the voice including hoarseness
- Breathlessness
- Swelling in the neck, face or arms
- Dizziness
- Headaches that are worse when bending forward
- More visible chest veins

PMBCL is considered to be a high-grade lymphoma. As such, PMBCL is typically treated in a similar way to DLBCL.[16]

What is follicular lymphoma grade 3B (FL Gr 3B)?

Follicular lymphoma (FL) is the most common type of **low-grade** (slow growing) NHL.[17] It accounts for approximately 22% of all NHL diagnoses. Approximately, 2,200 people are diagnosed with FL each year in the UK.[17, 18] FL Gr 3B is more common in women than men.[19, 20] FL Gr 3B is a subtype of FL which is associated with reduced survival for patients when compared with other forms of FL. It is estimated that approximately 5–10% of patients with FL have FL Gr 3B.[19] In addition, approximately 50% of patients with FL Gr 3B also have a lower-grade FL or DLBCL.[6, 20]

Symptoms of FL Gr 3B commonly include swelling in the neck, armpit or groin due to lymphoma cells building up in the lymph nodes.[21] Although different from DLBCL, many aspects of FL Gr 3B are similar to *de novo* DLBCL.[19, 20, 22, 23] As such, FL Gr 3B is typically treated in the same way as DLBCL.

Outcomes for patients with R/R LBCL

For patients with LBCL that have not been previously treated or have only been treated with one previous treatment, there are treatment options available that have the potential to be a cure. However, for patients who have received two or more previous treatment regimens, there are few.[24] As such, real-world clinical practice studies have regretfully shown that survival and time until progression is short for patients with R/R LBCL.[25] In one study involving patients with R/R DLBCL in the UK who received a combination of treatments called **Pola + BR** (see Section 2c for more information on Pola + BR), patients survived for 8.2 months on average and the time until cancer progression was 4.8 months on average.[25] There are limited data on the outcomes for other subtypes of LBCL, including PMBCL, HGBCL and FL Gr 3B, but it is suggested that outcomes for these patients are also poor.[26, 27]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is LBCL diagnosed?

First, a **general practitioner** (GP) will ask some questions about the patient's health and may conduct a simple physical examination. If necessary, the patient would then be referred by the GP to a hospital, where the patient may undergo a **biopsy**. A biopsy is a small procedure or operation that involves removing some or all of the swollen lymph node, which is then studied in a laboratory. It can often be carried out under a **local anaesthetic**. This is when the area where the biopsy is taking place is numbed but the patient is kept awake. However, if the swollen lymph node is not easily accessible, a **general anaesthetic** (where the patient is put to sleep) may be required.[28]

If a diagnosis of NHL is confirmed after the biopsy, the type of NHL will need to be determined. Further tests may include blood tests, chest x-ray, **bone marrow sample**, **CT scan**, **MRI scan**, **PET scan**, and **lumbar puncture**, where a small sample of spinal fluid is extracted.[a] Once testing is complete, the stage and **grade** of the disease is determined.[28]

[a] CT: computerised tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for LBCL?

In most instances PMBCL, HGBCL and FL Gr 3B are treated in a similar way to DLBCL. This was confirmed UK clinicians experienced in treating LBCL. [9, 13, 29, 30] As such, all types of LBCL follow a similar treatment pathway described in the following paragraphs.

Chemotherapy is a treatment that stops the growth of cancer cells, either by killing the cells or by stopping them from dividing. **Radiotherapy** is a treatment that kills cancer cells through radiation such as x-rays. **Targeted therapy** is a type of cancer treatment that uses drugs to target specific **genes** and proteins that help cancer cells survive and grow. Treatment usually begins with chemotherapy, radiotherapy, targeted therapy or a combination of these. All of these treatments require infusion into a patient's vein (**intravenous treatment**).

The most common combination that is often used first is called **R-CHOP** which is made up of the following drugs:[31-33]

- R – rituximab (a type of targeted therapy)
- C – cyclophosphamide (a chemotherapy drug)
- H – hydroxydaunomycin (a chemotherapy drug), also called doxorubicin
- O – vincristine (a chemotherapy drug)
- P – prednisone (a **steroid**)

A treatment called **Pola + R-CHP** has recently been recommended by the **National Institute for Health and Care Excellence** (NICE) as a treatment option for previously untreated DLBCL as well.[34] Pola + R-CHP is also named after the initials of the drugs used:

- Pola – polatuzumab vedotin (Polivy®) (a targeted therapy that delivers a chemotherapy drug to B-cells)
- R – rituximab (a targeted therapy that triggers the body's immune system to attack and destroy B-cells)
- C – cyclophosphamide (a chemotherapy drug)
- H – hydroxydaunomycin (a chemotherapy drug), also called doxorubicin

- P – prednisone (a steroid)

While the disease often responds to the first treatment and many people have a **complete response,** some people need more treatment after their first treatment. This might be the case if:

- The lymphoma did not respond to treatment (refractory lymphoma)
- The lymphoma is reduced but not completely cleared (**partial response**)
- The lymphoma comes back at least 6 months after completion of treatment, even if the lymphoma showed a complete response to the first treatment (relapsed lymphoma)

If a patient needs more treatment after their first treatment, the treatment they receive next might depend on whether they are well enough to endure an intensive therapy. **Immunotherapy** is a treatment that works by changing some of the body's immune cells to make them better at fighting cancer cells. Patients who have received one previous cancer therapy and who are well enough to have an intensive therapy are often treated with **chemoimmunotherapy** (which is a combination of chemotherapy and immunotherapy) and **stem cell transplantation** using a patient's own **stem cells** (**autologous** stem cell transplantation).[32, 35]

For patients who cannot receive intensive therapies such as autologous stem cell transplantation, Pola + BR is a treatment choice that is recommended by NICE.[31, 36] Pola + BR is named after the initials of the drugs used: [36, 37]

- Pola – polatuzumab vedotin (Polivy®; a targeted therapy that delivers a chemotherapy drug to B-cells)
- B – bendamustine (a chemotherapy drug)
- R – rituximab (a targeted therapy that triggers the body's immune system to attack and destroy B-cells)

However, following the recent recommendation of Pola + R-CHP by NICE, clinical experts in the UK stated that a patient would not receive Pola + BR if they have already received Pola + R-CHP as their first treatment. Pola + BR is anticipated to now only be used in a minority of patients who have not previously been treated with polatuzumab and cannot receive intensive therapies.[29]

For patients who have received two treatments and require further therapy, there are few standard treatment options currently available for use through the NHS. The treatment options continue to depend on whether a patient is well enough to receive an intensive therapy.

Patients who can have an intensive therapy to treat their disease might receive **chimeric antigen receptor T-cell (CAR-T) therapy** which is a type of immunotherapy. Axicabtagene ciloleucel and tisagenlecleucel are both types of CAR-T therapies that are recommended by NICE.[24, 38] Tisagenlecleucel is currently only recommended by NICE on the **Cancer Drugs Fund**. This means that the treatment is temporarily available while further evidence on **efficacy** and safety is collected.[13, 39]

Further chemoimmunotherapy followed by **allogenic stem cell transplantation** (alloSCT) may also be considered in these patients. AlloSCT is a procedure that involves transferring the stem cells from a healthy person to the patient's body after high-intensity chemotherapy or radiation.[32] However, clinical experts have noted that alloSCT has minimal use for this group of patients in UK clinical practice.[31]

For patients who cannot receive intensive therapies (such as CAR-T and alloSCT), or choose not to receive them, rituximab-based chemoimmunotherapy combinations are the primary treatment option, such as rituximab, gemcitabine and oxaliplatin (**R-GemOx**) and **R-Gem**. Alternatively, Pola + BR remains a treatment option if it was not used previously. However, as patients can now receive Pola + R-CHP as their first treatment, only a minority of patients are expected to receive Pola + BR if they have already received two treatments and require further therapy.

Following any further treatment failures, treatment options are limited to chemoimmunotherapy only or clinical trials if the patient is suitable. However, there is no agreement on specific therapies that can be used. Also, the benefit of continuing treatment in this population who have already received a large number of therapies is often carefully considered.[31] It is important to note pixantrone monotherapy is also recommended as a treatment option for this patient population by NICE.[40] However, clinicians in the UK state that pixantrone monotherapy is rarely used in UK clinical practice to treat R/R LBCL. This is because pixantrone monotherapy is not very effective and it has high toxicity.[41]

In summary, treatment options are limited for patients with R/R LBCL who have already received two or more previous treatment regimens. Despite advances in treatment options, such as the availability of CAR-T therapies, there is no standard of care that can be received and accessed by all eligible patients. Therefore, there remains a significant unmet need for new effective treatments for this patient population.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

AbbVie have collected patient-based evidence through the health-related **quality of life** (HRQoL) measures in the epcoritamab trials. The outcomes of the HRQoL measures from the key trial (EPCORE™ NHL-1) are presented in **Section 3e**. The section summarises

some of the key considerations from published literature about the impacts of LBCL on patients.

LBCL from the patient perspective

Given the range of symptoms experienced, LBCL can have a substantial and negative impact on a patient's HRQoL.[31] Patients with DLBCL specifically have been shown to be negatively impacted when compared with the general population. For example, patients who report having symptoms generally have significantly lower HRQoL when compared with patients who do not report symptoms from the disease.[31] Further, patients with DLBCL are also subsequently more likely to get infections or be admitted to hospital which can negatively affect a patient's HRQoL.[31]

In addition to the burden of the disease itself, current treatments for LBCL are associated with a number of side effects. For example chemotherapy is associated with:[42]

- Shivering
- Itching
- Skin rashes
- Flushes
- Dizziness
- Headaches
- Breathlessness
- Swelling of the face or mouth

Several later-line treatments for R/R LBCL, are also associated with frequent and severe side effects including **cytokine release syndrome** and **neurotoxicity**.[43, 44] Cytokine release syndrome is when the immune system responds to immunotherapy drugs more aggressively than it should. Neurotoxicity is damage to the brain or nervous system.

In addition, all currently available third-line treatments for R/R LBCL require infusion into a patient's vein (intravenous treatment). This can be uncomfortable for patients and disrupt their daily lives. A study conducted in patients with R/R DLBCL or FL demonstrated that the majority of patients prefer **subcutaneous treatment** (injection underneath the patient's skin) when compared with intravenous treatment. The most common reasons for this preference were that subcutaneous treatment "requires less time in the clinic" and "feels more comfortable during administration".[45] Therefore, an effective subcutaneous treatment for R/R LBCL may help to alleviate some of the burden associated with treatment for R/R LBCL.

There are also constraints associated with obtaining CAR-T therapies. To receive treatment with CAR-T therapies in the UK, patients must be approved by a panel of experts, meaning that patients cannot receive treatment immediately.[46] According to UK clinical experts, patients in the UK wait approximately seven weeks from being approved for treatment with CAR-T by this panel to receiving the infusion. This represents an additional source of disease burden, especially for patients who have disease that is getting worse quickly.[30] In addition, there are a limited number of places that can deliver

CAR-T therapies, so patients often have to travel long distances to receive their treatment. Therefore, even if a patient is eligible for CAR-T, they may choose not to receive it.

There is limited information on living with R/R LBCL, specifically. However, these patients with R/R disease would be expected to experience an increased burden of disease when compared with patients who have just been diagnosed or who are receiving their first treatment for LBCL. After their first treatment, patients whose disease is in complete remission have demonstrated significant improvements in their quality of life compared with patients whose disease did not achieve complete remission.[47] Furthermore, patients often undergo cycles of remission and relapse when they are having successive treatments for their disease. This imparts a mental and physical burden on patients which may be due to fears of relapse.[24] Even after successful treatment, patients may continue to experience anxiety related to the possibility of future relapse.

Patient-based evidence from Lymphoma Action

To further understand the impact of living with LBCL on patients, AbbVie sought input from Lymphoma Action. Lymphoma Action highlighted that diagnosis of LBCL can have a large psychological impact on patients, and many patients report experiencing insomnia, anxiety and a "constant fear of dying".[30] Further, the symptoms of LBCL can develop rapidly and cause patients to feel unwell for many months. This psychological burden, coupled with the range of symptoms experienced by patients, can severely impact on patient's quality of life.[31, 48]

During treatment for LBCL, patients often spend long periods of time in hospital which can make them feel isolated from family and friends.[30] On top of this, the side effects of intensive treatments themselves can be debilitating and patients can take a long time to recover, particularly from side effects such as fatigue or **peripheral neuropathy**.[30] This can make it difficult for patients to return to their normal lives. As such, many patients are unable to work during their treatment.[30]

Lymphoma Action also highlighted the impact of LBCL on the family and/or carers of people with LBCL as people with LBCL can be very ill and require support from those around them. For example, some carers take significant amounts of time off work to support the patient with LBCL.[30] Moreover, Lymphoma Action highlighted that it can be difficult for family and/or carers to understand what the individual with LBCL is experiencing.[30]

In summary, a diagnosis of LBCL can have immense physical, emotional, and social effects on patients, affecting all aspects of patients' lives.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

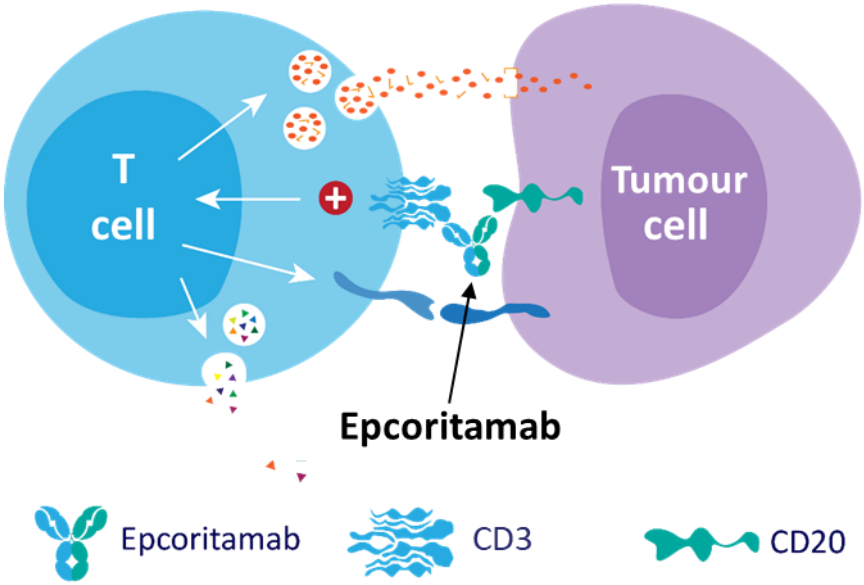
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Epcoritamab is given as an injection under the skin (subcutaneous) and is a type of **antibody** called a '**T-cell bispecific** antibody'. Most antibody treatments attach to one target **protein** but epcoritamab can attach to two targets on different cells (hence it is described as 'bispecific'). This means that can bring an immune cell and another cell together. Epcoritamab attaches to a protein called CD20 on B-cells and to a protein called CD3 on T-cells as shown below in **Figure 1**. This brings the healthy T-cells into close contact with the cancerous B-cells, boosting immune response with the aim to destroy the cancer.[49]

Figure 1: How epcoritamab works



This diagram demonstrates how epcoritamab attaches to a protein called CD20 on B-cells (tumour cell) and to a protein called CD3 on T-cells. This brings T-cells into close contact with the cancerous B-cells, boosting the body's immune response to the cancer.
Source: Adapted from AbbVie Oncology[50]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable – Epcoritamab is not proposed to be used in combination with any other medicines for treating R/R LBCL.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Epcoritamab is given as a subcutaneous injection only and should be administered by a licenced healthcare professional. Epcoritamab should be administered in the lower part of abdomen or the thigh.[51]

The following dosing schedule is used whereby doses are administered in 28-day cycles. For the first cycle, the dose of epcoritamab is increased from 0.16 mg on Day 1, to 0.8 mg on Day 8, to the full dose (48 mg) on Day 15 and Day 22. Following this, the full dose of epcoritamab (48 mg) is received on the days of the cycle indicated in **Table 1**.[51]

Table 1: Dosing schedule for epcoritamab

Cycle	1				2 and 3				4–9		10+
Frequency of administration	Weekly				Weekly				Every other week		Every fourth week
Day of cycle	1	8	15	22	1	8	15	22	1	15	1
Dose (mg)[a]	0.16	0.8	48	48	48	48	48	48	48	48	48

[a] 0.16 mg is a priming dose, 0.8 mg is an intermediate dose and 48 mg is a full dose.
Source: AbbVie, epcoritamab draft SmPC 2022.[51]

Epcoritamab should be administered until the disease gets worse or until side effects from the treatment are too severe to be managed.[51]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

One key **clinical trial** provides evidence on the efficacy and safety of epcoritamab for treating R/R LBCL after two or more previous treatment regimens. This trial is called EPCORE™ NHL-1. A summary of the key information about the trial is provided in **Table 2.** More information on this trial can be found in **Document B** in **Section B.2.2.**

The main source of evidence used in this submission is data from 30 June 2022 data cut-off of the EPCORE™ NHL-1 trial.

Another clinical trial called EPCORE™ DLBCL-1 is currently ongoing. This is a **Phase 3 trial** which is evaluating the safety and efficacy of epcoritamab compared with chemoimmunotherapy. Data from this trial are not yet available.

Table 2: Key clinical trial investigating epcoritamab

Trial name and number	Location	Trial design	Population	Treatment	Comparator
EPCORE™ NHL-1 (NCT03625037)	AUS, CA, DE, DK, ES, FI, FR, IT, KR, NL, PL, SE, SG, UK, US	**Phase 1/2**	Patients with R/R LBCL	Epcoritamab	No comparator

Abbreviations: AUS: Australia; CA: Canada; DE: Germany; DK: Denmark; ES: Spain; FR: France; IT: Italy; KR: Korea; NL: Netherlands; PL: Poland; SE: Sweden; SG: Singapore; UK: United Kingdom; US: United States.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Clinical trial results

The EPCORE™ NHL-1 clinical trial measured the effectiveness of epcoritamab as a treatment for R/R LBCL in patients who have already received two or more previous cancer treatment regimens. The trial was analysed by both the full LBCL population and by two subgroups:

- 'DLBCL' subgroup which included patients with DLBCL only
- 'Other' subgroup which included patients with HGBCL, FL Gr 3B and PMBCL only

The clinical data from the DLBCL subgroup were used for the **indirect treatment comparison** (see below for more details). Therefore, the trial results for this section focus on the DLBCL subgroup. However, trial results were similar for the full LBCL and other subgroup.

The main outcome for the trial was **overall response rate**. This measures the proportion of patients in the trial where tumours were destroyed or significantly reduced by the treatment. The overall response rate results showed that for over half of patients with DLBCL, their disease was destroyed or significantly reduced after treatment with epcoritamab. Also, in over a third of patients with DLBCL, their disease had a complete response (no detectable tumour) at the data cut-off timepoint.

Other outcomes in the trial included **duration of response**, which is the length of time that a tumour continues to respond to a treatment without the cancer growing or spreading. For patients with DLBCL, the response to epcoritamab lasted for over a year on average. This shows that epcoritamab can produce a durable, meaningful response as opposed to a temporary response without any lasting benefit. **Progression-free survival** was an additional endpoint, which measures how long a person lives without the disease worsening. Results from the trial indicate that epcoritamab was able to prevent the disease from progressing for more than four months.[52]

The average (median) **overall survival** (how long patients lived) for patients with DLBCL who received epcoritamab was approximately a year and half.[52] This demonstrates the value of epcoritamab in helping patients to survive once they have been diagnosed with the disease. The average **time to next anti-lymphoma therapy** is the time from the first dose of epcoritamab to the first recorded administration of subsequent anti-lymphoma therapy. The trial demonstrated that patients could remain on treatment with epcoritamab for over half a year before needing to start a new treatment.[52] Where the disease had a complete response to epcoritamab, patients were able to stay on treatment longer.

In summary, based on the June 2022 data cut-off from the EPCORE™ NHL-1 trial, epcoritamab demonstrated meaningful, deep and durable outcomes in patients with R/R LBCL who have already received two or more previous treatment regimens.

Epcoritamab compared with other available therapies

EPCORE™ NHL-1 is a **single-arm trial** where everyone enrolled in the trial was treated with epcoritamab. No data are yet available that compare epcoritamab to currently available treatments. Therefore, an analysis called an indirect comparison was undertaken to compare epcoritamab to the treatments commonly used to treat R/R LBCL in patients who have already tried two or more previous treatment regimens. These treatments include:

- Axicabtagene ciloleucel (CAR-T therapy)
- Rituximab-based chemoimmunotherapy
- Pola + BR, only for the minority of patients who have not previously used polatuzumab

This is a common approach in the evaluations of new medicines. This statistical analysis is explained in further detail in **Document B, Section B.2.8.**

Overall, compared with existing treatments, the indirect comparison showed that epcoritamab is more effective than rituximab-based chemoimmunotherapy at improving overall survival. The indirect comparison also showed that epcoritamab may be similarly effective as axicabtagene ciloleucel when measured in terms of overall survival and progression-free survival.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

During the EPCORE™ NHL-1 trials, the HRQoL of patients was assessed through several measures:

- Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym): a questionnaire developed to assess the HRQoL of patients with NHL[53]
- EuroQoL-5 dimensions-3 levels (EQ-5D-3L): a standardised measure of HRQoL[54]

Six questions from the FACT-Lym accessing body pain, fever, night sweats, lack of energy, tiring easily and weight loss were considered as the key symptoms of lymphoma.

Whilst receiving treatment with epcoritamab, there were marked improvements across all six symptoms based on the FACT-Lym questionnaire.

Patients also showed consistent and steady improvements in overall HRQoL as measured by the EQ-5D-3L.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

All treatments have side effects and the same treatment can produce different side effects in different people. Data on the side effects of epcoritamab were collected in the EPCORE™ NHL-1 clinical trial.

In clinical trials, side effects are graded on a scale from 1–5 (most clinical trials focus on grade 3 or higher events):[55]

- Grade 1–2: mild side effects that generally do not impact patients significantly and are not dangerous
- Grade 3–4: serious side effects that interfere with patients' ability to do basic things. They may also mean that patients need to be seen by their doctor for medical intervention
- Grade 5: fatal side effects

Most patients experienced a side effect that was related to treatment with epcoritamab. The most common side effects included:

- Cytokine release syndrome
- Fatigue
- Fever
- **Neutropenia**
- Injection site reaction
- **Diarrhoea**
- Feeling sick

The side effects of epcoritamab were usually of lower grades. However, a third of patients with LBCL experienced a grade 3 or higher side effect that was related to their treatment.[52] These side effects were generally manageable with appropriate monitoring and measures such as delaying treatment and/or providing additional medical support.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Epcoritamab is an effective treatment for R/R LBCL

The EPCORE™ NHL-1 trial demonstrated that epcoritamab can improve overall response rates for patients with LBCL and for many patients, their disease shows a complete response. Results from the trial also indicate that epcoritamab can prevent the disease from progressing and patients were seen to remain on treatment with epcoritamab for over half a year before needing to start a new treatment. This shows that epcoritamab is an effective treatment option for patients with R/R LBCL who have already received two or more previous treatment regimens.

Epcoritamab can improve HRQOL in patients with R/R LBCL

Patients with R/R LBCL often experience symptoms that impact on their daily lives. Having multiple treatments and/or disease that relapses places a substantial mental and physical burden on people with the disease, as well as their families and carers. This can be due to uncertainties around the outcome of their disease and fears of relapse. Epcoritamab demonstrated marked improvements in the HRQoL outcomes (FACT-Lym and EQ-5D-3L) included in the EPCPORE NHL-1 trial. Therefore, epcoritamab can provide a treatment option that can help alleviate disease burden in patients who are currently severely impacted by their disease.

Epcoritamab is a subcutaneous treatment option which can provide a convenient alternative to current intravenous therapies

All currently available treatment options for patients with R/R LBCL who have already received two or more previous treatment regimens require intravenous infusion. This can be both uncomfortable and inconvenient for patients. Epcoritamab is the first and only subcutaneous treatment available for this patient group. This subcutaneous administration enables fast administration across different practice settings when compared with currently available intravenous therapies. As such, epcoritamab can provide a treatment option that allows for greater flexibility and convenience for both clinicians and patients when compared with currently available intravenous therapies.

Epcoritamab provides a readily available treatment option for patients

Patients in the UK have to wait approximately seven weeks from being approved for treatment with CAR-T by a panel to receiving the infusion.[30] This means that patients cannot receive treatment with CAR-T therapies immediately which can be a burden for patients who have a disease that is likely to get worse quickly. Therefore, in some instances, patients eligible for CAR-T therapy may not be able to receive or may choose

not to receive the therapy. Epcoritamab provides a readily available treatment option for this patient group. Once it is decided that a patient should receive treatment with epcoritamab, they can receive the treatment almost immediately.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The side effects associated with epcoritamab are generally manageable with appropriate monitoring and measures such as delaying treatment and/or providing additional medical support. However, like all existing R/R LBCL therapies, some patients may experience side effects that are not manageable, and treatment may need to be temporarily or permanently stopped for some people.

Epcoritamab is administered until the disease progresses and current options are usually only given for a fixed amount of time. For all patients receiving epcoritamab beyond cycle 10, patients would require monthly hospital appointments to receive treatment.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

To allow health care services to decide if epcoritamab provides 'good value for money' compared with existing medicines, the pharmaceutical company used a health economic model to perform an economic analysis. This compared the costs and benefits of the new treatment (epcoritamab) with the currently available treatments, called the comparators (axicabtagene ciloleucel and rituximab-based chemoimmunotherapy).

How the model reflects R/R LBCL

The economic model was designed to reflect the key features of R/R LBCL and **clinical practice** in the UK. To do this, a model structure called a **partitioned survival model** was chosen. This is a model structured into three disease states, where people with LBCL either 1) are progression free, 2) have progressed disease, or 3) have died. In the progression free health state, patients have treatment with either epcoritamab or one of the comparators. People in the progression free health state can experience side effects and have other services provided by the NHS.

If the disease progresses, further treatments and additional NHS services are included for patients. The treatments offered when the disease has progressed to this stage have limited potential to increase survival and improve quality of life.

Modelling the impact on health of epcoritamab

Data from the EPCORE™ NHL-1 trial and the indirect comparisons comparing the effectiveness of epcoritamab with axicabtagene ciloleucel and R-based chemoimmunotherapy were used in the health economic model. The economic analysis considered how much epcoritamab extended both overall survival and progression-free survival. The model used the data on overall survival and progression-free survival to track how many patients live without the disease worsening over time.

For people with LBCL that were estimated to be progression-free 24 months after treatment, clinical experts told AbbVie that the risk of disease progression is low. After this time point in the model, people are not expected to experience progression of their disease. Instead, they have a risk of dying that is just slightly higher than the general population.

When the time spent without disease progression and alive is combined with the quality of life, both the quality and time is captured by **quality-adjusted life years (QALYs)**. Data on the quality of life of patients in the EPCORE™ NHL-1 trial were also used in the model. The quality of life is measured using **utility values**. Utility values are generally a number between 0, which represents death, and 1, which represents perfect health. QALYs are a health outcome measure that consider both the length and the quality of life provided by a treatment. A year spent in perfect health (i.e. a utility score of 1) represents one QALY. Side effects were taken into account by lowering patients' utility values, and therefore QALYs, when they experienced a side effect.

The model only considers the quality of life of people with LBCL In addition, people are assumed to have the same quality of life if they are progression-free or have progressed disease. This is because of limited data on the impact of some comparator treatments on quality of life for some comparators.

Modelling the costs of treatments

Different costs are included in the model for the different treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of monitoring the patients whilst they receive treatment

- The costs of managing the disease
- The costs of medicines received after epcoritamab, axicabtagene ciloleucel or R-based chemoimmunotherapy
- The cost of side effects that can happen during treatment

Epcoritamab is a treatment that should be administered until the disease gets worse or until side effects from the treatment are too severe to be managed.[51] This is different from axicabtagene ciloleucel, which is given once, and R-based chemoimmunotherapy, which is given for a fixed period. This is considered in the model.

Several assumptions were made in the model that were discussed with clinicians and aligned with previous NICE appraisals.[30, 36, 41] Information on these assumptions can be found in **Document B, Section B.3.9**.

Cost effectiveness results

The effectiveness of epcoritamab and the associated costs were modelled over a 45-year period (considered to be equal to a lifetime period). The resulting accumulation of costs and QALYs associated with each treatment, and the ratio between these values, indicates whether the treatments are cost effective or not. A ratio of £30,000 per QALY is considered cost-effective for a new treatment to be adopted by the NHS.

A **severity modifier** is a factor that takes into account the severity or impact of a disease when evaluating the cost-effectiveness of a particular treatment. When epcoritamab was compared with rituximab-based chemoimmunotherapy in the model, a severity modifier was applied to the QALY results. This is because the model calculates that more than 85% of QALYs are lost compared to the general population. This makes the QALYs higher than they would be if the severity modifier was not applied.

Overall, the results of the health economic model submitted by the company showed that when comparing epcoritamab and rituximab-based chemoimmunotherapy, epcoritamab is associated with an increased cost and increased QALYs. The ratio of costs and QALYs for epcoritamab compared to rituximab-based chemoimmunotherapy was £24,682 per QALY. When comparing epcoritamab and axicabtagene ciloleucel, epcoritamab was found to be associated with lower costs and increased QALYs.

It is important to note that the company's estimation of cost-effectiveness is not the only result considered by NICE. NICE may prefer some assumptions that are different from the assumptions that the company used in their model. In addition, some comparators treatments may have confidential discounts that AbbVie do not have access to.

Benefits of epcoritamab not captured in the economic analysis

Whilst the QALYs calculated within the economic model aim to capture all the benefits to patients' HRQoL associated with new treatments, it is not always possible to do so. Some benefits that are not captured in the economic analysis include:

- The benefits of greater flexibility and convenience for patients associated with having a subcutaneous treatment instead of intravenous infusions

- Reduced capacity burden for the NHS due to the reduced numbers of intravenous infusions
- The value of providing an innovative treatment option
- The positive impact on carers and/or relatives when patients with R/R LBCL have improved outcomes

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Epcoritamab would represent an important advancement in the treatment of R/R LBCL

Despite advances in treatment for patients with R/R LBCL who have already received two or more previous treatment regimens, there is no standard of care that is accessible for a broad range of patients. As such, overall survival and progression-free survival for patients with R/R LBCL have been demonstrated to be poor. Therefore, there is an unmet need for tolerable and effective treatments that drive deep and durable responses in this population and that are available to all eligible patients.

Furthermore, CAR-T therapies are associated with waiting times (approximately 7 weeks). This means that patients cannot receive treatment with CAR-T therapies immediately which can be a burden for patients who have a disease that is likely to get worse quickly. UK clinical experts highlighted this as an important benefit associated with epcoritamab in a patient group with rapidly progressing disease and symptoms that substantially impact on their daily lives. In addition, there are a limited number of places that can deliver CAR-T therapies meaning some patients have to travel long distances to receive their treatment. Therefore, epcoritamab has the potential to provide a readily available treatment option that could increase patient access for effective treatments for R/R LBCL.[30]

Lastly, as a bispecific antibody, epcoritamab adds a new **mechanism of action** to the existing R/R LBCL treatment options. Epcoritamab is also the first and only subcutaneous treatment for patients with R/R LBCL who have already received two or more previous treatment regimens. This enables rapid administration across clinical practice as well as greater flexibility and convenience for both clinicians and patients.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no equality issues that are anticipated for the use of epcoritamab in adults with R/R LBCL.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on LBCL: • Lymphoma Out Loud Lymphoma Signs and Symptoms - Lymphoma Out Loud • Cancer Research UK Diffuse large B cell lymphoma | non-Hodgkin lymphoma | Cancer Research UK • Lymphoma Research Foundation Diffuse Large B-Cell Lymphoma: Relapsed/Refractory • Blood Cancer UK Non-Hodgkin lymphoma (NHL) transformed treatment | Blood Cancer UK • Lymphoma Research Foundation High-Grade B-Cell Lymphoma - Lymphoma Research Foundation • Macmillan Cancer Support Primary mediastinal large B-cell lymphoma (PMBCL) | Macmillan Cancer Support • Lymphoma Action Primary mediastinal large B-cell lymphoma (PMBCL) | Macmillan Cancer Support • Macmillan Cancer Support Follicular lymphoma (a type of non-Hodgkin lymphoma) | Macmillan Cancer Support • NHS Non-Hodgkin lymphoma - Diagnosis - NHS (www.nhs.uk) • Macmillan Cancer Support Diffuse large B-cell lymphoma (DLBCL) - causes, symptoms | Macmillan Cancer Support **Further information on epcoritamab:** • NCT03625037 GEN3013, Epcoritamab Trial in Patients With Relapsed, Progressive or Refractory B-Cell Lymphoma EPCORE™ NHL-1 - Tabular View - ClinicalTrials.gov

- NCT04628494 A Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in R/R DLBCL - Tabular View - ClinicalTrials.gov

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black** in this document. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Antibody	A protective protein produced by the immune system in response to the presence of a foreign substance
Allogenic stem cell transplantation	A procedure that involves transferring the stem cells from a healthy person (the donor) to the patient's body after high-intensity chemotherapy or radiation
Autoimmune conditions	A condition arising from an abnormal immune response to a functioning body part

Autologous stem cell transplantation	A procedure that uses the patient's own stem cells to replace the stem cells that are damaged by high-dose chemotherapy
B-cell	A type of white blood cell
Biopsy	A medical procedure that involves taking a small sample of body tissue so it can be examined under a microscope
Bispecific	An antibody treatment that can attach to two targets on different cells
Blood vessel	A tube through which the blood is circulated in the body
Bone marrow sample	A type of biopsy using a long needle to remove a sample of bone marrow from the pelvis (performed using local anaesthetic)
Bone marrow	A soft, spongy tissue inside most bones where blood cells (red blood cells, white blood cells and platelets) are made
Cancer	A disease that results from the uncontrolled growth and division of abnormal cells
Cancer Drugs Fund	A source of funding for cancer treatments in England that provides temporary access to the treatment while further evidence on efficacy and safety is collected. This allows patients to access new cancer therapies more quickly. After more data are collected, the treatment may be routinely available for patients or the temporary funding may be removed for new patients.
Chimeric antigen receptor T-cell (CAR-T) therapy	A therapy that is specifically developed for each individual patient. It involves reprogramming the patient's own immune

	system cells which are then used to target their cancer
Cell	The building blocks for all living things
Chemotherapy	Treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing
Chemoimmunotherapy	Chemotherapy combined with immunotherapy
Clinical trial	A type of research study that evaluates how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. This is also called a clinical study
Clinical practice	The agreed-upon means of delivering health care by doctors, nurses and other healthcare professionals
Complete response	The disappearance of all signs of cancer in response to treatment. However, this does not always mean the cancer has been cured. This is also called complete remission
Computerised tomography scan (CT)	A scan that takes a series of X-rays to build up a 3D picture of the inside of the body
Cytokine release syndrome	When the immune system responds to immunotherapy drugs more aggressively than it should, causing symptoms such as fever (high temperature), dizziness due to low blood pressure and difficulty breathing
De novo	Cancer that is first diagnosed from the original site that it formed from

Diarrhoea	The condition of having at least three loose, liquid, or watery bowel movements each day
Duration of response	The length of time that a tumour continues to respond to treatment without the cancer growing or spreading
Diffuse	A disease that is not limited or localised and is instead widespread
Diffuse large B-cell lymphoma	The most common form of large B-cell lymphoma. It is an aggressive type of non-Hodgkin's lymphoma
Efficacy	The ability of a medicine to produce a desired positive effect on the patient's disease or illness
Follicular lymphoma	Follicular lymphoma is a type of large B-cell lymphoma in which tumour cells grow as groups and form nodules
Follicular lymphoma grade 3B	A subtype of follicular lymphoma that is similar to diffuse large B-cell lymphoma
General anaesthetic	A state of controlled unconsciousness. During a general anaesthetic procedure, medicines are used to put the patient to sleep, so they are unaware of surgery and do not move or feel pain while it is carried out
General practitioner	A doctor based in the community who treats patients with minor or chronic illnesses and refers those with serious conditions to a hospital

Genes	An inherited part of a cell in a living thing that controls physical characteristics, growth and development
Gland	A group of cells that secrete hormones, sweat, saliva, mucus or acids
Grade	A description of cancer cells based on how quickly they are likely to grow and spread. Lymphomas can be called low-grade (slow-growing) or high-grade (fast-growing)
High grade	A fast-growing form of lymphoma
High grade B-cell lymphoma	A particularly aggressive type of large B-cell lymphoma
Hodgkin lymphoma	A cancer of the immune system that develops from abnormal B-cells that is marked by the presence of Reed-Sternberg lymphocytes
Immune system	A network of biological processes that protects a person from diseases
Immunotherapy	Treatments that use the immune system to find and attack cancer cells
Indirect treatment comparison	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised trial
Intravenous treatment	A medical technique that delivers medicines through an injection directly into a person's vein
Large B-cell lymphoma	Cancer that affects the B-lymphocytes which is a type of white blood cell

Local anaesthetic	A type of medicine that numbs an area of the body. Unlike general anaesthetics, local anaesthetics do not cause the patient to lose consciousness
Low-grade	A slow-growing form of lymphoma
Lumbar puncture	A type of medical examination that includes using a thin needle to extract a sample of spinal fluid
Lymphatic system	A network of specialised blood vessels and organs that make up part of the immune system
Lymph node	Also known as a lymph gland, it is an organ of the lymphatic system and immune system
Lymphocyte	A type of white blood cell made in the bone marrow and found in the blood and lymph tissue
Lymphoma	A blood cancer that forms tumours in the lymphatic system
Marketing authorisation	A licence that sets out the conditions for the use of a treatment based on evidence for its safety and effectiveness
Mechanism of action	How a treatment works
Mediastinum	The area of the body that contains the gullet, windpipe, thymus, heart, large blood vessels and lymph nodes
Magnetic resonance imaging (MRI) scan	A scan that uses strong magnetic fields to build up a detailed picture of areas of the body

National Institute for Health and Care Excellence (NICE)	The body in England that decides whether to approve new medicines for funding on the NHS based on whether they can be demonstrated to be value for money
Non-Hodgkin's lymphoma	A cancer of the immune system that develops from abnormal lymphocytes that does not express Reed-Sternberg lymphocytes
Neurotoxicity	Damage to the brain or nervous system caused by exposure to toxic substances
Neutropenia	A condition characterised by abnormally low levels of white blood cells called neutrophils. The condition can increase the risk of infections
Organ	A collection of tissues joined in a structural unit to serve a common function
Overall survival	A clinical trial outcome that measures how long patients, who undergo a certain treatment regimen, live compared to patients who are in a control group
Overall response rate	The proportion of patients in a trial whose tumour is destroyed or significantly reduced by a treatment
Partial response	A decrease in the size of the cancer, or in the extent of cancer in the body, in response to treatment. Also called partial remission
Partitioned survival model	A type of model that is used to analyse the impact of different factors on survival estimates within distinct groups of a population

Peripheral neuropathy	Peripheral neuropathy develops when nerves in the body's extremities, such as the hands, feet and arms, are damaged. The symptoms depend on which nerves are affected but can include numbness and tingling in the feet or hands, burning/stabbing/shooting pain in affected areas, loss of balance and co-ordination, and muscle weakness (particularly in the feet)
Pola + BR	A treatment made up of polatuzumab vedotin (Polivy®), bendamustine and rituximab
Pola + R-CHP	A treatment that is made up of polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisone
Positron emission tomography (PET) scan	A scan that measures the activity of cells in different parts of the body. It is usually performed at same time as a CT scan to show precisely how the tissues of different parts of the body are working
Phase 1/2 clinical trial	A type of clinical trial that tests the efficacy of a drug and to further study its safety. A key focus of Phase 2 studies is determining the optimal dose or doses of a drug candidate, to determine how best to administer the drug to maximise possible benefits, while minimising risks
Phase 3 clinical trial	A type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects

Primary mediastinal B-cell lymphoma	An aggressive type of large B-cell lymphoma that mainly affects the mediastinum
Progression-free survival	An outcome of a clinical trial that indicated how long a person lives without the disease worsening
Protein	The basis of body structures, such as skin and hair; they are needed for the body to function properly
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living
Radiotherapy	The treatment of disease that kills cancer cells through radiation such as x-rays
R-CHOP	A treatment made up of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone

Reed-Sternberg lymphocyte	An abnormal type of B lymphocyte that is found in patients with Hodgkin lymphoma
R-GemOx	A chemoimmunotherapy combination including rituximab, gemcitabine and oxaliplatin
Refractory	A disease that is resistant at the beginning of treatment, or becomes resistant during treatment
Relapsed	When an unwell person's health becomes worse after a period of improvement
Remission	When the signs and symptoms of the disease have decreased
Severity modifier	A factor that takes into account the severity or impact of a disease or condition when evaluating the cost-effectiveness of the treatment
Single-arm trial	A clinical trial design where everyone enrolled will be treated with the same treatment and in the same way
Stage	A score used by healthcare professionals to indicate how far a cancer has spread
Stem cell transplant	Replacement of damaged or diseased stem cells with healthy cells
Stem cells	A cell from which other types of cells develop, such as muscle cells, blood cells or nerve cells.
Steroid	A type of medicine which reduces inflammation

Subcutaneous treatment	A medical technique that delivers a drug through a short needle injection into the tissue layer between the skin and the muscle
Targeted therapy	A type of cancer treatment that uses drugs to target specific genes and proteins that help cancer cells survive and grow
T-cell	One of the important types of white blood cells of the immune system
Time to next anti lymphoma therapy	A clinical trial outcome that measures the time from the first dose of the trial drug to the first recorded administration of subsequent anti-lymphoma therapy
Tissue	A group of cells that have a similar structure and act together
Thymus	A small gland at the top part of the chest
Tumour	An abnormal growth that may be cancer (depending on the type of growth)
Utility value	A measure of health-related quality of life, typically ranging from 0 (indicating death) and 1 (indicating perfect health)
White blood cell	Cells of the immune system that are involved in protecting the body against disease and foreign invaders

4c) References

1. Lymphoma Out Loud. Lymphoma Signs and Symptoms. Available at: https://lymphomaoutloud.org/signs-symptoms/ [Accessed: 10 February 2023].
2. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med 2021;384:842-858.
3. Cancer Research UK. Diffuse Large B-Cell Lymphoma. Available at: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma [Accessed: 1 November 2022].
4. Lymphoma. Diffuse Large B-Cell Lymphoma: Relapsed/Refractory. Accessed: https://lymphoma.org/understanding-lymphoma/aboutlymphoma/nhl/dlbcl/relapseddlbcl/#:~:text=Diffuse%20Large%20B-Cell%20Lymphoma%3A%20Relapsed%2FRefractory%20The%20term%20%E2%80%9Crelapsed%E2%80%9D,response%20to%20treatment%20does%20not%20last%20very%20long [Last Accessed: 16 January 2023]
5. Blood cancer UK. Diffuse large B-cell lymphoma (DLBCL) treatment and side effects. Accessed: https://bloodcancer.org.uk/understanding-blood-cancer/lymphoma/diffuse-large-b-cell-lymphoma/dlbcl-treatment-side-effects/treatment-transformed-non-hodgkin-lymphoma/ [Last Accessed: 26 January 2023]
6. The Haematological Malignancy Research Network. Prevalence. Estimated UK prevalence. Available at: https://hmrn.org/statistics/prevalence [Accessed: 18 January 2023].
7. The Haematological Malignancy Research Network. Prevalence. Estimated UK incidence. Available at: https://hmrn.org/statistics/incidence [Accessed: 9 March 2023].
8. Yang X, Laliberté F, Germain G, et al. Real-World Characteristics, Treatment Patterns, Health Care Resource Use, and Costs of Patients with Diffuse Large B-Cell Lymphoma in the U.S. Oncologist 2021;26:e817-e826.
9. Lymphoma Action. Diffuse Large B-Cell Lymphoma. Available at: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma [Accessed: 10 October 2022]
10. Lymphoma Research Foundation. High-Grade B-Cell Lymphoma. https://lymphoma.org/understanding-lymphoma/aboutlymphoma/nhl/hgbcl/ [Last Accessed 14 November 2022].
11. Deng M, Xu-Monette ZY, Pham LV, et al. Aggressive B-cell Lymphoma with MYC/TP53 Dual Alterations Displays Distinct Clinicopathobiological Features and Response to Novel Targeted Agents. Mol Cancer Res 2021;19:249-260.
12. Lymphoma Research Foundation. Understanding Lymphoma High-Grade B-Cell Lymphoma. Available at: https://lymphoma.org/wp-content/uploads/2022/07/LRF_High_Grade_B_Cell_Lymphoma_Fact_Sheet.pdf [Accessed: 18 January 2023].
13. Cwynarski K, Marzolini MAV, Barrington SF, et al. The management of primary mediastinal B-cell lymphoma: a British Society for Haematology Good Practice Paper. Br J Haematol 2019;185:402-409.
14. Dabrowska-Iwanicka A, Walewski JA. Primary mediastinal large B-cell lymphoma. Curr Hematol Malig Rep 2014;9:273-83.

15. Lymphoma Australia. Primary Mediastinal B-cell Lymphoma (PMBCL). Symptoms of PMBCL. Available at: https://www.lymphoma.org.au/types-of-lymphoma/non-hodgkin-lymphoma/aggressive-fast-growing-b-cell-nhl/primary-mediastinal-b-cell-lymphoma-pmbcl/#:~:text=These%20may%20include%3A%201%20Cough%202%20Pain%20or,you%20bend%20forward%208%20More%20visible%20chest%20veins [Accessed 4 April 2023].

16. Macmillan Cancer Support. Primary mediastinal large B-cell lymphoma (PMBCL). Available at: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/primary-mediastinal-large-b-cell [Accessed: 19 January 2023].

17. Lymphoma action. Follicular lymphoma. Available at: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/follicular-lymphoma. [Last Accessed 14 November 2022].

18. Galaznik A, Huelin R, Stokes M, et al. Systematic review of therapy used in relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. Future Sci OA 2018;4:Fso322.

19. Salaverria I, Siebert R. Follicular lymphoma grade 3B. Best Pract Res Clin Haematol 2011;24:111-9.

20. Barraclough A, Bishton M, Cheah CY, et al. The diagnostic and therapeutic challenges of Grade 3B follicular lymphoma. Br J Haematol 2021;195:15-24.

21. Macmillan Cancer Support. Follicular lymphoma (FL). Available at: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/follicular [Last Accessed 14 Nov 2022].

22. Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008;26:5165-9.

23. Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol 2015;33:2516-22.

24. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. Final appraisal document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document [Accessed: 1 November 2022].

25. Northend M, Wilson W, Osborne W, et al. Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. Blood Adv 2022;6:2920-2926.

26. Ahmed Z, Afridi SS, Shahid Z, et al. Primary Mediastinal B-Cell Lymphoma: A 2021 Update on Genetics, Diagnosis, and Novel Therapeutics. Clin Lymphoma Myeloma Leuk 2021;21:e865-e875.

27. Al-Juhaishi T, McKay J, Sindel A, et al. Perspectives on chemotherapy for the management of double-hit lymphoma. Expert Opin Pharmacother 2020;21:653-661.

28. NHS. Diagnosis. Non-Hodgkin lymphoma. Available at: https://www.nhs.uk/conditions/non-hodgkin-lymphoma/diagnosis/ [Accessed: 10 Feb 2023].

29. AbbVie Data on File. Epcoritamab for Treating Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL). UK Medical Advisory Board – Meeting Report. 22 February 2023.

30. AbbVie Data on File. Epcoritamab in Large B-Cell Lymphoma: Clinical Validation Interviews. December 2022–May 2023.

31. AbbVie Advisory Board. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). 14 July 2022.

32. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol 2016;174:43-56.

33. Macmillan. R-CHOP. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/r-chop [Accessed: 14 November 2022].

34. NICE. Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [TA874]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10785/documents [Accessed: 17 Feb 2023].

35. NICE. Non-Hodgkin's lymphoma: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng52/resources/nonhodgkins-lymphoma-diagnosis-and-management-pdf-1837509936325 [Accessed: 18 November 2022].

36. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Available at: https://www.nice.org.uk/guidance/ta649/resources/polatuzumab-vedotin-with-rituximab-and-bendamustine-for-treating-relapsed-or-refractory-diffuse-large-bcell-lymphoma-pdf-82609146587077 [Accessed: 10 October 2022].

37. Macmillan Cancer Support. Pola-BR. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/pola-br [Accessed: 20 Feb 2023].

38. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA559]. Available at: https://www.nice.org.uk/guidance/TA559 [Accessed: 18 November 2022].

39. NICE. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. Available at: https://www.nice.org.uk/guidance/TA567 [Accessed: 18 November 2022].

40. NICE. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma [TA306]. Available at: https://www.nice.org.uk/guidance/ta306 [Accessed: 18 November 2022].

41. NICE. Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10645/documents [Accessed: 25 November 2022].

42. Macmillan. R-CHOP. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/r-chop [Last Accessed 14 November 2022].

43. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531-2544.

44. Macmillan Cancer Support. CAR T-cell therapy. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/car-t-cell-therapy [Accessed 20 Feb 2023].

45. Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). Ann Oncol 2017;28:836-842.

46. NHS 75 England. CAR-T Therapy. Available at: https://www.england.nhs.uk/cancer/cdf/car-t-therapy/ [Accessed: 23 Feb 2023].

47. Gye A, Goodall S, De Abreu Lourenco R. A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared With Older Patients. Value Health 2022;25:47-58.

48. , AbbVie Data on File. DLBCL statement - patient experience. .

49. Lymphome Action. Epcoritamab: A phase 1b/2 trial of a targeted treatment, epcoritamab, in combination with different chemotherapy regimens, in people with B-cell non-Hodgkin lymphoma. Available at: https://lymphoma-action.org.uk/trial/epcoritamab-phase-1b2-trial-targeted-treatment-epcoritamab-combination-different-chemotherapy#Treatments [Accessed: 20 Feb 2023].

50. AbbVie Oncology. Investigational Drugs for Cancer. Available at: https://abbviescience.com/oncology/pipeline [Accessed: 24 November].

51. AbbVie Data on File. Epcoritamab Draft SmPC. 8 November 2022.

52. Thieblemont C, Phillips T, Ghesquieres H, et al. ABCL-422 Subcutaneous Epcoritamab in Patients With Relapsed or Refractory Large B-Cell Lymphoma (EPCORE NHL-1): Pivotal Results from a Phase 2 Study. Clinical Lymphoma Myeloma and Leukemia 2022;22:S379.

53. FACIT. FACT-Lym Functional Assessment of Cancer Therapy – Lymphom. Available at: https://www.facit.org/measures/FACT-Lym [Accessed: 23 Feb 2023].

54. Euroqol. EQ-5D-3L About. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/ [Accessed: 23 Feb 2023].

55. DIPG. Side Effects in Clinical Trials. Available at: https://www.dipg.org/dipg-research/clinical-trials-for-dipg/side-effects/#:~:text=Adverse%20events%20are%20graded%20on%20a%20scale%20from,with%20doing%20some%20activities%20but%20are%20not%20dangerous. [Accessed: 22 March 2023].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Clarification questions

May 2023

File name	Version	Contains confidential information	Date
ID4045 epcoritamab for relapsed or refractory LBCL – EAG clarification letter 10.05.23 [AIC]	**V1.0**	**Yes**	**10/05/2023**
ID4045 epcoritamab EAG clarification letter v2 for PM 160523 HS [AIC].docx	**V2**	**Yes**	**16/05/2023**
ID4045 epcoritamab EAG clarification letter v3 for PM 180523 HS [AIC]	**V3**	**Yes**	**18/05/2023**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

EPCORE NHL-1 trial

A1. Priority question. The EAG notes that subgroup results for ORR have been provided in Figure 10 of the CS and other outcome results are in the CSR. Please could KM plots (as provided in Figures 6 and 8 of the CS, including numbers at risk) for OS and PFS be provided for the following subgroups:

a) Prior vs no prior CAR-T therapy

The Kaplan–Meier (KM) plots of overall survival (OS) and progression-free survival (PFS) by prior chimeric antigen receptor T-cell (CAR-T) therapy from the [redacted] data cut of EPCORE™ NHL-1, for the diffuse large B-cell lymphoma (DLBCL) and large B-cell lymphoma (LBCL) populations are presented in Figure 1–Figure 4. Overall, the OS and PFS KM plots by prior CAR-T therapy demonstrate that epcoritamab has the potential to provide benefits in OS and PFS, regardless of prior CAR-T therapy status.

Figure 1: KM plot of OS by prior CAR-T – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; OS: overall survival; NR: not reached.
Source: Figure 901.3_04.01.03 AbbVie, EPCORE™ NHL-1 Figures, [redacted] [1]

Figure 2: KM plot of OS by prior CAR-T – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; NR: not reached.
Source: Figure 901.3_04.01.03 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 3: KM plot of PFS by prior CAR-T – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; PFS: progression-free survival.
Source: Figure 901.3_03.01.03 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 4: KM plot of PFS by prior CAR-T – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival.
Source: Figure 901.3_03.01.03 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

b) 2, 3 and 4+ prior anti-lymphoma treatments

The KM plots of OS and PFS by prior anti-lymphoma treatments from the [redacted] data cut of EPCORE™ NHL-1, for the DLBCL and LBCL population are presented in Figure 5–Figure 8. Similarly to the subgroup analyses conducted by prior CAR-T therapy status, overall, the OS and PFS KM plots by prior anti-lymphoma treatments demonstrate that epcoritamab has the potential to provide benefits in OS and PFS, regardless of the number of prior lines of anti-lymphoma treatments received. The OS and PFS data are consistent between DLBCL and LBCL populations, with the highest OS observed in patients with two prior lines of therapy (median OS of [redacted] for both DLBCL and LBCL populations) and in patients with three prior lines of therapy (median OS is [redacted] for both DLBCL and LBCL populations). Furthermore, the PFS data appear to show similar long-term outcomes regardless of prior CAR-T, which supports extended responses in patients. This supports the proposed positioning of epcoritamab in patients with LBCL treated with two prior lines of therapy.

Figure 5: KM plot of OS by number of prior lines of therapy – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; OS: overall survival; NR: not reached; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_04.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 6: KM plot of OS by number of prior lines of therapy – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; NR: not reached; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_04.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 7: KM plot of PFS by number of prior lines of therapy – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; PFS: progression-free survival; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_03.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 8: KM plot of PFS by number of prior lines of therapy – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_03.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

A2. Priority question. Please provide a breakdown of adverse events (as provided already in Tables 32 to 36 of the CS for the overall population) for the following subgroups:

a) Prior vs no prior CAR-T experience

All safety analyses were conducted on the safety analysis set (SAF; N=157), as stated in Document B (Section B.2.4.1), in order to utilise the maximum sample size available from EPCORE™ NHL-1. However, in response to the request from the EAG, the summary of adverse events (AEs) split by prior CAR-T therapy and no prior CAR-T therapy are provided in Table 1–Table 5.

Overall, the AEs for patients with prior and no prior CAR-T therapy are consistent across the majority of AEs. Considering individual treatment-emergent adverse events (TEAEs), no differences in frequency of 10% or more occurred between the subgroups, except for cytokine release syndrome (CRS); patients who had received prior CAR-T were less likely to experience a CRS event compared with those who had not received prior CAR-T therapy. However, in both subgroups, the majority of CRS events were grade 1 or 2, with [redacted] and [redacted] experiencing grade 3 CRS events in the prior CAR-T and no prior CAR-T subgroups of the LBCL population. For grade 3 or higher TEAEs, no differences in frequency of 10% or higher occurred between the subgroups.

Table 1: Summary of TEAEs for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

Number of patients (%)	Prior CAR-T		No prior CAR-T	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Number of patients with ≥1				
TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by worst toxicity grade				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients (%)	Prior CAR-T		No prior CAR-T	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
TEAE leading to dose delay/interruption	[redacted]	[redacted]	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Fatal related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
AESI; Number of patients with ≥1				
CRS	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]
CTLS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Tables 901.4_01.01.03, 901.4_10.01.03, 901.4_11.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 2: Most common (at least 10% in any group) TEAEs by SOC and PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	Prior CAR-T				No prior CAR-T			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 TEAE	[redacted]							
General disorders and administration site conditions	[redacted]							
Pyrexia	[redacted]							
Fatigue	[redacted]							
Injection site reaction	[redacted]							
Oedema peripheral	[redacted]							
Gastrointestinal disorders	[redacted]							
Diarrhoea	[redacted]							
Nausea	[redacted]							
Abdominal pain	[redacted]							
Constipation	[redacted]							
Vomiting	[redacted]							
Immune system disorders	[redacted]							
CRS	[redacted]							
Infections and infestations	[redacted]							
COVID-19	[redacted]							
Blood and lymphatic system disorders	[redacted]							
Neutropenia	[redacted]							
Anaemia	[redacted]							

Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 901.4_02.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 3: Most common (2% or more in any group) serious TEAEs by SOC and PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	Prior CAR-T				No prior CAR-T			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 901.4_04.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 4: Summary of AESIs for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

Number of patients (%)	Prior CAR-T		No prior CAR-T	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Patients with ≥1 ICANS event	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 CRS event[a]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]

[a] CRS events are graded according to Lee et al, 2019.[2]

Abbreviations: AESI: adverse events of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set.

Source: Tables 901.4_10.01.03, 901.4_11.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 5: Summary of fatal TEAEs by PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

Preferred Term	Prior CAR-T				No prior CAR-T			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]							
COVID-19	[redacted]							
COVID-19 pneumonia	[redacted]							
Progressive multifocal leukoencephalopathy	[redacted]							
ICANS	[redacted]							
Myocardial infarction	[redacted]							
General physical health deterioration	[redacted]							
Hepatotoxicity	[redacted]							
Pulmonary embolism	[redacted]							

[a] AEs are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 901.4_09.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

b) 2, 3 and 4+ prior anti-lymphoma treatments

The summary of AEs split by number of prior lines of treatment are presented in Table 6–Table 10. Overall, the AEs split by number of prior lines of treatment are highly consistent across the subgroups. Considering the AEs of special interest (AESIs) for instance, the number of patients with LBCL experiencing one or more CRS event was [redacted], [redacted] and [redacted] in the subgroup of patients that had received two, three or four lines and beyond, respectively; the number of patients with LBCL experiencing one or more immune effector cell-associated neurotoxicity syndrome (ICANS) event was [redacted], [redacted] and [redacted] in the subgroup of patients that had received two, three or four lines and beyond, respectively.

Table 6: Summary of TEAEs by number of prior lines of therapy (SAF; [redacted] data cut-off)

Number of patients (%)	2L		3L		4L+	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Number of patients with ≥1						
TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by worst toxicity grade						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to dose delay/interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AESI; Number of patients with ≥1						

Number of patients (%)	2L		3L		4L+	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
CRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 901.4_01.01.02a, 901.4_10.01.02a, and 901.4_11.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted] [1]

Table 7: Most common (at least 10% in any group) TEAEs by SOC and PT by number of prior lines of therapy (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	2L				3L				4L+			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 TEAE	[redacted]											
General disorders and administration site conditions	[redacted]											
Pyrexia	[redacted]											
Fatigue	[redacted]											
Injection site reaction	[redacted]											
Oedema peripheral	[redacted]											
Gastrointestinal disorders	[redacted]											
Diarrhoea	[redacted]											
Nausea	[redacted]											
Abdominal pain	[redacted]											
Constipation	[redacted]											
Vomiting	[redacted]											
Immune system disorders	[redacted]											
CRS	[redacted]											

Infections and infestations	[redacted]											
COVID-19	[redacted]											
Blood and lymphatic system disorders	[redacted]											
Neutropenia	[redacted]											
Anaemia	[redacted]											
Thrombocytopenia	[redacted]											
Musculoskeletal and connective tissue disorders	[redacted]											
Back pain	[redacted]											
Metabolism and nutrition disorders	[redacted]											
Decreased appetite	[redacted]											
Nervous system disorders	[redacted]											
Headache	[redacted]											
Psychiatric disorders	[redacted]											
Insomnia	[redacted]											

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.

Source: Table 901.4_12.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 8: Most common (2% or more in any group) serious TEAEs by SOC and PT by number of prior lines of therapy (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	2L				3L				4L+			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 serious TEAE	[redacted]											
Immune system disorders	[redacted]											
CRS	[redacted]											
Infections and infestations	[redacted]											
Sepsis	[redacted]											
COVID-19	[redacted]											
Pneumonia	[redacted]											
Nervous system disorders	[redacted]											
ICANS	[redacted]											
Respiratory, thoracic, and mediastinal disorders	[redacted]											
Pleural effusion	[redacted]											
Blood and lymphatic system disorders	[redacted]											

Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.

Source: Table 901.4_13.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 9: Summary of AESIs by number of prior lines of therapy (SAF; [redacted] data cut-off)

Number of patients (%)	2L		3L		4L+	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Patients with ≥1 ICANS event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 CRS event[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] CRS events are graded according to Lee et al, 2019.[2]

Abbreviations: AESI: adverse events of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.

Source: Tables 901.4_10.01.02a and 901.4_11.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 10: Summary of fatal TEAEs by PT by number of prior lines of therapy (SAF; [redacted] data cut-off)

Preferred Term	2L				3L				4L+			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]											
COVID-19	[redacted]											
COVID-19 pneumonia	[redacted]											
Progressive multifocal leukoencephalopathy	[redacted]											
ICANS	[redacted]											
Myocardial infarction	[redacted]											
General physical health deterioration	[redacted]											
Hepatotoxicity	[redacted]											
Pulmonary embolism	[redacted]											

[a] AEs are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.

Source: Table 901.4_09.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

A3. Priority question. In Table 14.1.2.4 of the CSR data tables (June 2022), please clarify what is meant by "subsequent anti-lymphoma treatments":

a) **Are these treatments that were received after epcoritamab was stopped (due to progression or toxicity) in each patient?**

The date of the [redacted] data cut of EPCORE™ NHL-1 is academic-in-confidence (AIC). As such, AbbVie request that this is marked accordingly in Clarification Question A3, and throughout the Clarification Questions as required.

Of the [redacted] patients who received any subsequent anti-lymphoma therapy in EPCORE™ NHL-1, all were initiated after epcoritamab was discontinued. The cause of discontinuation for these patients was primarily due to disease progression; of the [redacted] patients who received subsequent anti-lymphoma therapy, [redacted] patients discontinued epcoritamab due to disease progression, [redacted] discontinued due to AEs, [redacted] discontinued to receive transplant and [redacted] discontinued to receive bridging therapy.

b) **Were patients using these subsequent treatments still included in outcome analyses (e.g. OS, PFS and TTD) past the point at which they started using them or where they censored from analyses at this point?**

As described in the statistical analysis plan, the primary definition of the PFS analysis accounts for subsequent anti-lymphoma therapy and censors PFS at the last evaluable tumour assessment on or prior to the date of subsequent anti-lymphoma therapy. As per Table 17 of the company submission (CS), [redacted] patients with DLBCL were censored in this PFS analysis. In contrast, the secondary definition of PFS does not account for subsequent anti-lymphoma therapy; [redacted] patients with DLBCL were censored in the PFS analysis using the secondary definition. As stated in response to Clarification Question B3, all PFS data presented in the CS and used in the cost-effectiveness model are based on Independent Review Committee assessment, Lugano criteria, primary definition.

The OS definition is also irrespective of subsequent therapy and does not account for subsequent anti-lymphoma therapy; if a patient is not known to have died, then OS was censored at the latest date the patient was known to be alive.

Time to treatment discontinuation (TTD) is defined as the time from the start date of first treatment until discontinuation or death due to any cause, whichever occurs first. If a patient is not known to have discontinued, then TTD will be censored at the last known alive date. As all patients who received any subsequent anti-lymphoma therapy initiated this after epcoritamab was discontinued, TTD does not account for subsequent anti-lymphoma therapy.

A4. Priority question. Please provide the following outcomes from the EPCORE NHL-1 trial specifically for the following groups (DLBCL, no prior CAR-T [n=86], and LBCL with no prior CAR-T and CAR-T eligible [n=57]):

a) **Adverse events as described in Tables 32 to 36 of the CS**

The total number of patients in the DLBCL, no prior CAR-T subgroup ([redacted]) and the LBCL, no prior CAR-T, CAR-T eligible subgroup ([redacted]) are AIC. As such, AbbVie request that these are marked accordingly in Clarification Question A4, and throughout the Clarification Questions as required.

The summary of AEs for the DLBCL, no prior CAR-T ([redacted]) subgroup are presented in Table 1–Table 5 (Clarification Question A1).

A summary of the AEs for the LBCL, no prior CAR-T, CAR-T eligible subgroup ([redacted]) based on the [redacted] data cut of EPCORE™ NHL-1 are presented in Table 11–Table 15.

Table 11: Summary of TEAEs for CAR-T eligible subgroup (SAF; [redacted] data cut-off)

Number of patients (%)	LBCL ([redacted])
Number of patients with ≥1	
TEAE	[redacted]
Related TEAE	[redacted]
Grade 3 and higher TEAE	[redacted]
Grade 3 and higher related TEAE	[redacted]
TEAE by worst toxicity grade	
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
Serious TEAE	[redacted]
Serious related TEAE	[redacted]
TEAE leading to treatment discontinuation	[redacted]
TEAE leading to dose delay/interruption	[redacted]
Fatal TEAE	[redacted]
Fatal related TEAE	[redacted]
AESI; Number of patients with ≥1	
CRS	[redacted]
ICANS	[redacted]
CTLS	[redacted]

Abbreviations: AESI: adverse event of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Tables 901.4_01.01.07, 901.4_11.01.07, 901.4_10.01.07 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 12: Most common (at least 10% in any group) TEAEs by SOC and PT for CAR-T eligible subgroup (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	LBCL ([redacted])	
	All	Related
Patients with ≥1 TEAE	[redacted]	[redacted]

General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 901.4_02.01.07 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 13: Most common (2% or more in any group) serious TEAEs by SOC and PT for CAR-T eligible subgroup (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	LBCL ([redacted])	
	All	Related
Patients with ≥1 serious TEAE	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
ICANS	[redacted]	[redacted]

Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 901.4_04.01.07 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 14: Summary of AESIs for CAR-T eligible subgroup (SAF; [redacted] data cut-off)

Number of patients (%)	LBCL ([redacted])
Patients with ≥1 ICANS event	[redacted]
Grade 1	[redacted]
Patients with ≥1 CRS event	[redacted]
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	[redacted]

CRS events are graded according to Lee et al, 2019.[2]

Abbreviations: AESI: adverse events of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set.

Source: Tables 901.4_11.01.07, 901.4_10.01.07 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 15: Summary of fatal TEAEs by PT for CAR-T eligible subgroup (SAF; [redacted] data cut-off)

Preferred Term	LBCL ([redacted])	
	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Progressive multifocal leukoencephalopathy	[redacted]	[redacted]

[a] Adverse events are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: Table 901.4_09.01.07 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted] [1]

b) EQ-5D-3L results as reported in Table 21 of the CS

A summary of the EQ-3D-3L based on the [redacted] data cut for EPCORE™ NHL-1 for the DLBCL, no prior CAR-T population and the LBCL, no prior CAR-T, CAR-T eligible population are presented in Table 16.

Table 16: Mean scores for EQ-5D-3L health utility score while on treatment by subgroup (FAS; [redacted] data cut-off)

Time point	DLBCL no prior CAR-T		LBCL CAR-T eligible	
	Sample size	Health utility score, mean (SD)	Sample size	Health utility score, mean (SD)
C1D1	[redacted]	[redacted]	[redacted]	[redacted]
C3D1	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
C5D1	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma; EQ-5D-3L: EuroQoL-5 diminesions-3 levels; FAS: full analysis set; LBCL: large B-cell lymphoma; SD: standard deviation.
Source: Tables 901.3_10.01.03, Table 901.3_10.01.07 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A5. Please confirm whether diagnosis of LBCL, to be included in the EPCORE NHL-1 trial, was based on review by a single individual within each centre or whether this was based on MDT review.

For every patient enrolled in EPCORE™ NHL-1, the confirmation of LBCL diagnosis was made at a local/site level, with the site providing a pathology report as confirmation of diagnosis; the pathology report contained information on the relevant markers associated with the LBCL subtype, assessed by histology, cytogenetics, fluorescent in situ hybridisation or polymerase chain reaction.

Information regarding whether the site involved an individual or multidisciplinary (MDT) review of that report to confirm diagnosis was not collected in the trial database.

MAIC analyses

The EAG is concerned with the use of a HR to derive survival curves for POLA+BR and axi-cel in the model, as the underlying KM data for epcoritamab and Sehn and ZUMA-1, respectively, cross for OS and PFS outcomes. Therefore, in questions A7 to A10, the EAG suggests that the company changes their approach and fits parametric survival curves independently for all treatments. For consistency, the EAG requests that the company follows the same approach for the comparison with R-CIT.

The EAG is aware that its requests regarding matching to each individual comparator trial will mean there is not a common comparator population for the comparisons vs R-CIT and POLA+BR. However, the EAG considers its suggestions to address issues in the current analyses and make a more robust use of the available data to inform the comparisons.

A6. Priority question. The EAG notes that for unanchored MAICs, it is critical that attempts to adjust for all potential prognostic factors and treatment effect modifiers that are in imbalance between arms are made, as outlined in NICE DSU TSD18.[3] Given the difficulty in confirming which factors are prognostic/effect modifying, the EAG considers it best practice to adjust for all baseline characteristics reported in the relevant studies.

In particular, the EAG's clinical experts consider the following to be potentially important prognostic factors: age >65 years, ECOG score, disease stage III-IV, IPI score, number of prior treatment lines, primary refractoriness and refractory vs relapse to last treatment.

For updated MAICs requested in questions A7 to A10 below, please consider the following:

a) **While the EAG notes that rationale for not including some of those mentioned above (e.g. line of therapy and IPI) has been provided in the CS, please reconsider whether it is possible to include them in updated analyses requested in subsequent questions (in addition to any others identified)**

Please see response under part b of this Clarification Question to address all queries related to Clarification Question A6.

b) Please comment on any factors that could not be adjusted for and the impact this lack of adjustment is expected to have on the results.

As outlined in the CS (Section B.2.8.1), the effect modifiers and prognostic variables to be adjusted for in the matching adjusted indirect comparisons (MAICs) were carefully considered and identified via an evidence-based process.

The variables to adjust for in the MAICs were identified based on published literature (including peer-reviewed published indirect treatment comparisons (ITCs) and consideration of previous NICE evaluations in the indication of interest), empirical testing of prognostic status in the EPCORE™ NHL-1 trial and input from UK clinical experts as to whether certain characteristics are important to adjust for in a R/R LBCL population.[4-6] Furthermore, AbbVie conducted validation with health economics experts, who confirmed that the approach used to identify variables to include in the adjustment was suitable and robust.

The identification of variables to be included for adjustment was conducted in line with the guidance provided in NICE DSU TSD18, which outlines that including too many variables for adjustment will reduce the effective sample size, negatively affecting the precision of the estimate.[7] As such, based on the above evidence-based process, AbbVie identified the most relevant variables for adjustment. The MAICs conducted in response to the following requests from the EAG have maintained the same approach and not adjusted for all reported baseline characteristics. Instead, all important effect modifiers and prognostic variables identified have been adjusted for, without over-adjusting for too many variables such that the effective sample size is decreased to an unnecessary degree. Over-adjusting the epcoritamab population to match the comparator populations would result in broader 95% confidence intervals, lower sample sizes and increased p-values. This would have led to more uncertain results compared with those incorporated into the base case analyses.

A list of all variables identified as important prognostic factors, and those ultimately adjusted for in the base case analyses is presented in Table 17. Of the variables identified as important prognostic factors by the EAG's clinical experts (age >65 years, Eastern Cooperative Oncology Group [ECOG] score, disease stage III-IV, International Prognostic Index [IPI] score, number of prior treatment lines, primary refractoriness and refractory versus relapse to last treatment), almost all variables were adjusted for in the MAICs (unless the relevant data were not available in the comparator studies). The only factors not adjusted for are the number of prior lines of therapy, IPI score and refractory versus relapse to last treatment. Justification as to why these variables were not adjusted for is provided in the subsequent paragraphs.

Table 17: Variables adjusted for in the base case MAICs

Variable	Variables identified as prognostic variables[a]	Epcoritamab versus SCHOLAR-1 (updated base case A)[b]	Epcoritamab versus ZUMA-1 (updated base case B)[b]
Age > 65 years	✓	✓	✓
ECOG score	✓	✓	✓
Disease stage III-IV	✓	✓	✓
IPI score	× (disease stage is adjusted for)	×	×
Number of prior lines of treatment	× (due to variability in the number of lines of therapy)	×	×
Primary refractoriness	✓	✓	✓
Refractory versus relapse to last treatment	× (other variables associated with refractoriness are adjusted for)	×	×
Refractory to two or more consecutive liens of therapy	✓	✓	✓
Relapse within 12 months of ASCT	✓	✓	✓
Gender (male)	✓	✓	✓
DLBCL histology versus not DLBCL	✓	×	×
Refractory to last prior anti-CD20 agent	✓	×	×
Prior CAR-T therapy	✓	×	×
Prior ASCT	✓	×	×

Bold highlighted variables are those identified as important prognostic variables by the EAG's clinical experts. Variables adjusted for in the analyses are indicated with a ✓; variables not adjusted for are indicated with a ×. [a] Identified based on published literature (including peer-reviewed published ITCs and consideration of previous NICE evaluations in the indication of interest), empirical testing of prognostic status in the EPCORE™ NHL-1 trial and input from UK clinical experts as to whether certain characteristics are important to adjust for in a R/R LBCL population.[4-6] [b] The availability of information of the variables identified as to be adjusted for in the comparator studies guided the final list of variables adjusted in that analysis.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; IPI: individual patient data; MAIC: matching adjusted indirect comparisons.

As outlined in the CS (Section B.2.8.1), number of prior lines of therapy was not adjusted for due to variability in the number of prior lines of therapy in each trial, exact regimens administered and corresponding sequence of administration. Furthermore, number of prior lines of therapy is influenced by refractoriness, ECOG PS and age; as all of these variables were adjusted for, number of prior lines of therapy was not adjusted for to avoid issues associated with multicollinearity and over-adjustment of the data. In addition, as demonstrated by the subgroup analysis of overall response rate (ORR) from EPCORE™ NHL-1 (CS, Section B.2.7), number of prior lines of therapy alone is not prognostic.

Refractoriness to last therapy was not adjusted for due to the heterogeneity in the number of prior lines of therapy, as highlighted above. Instead, more specific variables were adjusted for, such as primary refractoriness, refractory to two or more consecutive lines of therapy and refractory to last prior anti-CD20 agent. These variables, which are related to refractory to last therapy, should sufficiently cover adjustment for refractoriness, as advised by UK clinical experts. Any additional adjustment would likely lead to issues associated with multicollinearity and over-adjustment.

IPI score was not adjusted for based on feedback from UK clinician experts that this is not required if disease stage is adjusted for; this is because disease stage (as well as ECOG PS and age) informs the IPI score (CS, Section B.2.8.1). As such, following the guidance of UK clinical experts, IPI score was not adjusted for in order to avoid issues associated with over-adjustment of the data. Although it may be possible to adjust for IPI score in the MAICs, the benefits associated with adjusting for IPI score would *not* outweigh the disadvantages associated with the reduced effective sample size, based on feedback from UK clinical experts.[8] Furthermore, IPI score ≥3 is already well-balanced in the MAICs conducted when adjusting for the variables identified as important prognostic factors. For example, for the MAIC of epcoritamab versus SCHOLAR-1, after adjustment, the proportion of patients with IPI score ≥3 is [redacted]% and 27.7% in the epcoritamab and SCHOLAR-1 populations, respectively.

Furthermore, AbbVie wish to highlight that a number of important prognostic factors other than those identified by the EAG's clinical experts have been adjusted for within the company's MAIC analyses, such as prior autologous stem cell transplant (ASCT), relapse within 12 months of ASCT and refractory to last anti-CD20 agents.

Lastly, although the MAICs adjusted for clinically important variables as identified through the above evidence-based process, AbbVie are aware that bias due to residual confounding cannot be excluded. However, through examination of the baseline characteristics of the adjusted epcoritamab populations versus the relevant comparator trials, it is likely that the analyses bias against epcoritamab; for example, for the comparison of epcoritamab versus Rituximab (R)-based chemoimmunotherapy (CIT), after adjustment of the epcoritamab DLBCL population to SCHOLAR-1 (see response to Clarification Question A7 for further details), EPCORE™ NHL-1 included a higher proportion of patients older than 65 ([redacted] versus 16.5%), with disease stage III–IV ([redacted] versus 64.5%), with more than three prior lines of treatment ([redacted] versus 28.8%), and with primary refractoriness ([redacted] versus 37.1%). As such, the approach of only adjusting for those variables identified as most clinically important is likely to be conservative in relation to the relative efficacy estimates produced for epcoritamab. Exploration of the residual bias for the comparison of epcoritamab versus ZUMA-1 is presented in response to Clarification Question A9.

A7. Priority question. For base case A, the EAG considers that adjustment to the Sehn trial rather than SCHOLAR-1, and use of a secondary publication for SCHOLAR-1 (n=340) rather than the original population (n=636, Crump 2017[9]) are associated with limitations:

Please perform an analysis where the Sehn trial is excluded from the comparison with R-CIT. Please conduct an MAIC between EPCORE NHL-1 and the SCHOLAR-1 trial using the data from the Crump 2017 paper.

Please ensure that all reported baseline characteristics are balanced within the MAIC (as per question A6 above).

As highlighted in the CS (Section B.2.8.1), the approach of adjusting the epcoritamab DLBCL population to match the Sehn *et al.* 3L+ population and then comparing it to R-based CIT based on SCHOLAR-1 was taken based on feedback from UK clinical experts, to ensure alignment with the specific population of interest in this submission and as the Sehn *et al.* 3L+ baseline characteristics are reflective of the population of interest.[10] However, AbbVie acknowledge that this approach is associated with some limitations, as the epcoritamab population is not fully adjusted to match R-based CIT (CS, Section B.2.8.3).

As such, in response to the request from the EAG, AbbVie have conducted a MAIC in which the epcoritamab DLBCL, no prior CAR-T population is adjusted to match the R-based CIT population from SCHOLAR-1. AbbVie have maintained the approach of conducting this MAIC using data from Neelapu *et al.* (2021) for SCHOLAR-1 (n=340), as the data reported in this secondary publication are for patients who have received two or more prior lines of therapy. In contrast, of the 636 patients included in the analysis presented by Crump *et al.* (2017), 28% of patients received only one prior line of therapy, so this population is not representative of the decision problem in this submission.[9] As such, these data cannot be used to conduct a MAIC of epcoritamab versus R-based CIT in this indication. This approach is aligned with previous NICE appraisals in R/R LBCL, such as TA559.[11]

As outlined in response to Clarification Question A6, AbbVie have adjusted for all clinically important variables reported in the SCHOLAR-1 publication, rather than all reported variables, in order to avoid decreasing the effective sample size to an unnecessary degree and to align with NICE DSU TSD18.[7] This approach is consistent with published comparisons of epcoritamab versus axi-cel, and axi-cel versus R-based CIT.[12, 13]

The results of the MAIC in which the epcoritamab DLBCL, no prior CAR-T therapy population is adjusted to match SCHOLAR-1 are presented in Table 19. As outlined in response to Clarification Question B9, AbbVie have updated base case analysis A such that the efficacy data are informed by the MAIC outlined in this question, in which the DLBCL, no prior CAR-T population is adjusted to match SCHOLAR-1. This is hereafter referred to as 'Updated base case analysis A'.

Table 18: Baseline characteristics for updated base case analysis A (epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Unadjusted epcoritamab DLBCL, no CAR-T ([redacted])	Adjusted epcoritamab DLBCL, no CAR-T ([redacted])*	SCHOLAR-1 CIT (N=340)
Age			
Median (years)	[redacted]	[redacted]	**55**
≥ 65 years	[redacted]	[redacted]	16.5%
Male	[redacted]	[redacted]	**67.9%**
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]	**100.0%**
Disease stage III-IV	[redacted]	[redacted]	**64.5%**
IPI score ≥3	[redacted]	[redacted]	27.7%
Number of prior lines		[redacted]	
≥3 lines of chemo and ASCT	[redacted]	[redacted]	28.8%
Primary refractory	[redacted]	[redacted]	**37.1%**
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]	**50.0%**
Relapse within 12 months of ASCT	[redacted]	[redacted]	**21.8%**
SCT any time after refractory disease	[redacted]	[redacted]	37.1%

Bold highlighted values are adjusted for: age (≥65 years), male, ECOG performance status, disease stage, primary refractory, refractory to ≥2 consecutive lines of therapy, and relapse within 12 months of ASCT; weights truncated at 1% and 99%

Abbreviations: ASCT, autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; SCT, stem cell transplant

Figure 9: Adjustment weights distribution for updated base case analysis A (epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

A) Without truncation

B) With truncation at 1% & 99%

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large-B-Cell lymphoma.

Table 19: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (updated base case analysis A – epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Unadjusted epcoritamab ( )	Adjusted epcoritamab ( )
OS		
Response rates		
CR (epcoritamab vs R-based CIT)		
Difference, % (95% CI)		
OR (epcoritamab vs R-based CIT)		
Difference, % (95% CI)		

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI, confidence interval; CIT, chemoimmunotherapy; CR: complete response; DLBCL: diffuse large B-cell lymphoma; NA, not applicable; Neff, effective sample size; OR: overall response; OS: overall survival; PFS: progression-free survival; R: rituximab.

Figure 10: Unadjusted and adjusted OS compared to R-based CIT (updated base case analysis A - DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

* Number at risk for SCHOLAR was derived from the synthetic IPD because the number at risk was not reported in the published article.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; OS: overall survival; R: rituximab.

a) Subsequently to conducting the fully adjusted MAIC between EPCORE and SCHOLAR-1, and generating adjusted KM curves for epcoritamab, please proceed to independently fit the OS KM curves for both epcoritamab and R-CIT with parametric survival distributions according to NICE TSD DSU 19.[14]

An assessment of the proportional hazards (PH) assumption for epcoritamab versus R-based CIT, based on the MAIC informing the updated base case analysis A (Clarification Question A6), is presented in 0. This assessment demonstrated that the hazards are proportional and the PH assumption cannot be rejected. As such, AbbVie maintain that modelling R-based CIT via application of a hazard ratio (HR) is a more appropriate and robust method, considering the conclusions of the PH assessment.[7] Fitting independent models would not be more informative than the current base case which utilises the HR approach and aligns with NICE methods.[15]

As such, AbbVie have maintained the approach of applying a HR to model R-based CIT and the EAG's request to independently extrapolation OS for epcoritamab and R-based CIT has not been implemented.

b) Please use the reweighted EPCORE NHL-1 population in this analysis to derive a PFS and TTD curve specific to this adjusted epcoritamab population for use in the economic model

As outlined in response to part A of this Clarification Question, the base case analysis A has been updated to use the MAIC based on the epcoritamab population adjusted to the SCHOLAR-1 population.

Information regarding the extrapolations selected to model PFS and TTD in the updated base case analysis A are provided in 0.

A8. Priority question. For the comparison vs Pola+BR, please perform an updated MAIC to ensure all reported baseline characteristics are balanced between the epcoritamab and Sehn studies (see question A6 above):

As outlined in response to Clarification Question A6, AbbVie have maintained the approach of adjusting for all clinically important variables, rather than all reported variables, in order to avoid decreasing the effective sample size to an unnecessary degree and to align with NICE DSU TSD18.[7] As such, no additional MAICs have been conducted in response to Clarification Question A8.

a) **Subsequently to conducting the fully adjusted MAIC between EPCORE and Sehn, and generating adjusted OS and PFS KM curves for epcoritamab, please proceed to independently fit the OS and PFS KM curves for both epcoritamab and POLA+BR with parametric survival distributions according to NICE TSD DSU 19.[14]**

As outlined in response to Clarification Question A6, no additional MAICs have been conducted in response to Clarification Question A8. For the submitted MAIC of epcoritamab versus polatuzumab vedotin with rituximab and bendamustine (Pola + BR), based on Sehn et al. 3L+, assessment of the PH assumption suggested that it may be violated. As such, a piecewise HR approach was adopted in which one HR was calculated up to the point of the crossing of the epcoritamab and Pola + BR curves ([redacted]) and a second HR was calculated after this timepoint (CS appendices, Appendix N.2.1).

This approach was validated as clinically plausible based on the mechanisms of action of Pola + BR and epcoritamab by UK clinical experts; as Pola + BR is given for a fixed duration, it is plausible that patients might be more likely to relapse once they have stopped treatment with Pola + BR.[16] This is further supported by feedback from UK clinical experts, stating that real-world evidence (RWE) data on Pola + BR used after two prior therapies has demonstrated worse outcomes than those observed in clinical trials and patients on Pola + BR are rarely seen to be in long-term remission in real-world clinical practice. Moreover, the mechanism of action of epcoritamab means that the efficacy builds up over the first month during the dosage increase. As such, it is plausible that the efficacy associated with epcoritamab would increase over the first few months of administration.

As such, AbbVie maintain that the piecewise HR approach adopted in the CS is clinically plausible and a robust method for modelling epcoritamab and Pola + BR.

b) **Please use the reweighted EPCORE NHL-1 population in this analysis to derive a TTD curve specific to this adjusted epcoritamab population for use in the economic model**

As stated, in response to part a of this Clarification Question, the MAIC informing scenario analysis A.1 (epcoritamab versus Pola + BR, based on Sehn *et al.* 3L+) uses the epcoritamab population adjusted to the Sehn *et al.* 3L+ population.

A9. Priority question. For the MAIC vs axi-cel, the EAG prefers the LBCL population in EPCORE NHL-1 (scenario B.1 rather than base case B) to be used given the

ZUMA-1 trial is not limited to DLBCL. For scenario B.1, please update the MAIC to include the following when the epcoritamab population and results are matched and adjusted to the ZUMA-1 axi-cel arm:

a) 5-year data from the ZUMA-1 trial published in February 2023[17]

AbbVie thank the EAG for highlighting the existence of 5-year data from the ZUMA-1 trial. As this was published after the date that the searches for the clinical systematic literature review (SLR) were most recently updated (December 2022), this publication was not identified by the SLR and therefore not included in the MAICs at the time of submission. An updated MAIC using the 5-year data has not been conducted in response to the Clarification Questions, but AbbVie would consider providing these analyses should more mature data from EPCORE™ NHL-1 become available throughout the NICE evaluation. Based on the [redacted] data cut of EPCORE™ NHL-1, the median follow up is [redacted] versus 5-years for the long-term ZUMA-1 data. More mature data from EPCORE™ NHL-1 may help to mitigate the impact of the substantial differences in length of follow-up between the two trials compared with conducting this analysis based on current EPCORE™ NHL-1 data.

b) Please ensure that all reported baseline characteristics are balanced between the studies. See question A6 above.

As outlined in response to Clarification Question A6, AbbVie have maintained the approach of adjusting for all clinically important variables in these MAICs, rather than all reported variables, in order to avoid decreasing the effective sample size to an unnecessary degree and to align with NICE DSU TSD18.[7]

As outlined in response to Clarification Question A6, AbbVie are aware that bias due to residual confounding cannot be excluded. However, through examination of the baseline characteristics of the adjusted epcoritamab populations versus the relevant comparator trials, it is likely that the analyses bias against epcoritamab.

For the comparison of epcoritamab versus axicabtagene ciloleucel (axi-cel), after adjustment of the epcoritamab LBCL population to ZUMA-1, EPCORE™ NHL-1 included a higher proportion of patients older than 65 ([redacted] versus 23.8%), with history of primary refractoriness ([redacted] versus 25.7%), and refractory to second-line or subsequent therapy ([redacted] versus 77.2%) (CS, Section B.2.8.2, Table 28). As such, the approach of only adjusting for those variables identified as most clinically important is likely to be conservative in relation to the relative efficacy estimates produced for epcoritamab.

In the original base case analysis B and scenario analysis B.1, the results of the unadjusted comparison of epcoritamab versus ZUMA-1 were used as the unadjusted analysis used comparatively conservative results and maintained the maximum sample size (CS, Section B.2.8.3). However, in order to align with the EAG's preference for using an adjusted analysis, the cost-effectiveness model has been updated to include the results of the MAICs in which the epcoritamab population is adjusted to the ZUMA-1 population, using both the DLBCL population (scenario analysis B.2) and the LBCL population (updated base case analysis B). Further information is provided in response to Clarification Question B17.

In addition to the change from the unadjusted to the adjusted MAICs, in response to the EAG's preference for the LBCL population from EPCORE™ NHL-1 to inform the MAICs, AbbVie have updated base case B so that the epcoritamab efficacy data are informed by the LBCL, no prior CAR-T, CAR-T eligible population adjusted to match ZUMA-1. The cost-effectiveness results of the updated base case analyses (A and B) are presented at the end of this response document (Table 39–Table 50) with the incremental impact of each change presented in Table 38.

A10. Priority question. Please use the MAIC-adjusted OS and PFS KM curves for epcoritamab as requested in question A9 to independently fit the OS and PFS KM curves for epcoritamab and axi-cel with parametric survival distributions according to NICE TSD DSU 19[14]:

a) Please also use the reweighted EPCORE NHL-1 population in this analysis to derive a TTD curve specific to this adjusted epcoritamab population for use in the economic model

Whilst AbbVie acknowledge that fitting independent models is sometimes preferred, this approach is associated with a number of limitations, especially considering that AbbVie do not have access to direct individual patient data (IPD) from ZUMA-1. As such, fitting independent models may lead to increased uncertainty in the results compared with the approach in the CS. As such, AbbVie maintain that modelling axi-cel via application of a HR is a more appropriate and robust method, considering the data available.

Nonetheless, an assessment of the PH assumption for epcoritamab versus axi-cel was reconducted based on the updated base case analysis B and is included in 0. Based on examination of the log-cumualtive hazard plot, the Schoenfeld residual plot and Grambsch and Therneau test, this analysis suggests that the PH assumption may be violated. As such, in order to explore alternative approaches, and in line with the approach adopted in scenario analysis A.1, a piecewise HR approach was considered in which one HR was calculated up to the point of the crossing of the epcoritamab and axi-cel hazard curves ([redacted]) and a second HR was calculated after this timepoint. The results of this piecewise analysis conducted for updated base case analysis B and scenario analysis B.2 are presented in Table 20.

Table 20: Adjusted outcomes for epcoritamab versus axi-cel (ZUMA-1) using a piecewise approach

	Epcoritamab adjusted (N_{eff}=[redacted])	
	Up to [redacted]	After [redacted]
LBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1		
OS, HR (95% CI)	[redacted]	[redacted]
PFS, HR (95% CI)	[redacted]	[redacted]
DLBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1		
OS, HR (95% CI)	[redacted]	[redacted]
PFS, HR (95% CI)	[redacted]	[redacted]

Abbreviations: DLBCL: diffuse large B-cell lymphoma; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; HR: hazard ratio; LBCL: large B-cell lymphoma; OS: overall survival; PFS: progression-free survival.

The HRs generated for OS for after [redacted] in both populations were considered to be implausibly low and would therefore generate clinically implausible results for axi-cel if applied in the cost-effectiveness model. As such, the single HR approach used in the CS was deemed to be the most appropriate approach for modelling axi-cel. While AbbVie acknowledge that PH may be violated, clinical expert feedback indicates that applying a single HR produces a clinically plausible comparison between epcoritamab and axi-cel.

A11. Priority question. For the updated MAIC vs Pola+BR requested in A8 above, please state the proportion within the EPCORE NHL-1 population that were naive to Pola+BR (i.e. had not used these treatments at earlier therapy lines).

In the unadjusted DLBCL, no prior CAR-T therapy population (N=[redacted]), [redacted] patients ([redacted]) had received prior treatment with polatuzumab. As such, the majority of patients from the EPCORE™ NHL-1 trial were polatuzumab-naïve. This is due to polatuzumab not being broadly available as a second-line or earlier treatment at the time of study conduct. As the key comparator trials in this indication did not include patients that had received prior treatment with polatuzumab (due to the time of study conduct), the EPCORE™ NHL-1 trial aligns with comparator trials in this regard, aiding a balanced comparison of efficacy outcomes.

A12. Priority question. For all MAICs provided in the CS and new ones provided as a result of clarification questions, please provide the distribution of participant weights within adjusted epcoritamab populations.

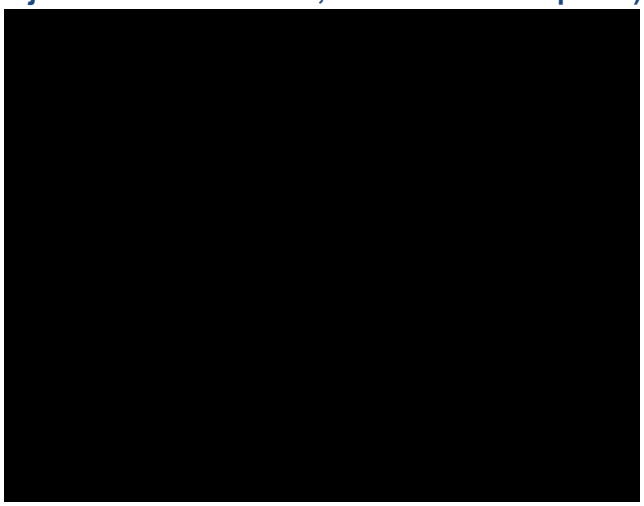
The distribution of participant weights for the MAICs presented in the CS (MAICs informing the original base case A, scenario analysis A.1–A.3, the original base case B and scenario analysis B.1) are provided in Figure 11–Figure 15.

The distribution of participant weights for the MAIC of epcoritamab versus R-based CIT, based on SCHOLAR-1, are presented in response to Clarification Question A7.

Figure 11: Adjustment weights distribution for the original base case analysis A and scenario analysis A.1 (epcoritamab DLBCL population adjusted to Sehn et al. 3L+; no truncation required)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; 3L+: third-line and beyond.

Figure 12: Adjustment weights distribution for the scenario analysis A.2 (epcoritamab DLBCL adjusted to Liebers et al; no truncation required)



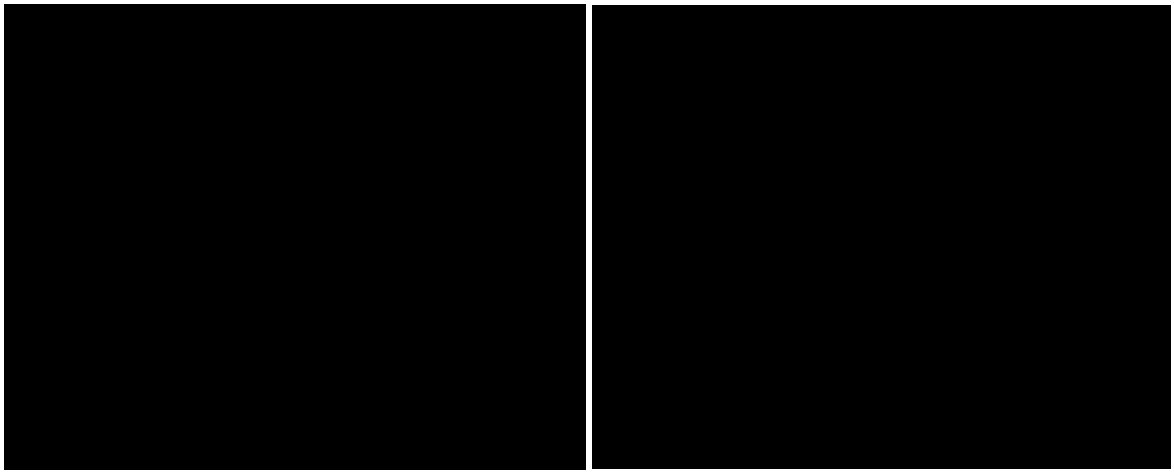
Abbreviations: DLBCL: diffuse large B-cell lymphoma; 3L+: third-line and beyond.

Figure 13: Adjustment weights distribution for the scenario analysis A.3 (epcoritamab LBCL adjusted to Liebers et al; no truncation required)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; 3L+: third-line and beyond.

Figure 14: Adjustment weights distribution for the original base case analysis B (epcoritamab DLBCL, CAR-T eligible unadjusted vs axi-cel)

A) Without truncation **B) With truncation at 1% & 99%**



Abbreviations: Axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; 3L+: third-line and beyond.

Figure 15: Adjustment weights distribution for scenario analysis B.1 (epcoritamab LBCL, CAR-T eligible unadjusted vs axi-cel)

A) Without truncation **B) With truncation at 1% & 99%**

Abbreviations: Axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; 3L+: third-line and beyond.

A13. Priority question. Please clarify where the KM curves and numbers at risk presented in the CS appendices (Figures 14 and 15) for Pola+BR (n=29) came from as the EAG could not find these data in any of the publications cited (Sehn 2019/2022 or EUnetHTA submission).

As highlighted in the CS Appendices (Appendix N.1), in the Sehn *et al.* (2019) trial of Pola + BR as a treatment for R/R DLBCL, out of the total 40 patients included, 11 (27.5%) patients had received just one prior line of therapy.[18] In order to align with the decision problem of this submission (two or more prior lines of therapy), OS and PFS KM curves for a population who had received two or more prior lines of therapy were derived from the data published by Sehn *et al.* (2019) and the EUnetHTA submission for Pola + BR.[18, 19] The methodology used to derive the synthetic KM curves is provided in detail in the CS Appendices (Appendix N.1).

The OS and PFS KM curves presented in the CS (CS Appendices, Appendix N.2.1, Figure 14 and Figure 15, respectively), and the corresponding numbers at risk, are the derived synthetic curves; the KM curves and numbers at risk are not expected to align with those presented in the Pola + BR publications. As presented in the CS Appendices (Appendix N.1, Table 93), the reported (based on Sehn *et al.* [2019] and the EUnetHTA submission for Pola + BR) and derived PFS and OS summary statistics for Pola + BR and BR by treatment line are highly similar, demonstrating the robustness of the analyses conducted.

A14. For scenario B.1 (from page 80 of the CS) the EAG notes a number of potential errors:

a) Figure 14 in the CS appears to be incorrect and is a duplicate of Figure 13 for PFS in the DLBCL population (rather than OS in the LBCL population). Please ensure the correct figure is provided.

As stated by the EAG, Figure 14 in the CS was a duplicate of Figure 13. AbbVie thank the EAG for highlighting this error and for the opportunity to provide the correct figure. The figure presenting OS for the LBCL, no prior CAR-T, CAR-T eligible population from epcoritamab versus axi-cel based on ZUMA-1, has been provided in Figure 16.

Figure 16: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; PFS: progression-free survival.

b) The heading for Table 30 suggests the population is DLBCL rather than LBCL - please check and confirm that the correct results for the LBCL population have been provided in this table despite the heading error.

Table 30 in the CS presents the results of the MAIC informing base case B (epcoritamab versus axi-cel); efficacy data for epcoritamab in base case B are informed by the DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 (n=[redacted]). As such, the heading of Table 30 is correct and the results presented are for the DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 versus axi-cel based on ZUMA-1.

However, the caption of Table 31 in the CS incorrectly states that the population is the DLBCL, CAR-T eligible population. This should read 'LBCL, CAR-T eligible' (n=[redacted]). AbbVie can confirm that the results presented in Table 31 of the CS relate to the MAIC of epcoritamab, based on the LBCL, CAR-T eligible population from EPCORE™ NHL-1 versus axi-cel, based on ZUMA-1.

A15. Please provide a breakdown of other studies identified (e.g. in Table 15 of the CS appendices/SLR report document provided alongside the submission) that were considered as options for providing comparator data (R-based CIT, axi-cel or Pola+BR) for use in MAICs and the rationale for why they were not used.

As highlighted in the CS (Section B.2.8.1), the SLR identified a number of studies reporting survival and/or response outcomes of relapsed and/or refractory (R/R) LBCL treatments. Of the studies identified from the SLR, one study for each comparator of interest in the base case (axi-cel and R-

based CIT) and for scenario analyses (Pola + BR) was selected, along with other observational sets where appropriate, for inclusion in the ITC based on the following additional criteria:

- Included patients that had received two or more prior lines of therapy
- Reported key baseline patient characteristics
- Included a KM curve for OS and PFS that clearly displays the survival and progression events or enough information to extract or estimate curves for the population of interest
- Reported outcomes that were similarly defined as in the EPCORE™ NHL-1 trial

In instances where the included study could not provide appropriate information the exact treatment line of interest or sufficient information on baseline characteristics to enable the matching and adjustment, these data sources were deprioritised and RWE that could serve these purposes was considered.

Of the studies presented in the CS appendices (Table 15), the majority of studies were excluded as options for providing comparator data on the basis that they reported on treatments other than the comparators relevant for this submission (i.e., comparators other than R-based CIT, axi-cel or Pola + BR). Of the remaining studies, the CORAL and ZUMA-9 studies were excluded as insufficient information were available on the baseline characteristics. As such, SCHOLAR-1 and ZUMA-1 were selected to inform comparative efficacy of R-based CIT and axi-cel, respectively. The DLC-001 study was excluded as some patients had received only one prior line of therapy, meaning that the population was not aligned with the decision problem of this submission.

An overview of the reason for exclusion from the MAICs for all studies included in the clinical SLR is presented in Table 21.

Table 21: Overview of trials included in clinical SLR and reason for exclusion from the MAICs

No	Trial acronym/NCT code	Treatments included	Reason for exclusion from the MAICs
1	CORAL	Salvage chemotherapy	Insufficient information on baseline characteristics available
2	CHECKMATE-436	Nivolumab + brentuximab vedotin	Irrelevant comparator
3	DLC-001	Lenalidomide; Investigator's choice (gemcitabine, rituximab, etoposide, or oxaliplatin)	Irrelevant population; some patients had received only 1 prior line of therapy
4	EPCORE™ NHL-1	Epcoritamab	NA – Included
5	GO29365	Polatuzumab vedotin + bendamustine + rituximab; Bendamustine + rituximab	NA – Included
6	JULIET	Tisa-cel	Irrelevant comparator
7	KEYNOTE-013	Pembrolizumab	Irrelevant comparator
8	KEYNOTE-170	Pembrolizumab	Irrelevant comparator
9	L-MIND	Tafasitamab + lenalidomide	Irrelevant comparator
10	LOTIS-2	Loncastuximab tesirine	Irrelevant comparator
11	NHL-002	Lenalidomide	Irrelevant comparator
12	NHL-003	Lenalidomide	Irrelevant comparator
13	OUTREACH[c]	Liso-cel	Irrelevant comparator
14	PLRG8	Ofatumumab with iphosphamide, etoposide + cytarabine	Irrelevant comparator
15	ROMULUS[d]	Polatuzumab vedotin + rituximab; Pinatuzumab vedotin + rituximab	Irrelevant comparator

No	Trial acronym/NCT code	Treatments included	Reason for exclusion from the MAICs
16	R2-GDP-GOTEL	Lenalidomide with rituximab, cisplatin, gemcitabine + dexamethasone	Irrelevant comparator
17	SADAL	Selinexor	Irrelevant comparator
18	SCHOLAR-1	Salvage chemotherapy	NA – Included
19	TRANSCEND	Liso-cel	Irrelevant comparator
20	ZUMA-1	Axi-cel	NA – Included
21	ZUMA-9	Axi-cel	Insufficient information on baseline characteristics available
22	ZUMA-14	Axi-cel + rituximab	Irrelevant comparator
23	NCT01660451	Copanlisib	Irrelevant comparator
24	NCT03075696	Glofitamab	Irrelevant comparator
25	NCT00088530	Pixantrone; Vinorelbine/ oxaliplatin/ ifosfamide/ etoposide/ mitoxantrone/ gemcitabine	Irrelevant comparator
26	NCT04432506	Axi-cel + anakinra	Irrelevant comparator
27	NCT03103971	Fully human CD19-targeted scFv (JCAR021)	Irrelevant comparator
28	NCT00968331	Lenalidomide + rituximab	Irrelevant comparator
29	NCT02910063	Blinatumomab	Irrelevant comparator
30	NR	High-dose cyclophosphamide ± rituximab	Irrelevant comparator
31	NR	Lenalidomide	Irrelevant comparator

Abbreviations: SLR: systematic literature review; MAIC: matching-adjusted indirect comparison; NA: not applicable; NR: not reported.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base-case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base-case assumptions are provided with the response along with a log of changes made to the company base-case.

The EAG notes that some requests made by the EAG contemplate the possibility that the company will keep its base case analysis unaltered. However, the EAG notes that if the company adopts a new base case reflecting the EAG's requests in clarification questions A7; A8; and A10, the requests for additional analysis in Section B using the company's current MAIC and ITCs can be ignored (as these should all be based in the EAG-preferred MAIC requests).

Treatment effectiveness in the model

B1. Priority question. Can the company please confirm which populations in the model are used when in the dropdown menu in the "Main board" sheet, the third and fourth options are chosen ("Scenario analysis A.2: Ineligible for, or choose not to receive, intensive therapy DLBCL, unadjusted"; and; "Scenario analysis A3: Ineligible for, or choose not to receive, intensive therapy LBCL, unadjusted"). There are several inconsistencies in the model and CS regarding scenarios A2 and A3, with: 1) These scenarios apparently being matched in the "Labels&constants" tab to "Epco - DLBCL irrespective of CAR-T status (unadjusted)" and "Epco - LBCL irrespective of CAR-T status (unadjusted)", respectively, according to the population index on cell AK4; and 2) with these scenarios being described in Appendix N2 as "EPCORE™ NHL-1 DLBCL patients being reweighted to match to the Liebers et al. population" and "EPCORE™ NHL-1 LBCL patients being reweighted to match to the Liebers et al. population", respectively for scenario A2 and A3.

The third and fourth options of the 'Main board' sheet of the cost-effectiveness model refer to scenario analyses A.2 and A.3. Both scenario analyses correspond to base case population A: patients ineligible for, or choose not to receive, intensive therapy.

For the MAIC informing scenario analysis A.2, the unadjusted DLBCL population from EPCORE™ NHL-1 is compared to Pola + BR based on Liebers *et al.* real-world evidence (RWE). For the MAIC informing scenario analysis A.3, the unadjusted LBCL population from EPCORE™ NHL-1 is compared to Pola + BR based on Liebers *et al.* RWE. As stated in the cost-effectiveness model, these are the overall DLBCL (N=139) and LBCL (N=157) populations from the clinical trial, as such it is correct that they are 'irrespective of CAR-T status'.

Regarding Appendix N.2, which states that the patients from EPCORE™ NHL-1 were reweighted to match the Liebers *et al.* population, this statement is outlining the MAICs that were conducted. However, as stated in the CS Appendices (Appendix N.2 and Appendix P.4.2), the unadjusted population from EPCORE™ NHL-1 was deemed to be similar enough to the Liebers *et al.* population for the unadjusted results to be used in scenario analyses A.2 and A.3.

B2. Priority question. Can the company please explain how the different criteria for response assessment (i.e., Lugano vs LYRIC criteria) influenced the KM PFS estimations? For example, Table 14.2.1.12.1 in the CSR shows considerably different proportions of patients in the PFS curve at 6 months ([redacted] for LBCL) from those in Table 14.2.1.14.1 ([redacted] for LBCL) depending on the clinical criteria used to assess response.

As outlined in the CS (Section B.2.3.1), response assessed by both Lugano criteria and Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) were included as secondary outcomes in EPCORE™ NHL-1. The LYRIC introduced Indeterminate Response (IR) as a more flexible

classification for progression than that included in Lugano classification. IR provides the flexibility to allow patients to continue treatment past IR in some circumstances with a mandatory subsequent evaluation within 12 weeks to confirm or refute true progressive disease.[20, 21]

As such, the differences observed between PFS determined by Lugano criteria versus PFS determined by LYRIC can be explained by the fact that when determined by LYRIC, there were 17 patients with IR; these patients were considered to not yet have experienced a progression event, and hence were censored for the PFS analysis at the time of their IR response assessment. As such, the median PFS as determined by LYRIC was prolonged compared to the median PFS as determined by Lugano. Due to the same reason, the landmark rates for PFS as determined by LYRIC were higher than the landmark rates for the PFS as determined by Lugano criteria.

B3. Priority question. Can the company please confirm which dataset is being used to estimate the PFS KM data underpinning the survival extrapolations in the model? (i.e., Lugano vs LYRIC criteria; primary vs secondary definition of PFS; IRC vs Investigator assessed):

a) **If the following dataset was not originally used, please provide the PFS KM data using the Lugano criteria, primary definition of PFS, IRC. Please provide this separately for population A and population B.**

The Company confirms that all PFS data from EPCORE™ NHL-1 presented in the CS and used in the cost-effectiveness model (population A and population B) are PFS based on Independent Review Committee assessment, Lugano criteria, primary definition.

B4. Priority question. Page 106 of the CS states that OS extrapolations could not be validated with external data sources from the SLR at 24 months or later given the "historically poor outcomes" for DLBCL. This statement seems in contradiction with the company's assumption around long-term remission being achieved at 24 months, and the company's estimated proportion of patients alive at 24 months in the base case model (for example, 52% for axi-cel). Furthermore, the two key sources used in the model to estimate survival for comparator treatments seem to provide follow-up estimates up to at least 33 months for SCHOLAR-1 and 5 years for ZUMA-1. Therefore, can the company please provide a table with landmark estimates of survival (for OS PFS; and TTD where available) for all the comparators included in the model (axi-cel; R-CIT; and POLA-BR) and compare these with:

a) **The underlying studies used to derive the compators' effectiveness (ZUMA-1; SCHOLAR-1; and Sehn et al.) for the longest follow-up data cuts available.**

The statement from the EAG that "*Page 106 of the CS states that OS extrapolations could not be validated with external data sources from the SLR at 24 months or later given the 'historically poor outcomes' for DLBCL*" is incorrect. As stated in the CS (Section B.3.3.3), AbbVie conducted validation of the OS extrapolations versus published long-term OS data, however, the only trial reporting landmark survival data at 24 months or later was the CORAL trial, which included patients receiving R-based CIT

regimens. As outlined in response to Clarification Question A15, the CORAL trial reported limited baseline characteristics, especially regarding refractoriness. As such, a naïve comparison of the survival estimates observed in this trial had limited use in validating the OS extrapolation for the epcoritamab arm.

In response to the request from the EAG, the landmark survival estimates for OS, PFS and TTD (pending data availability) from SCHOLAR-1, ZUMA-1 and Sehn *et al*., alongside the landmark survival estimates for each comparator included in the model, are presented in Table 22 and Table 23 (for OS and PFS, respectively). TTD data were not available from any of the comparator studies and PFS data were not available for R-based CIT from SCHOLAR-1. This has been populated based on the data extracted from the clinical SLR; as such, data from the 5-year follow-up of ZUMA-1 is not included as these data were published after the clinical SLR was conducted (see response to Clarification Question A9).

These survival estimates do not account for heterogeneity in the patient populations when compared to the epcoritamab population. As such, without adjustment, these estimates have limited use in validating the extrapolations used in the cost-effectiveness model. The landmark survival estimates for each comparator in the cost-effectiveness model incorporate available information from published data sources, adjustment to the relevant epcoritamab population and validation with UK clinical experts.

In conclusion, AbbVie maintain that outcomes are historically poor when CAR-T therapy is not an option, based on the published literature. Although CIT can induce CR for R/R LBCL or DLBCL previously treated with two prior lines of therapy, clinical experts highlighted that regretfully only a small proportion of patients will achieve and maintain CR following treatment with CIT.

Table 22: Landmark OS estimates for each comparator based on published data and extrapolation within the CEM

Treatment	Data source	Median follow-up, months	Month		
			12	24	60
R-based CIT	SCHOLAR-1[4]	27.1	26%	20%	NR
	CEM (updated base case A)	NA	[redacted]	[redacted]	[redacted]
Axi-cel	ZUMA-1[22]	27.1	NR	50.5%	NR
	CEM (updated base case B)	NA	[redacted]	[redacted]	[redacted]
Pola + BR	Sehn *et al.*[19]	22.3	NR	NR	NR
	CEM (scenario analysis A.1)	NA	[redacted]	[redacted]	[redacted]

Abbreviations: Axi-cel: axicabtagene ciloleucel; CEM: cost effectiveness model; CIT: chemoimmunotherapy; NA: not applicable; NR: not reported; OS: overall survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; R: rituximab.

Table 23: Landmark PFS estimates for each comparator based on published data and extrapolation within the CEM

Treatment	Data source	Median follow-up, months	Month		
			12	24	60
Axi-cel	ZUMA-1[22]	27.1	72%	NR	NR

Treatment	Data source	Median follow-up, months	Month		
			12	24	60
	CEM (updated base case B)	NA	[redacted]	[redacted]	[redacted]
Pola + BR	Sehn *et al.*[19]	22.3	NR	NR	NR
	CEM (scenario analysis A.1)	NA	[redacted]	[redacted]	[redacted]

PFS data are not available for R-based CIT from SCHOLAR-1.
Abbreviations: Axi-cel: axicabtagene ciloleucel; CEM: cost effectiveness model; NA: not applicable; NR: not reported; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; R: rituximab.

b) Any alternative available literature sources containing survival outcomes.

Landmark survival estimates for the studies included in the clinical SLR and deemed relevant for inclusion in the MAICs are presented in response to part a of this clarification question. AbbVie have not presented the survival estimates from any alternative literature reporting survival estimates, as any other studies identified by the clinical SLR were not considered appropriate for validating the model's long-term projections or for use in the MAICs (as detailed in response to Clarification Question A15).

B5. The EAG notes that the extrapolations provided in the CS (both through figures or landmark tables), which reportedly served as the basis for the clinical expert validation of survival models undertaken by the company, do not take into account the 2-year long-term remission assumptions made by the company in the model. For example, when the exponential distribution is used to model OS for population B, the 180-months survival estimated in the model seems to be about [redacted], as reported in Table 48 of the CS. The same is true for population A and for the other parametric distributions. Therefore, can the company please provide updated landmark tables and model traces demonstrating the appropriate long-term survival predictions in the model when different distributions are used for both OS; PFS; and ToT.

a) In case the company undertook the clinical analysis requested in question A7; A8 and A10 please provide the same landmark tables with OS and PFS outcomes resulting from running that scenario.

The survival estimates at landmark time points including the durable remission assumption for OS, PFS and ToT are presented in Table 24–Table 26 for updated base case analysis A (Clarification Question A7) and Table 27–Table 29 for updated base case analysis B (Clarification Question A9). All survival estimates incorporate the durable remission assumption.

Table 24: Predicted and observed OS for epcoritamab (DLBCL, adjusted to SCHOLAR-1) at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Month[a]					
	12	24	48	60	120	180
Exponential	[redacted]					
Gamma	[redacted]					
Generalised gamma	[redacted]					
Gompertz	[redacted]					
Log-logistic	[redacted]					
Log-normal	[redacted]					
Weibull	[redacted]					

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; DLBCL: diffuse large B-cell lymphoma; NR: not reported; OS: overall survival.

Table 25: Predicted and observed PFS for epcoritamab (DLBCL, adjusted to SCHOLAR-1) at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed	[redacted]					
Exponential	[redacted]					
Gamma	[redacted]					
Generalised gamma	[redacted]					
Gompertz	[redacted]					
Log-logistic	[redacted]					
Log-normal	[redacted]					
Weibull	[redacted]					

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; DLBCL: diffuse large B-cell lymphoma; NR: not reported; PFS: progression-free survival.

Table 26: Predicted and observed ToT for epcoritamab (DLBCL, adjusted to SCHOLAR-1) at several landmarks for each extrapolation: base case analysis A – ineligible for, or choose not to receive, intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed	[redacted]					
Exponential	[redacted]					
Gamma	[redacted]					
Generalised gamma	[redacted]					
Gompertz	[redacted]					

Distribution	Month[a]					
	12	24	48	60	120	180
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model ToT for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; DLBCL: diffuse large B-cell lymphoma; NR: not reported; ToT: time on treatment.

Table 27: Predicted and observed OS for epcoritamab (LBCL, adjusted to ZUMA-1) at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.
Abbreviations: CI: confidence intervals; LBCL: large B-cell lymphoma; N/A: not applicable; OS: overall survival.

Table 28: Predicted and observed PFS for epcoritamab (LBCL, adjusted to ZUMA-1) at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B.
Abbreviations: CI: confidence intervals; LBCL: large B-cell lymphoma; N/A: not applicable; PFS: progression-free survival.

Table 29: Predicted and observed ToT for epcoritamab (LBCL, adjusted to ZUMA-1) at several landmarks for each extrapolation: base case analysis B – eligible for intensive therapy

Distribution	Month[a]					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model ToT for epcoritamab in the updated base case analysis B.
Abbreviations: CI: confidence intervals; LBCL: large B-cell lymphoma; NR: not reported; ToT: time on treatment.

B6. The EAG notes that whereas the PFS KM curves have a steep drop from month 16 in both populations A and B, and drop to 0% at the end of follow-up period, the TTD curves do not show the same pattern. Can the company please discuss the clinical plausibility and the reason behind the difference in the shape of the KM TTD and PFS curves over the last months of the EPCORE™ NHL trial for both populations.

AbbVie acknowledge the PFS KM curves (for populations A and B) from EPCORE™ NHL-1 include a drop towards the tail-end of the curve. However, at the time of the EPCORE™ NHL-1 [redacted] data cut, the median follow-up for PFS was [redacted]. As such, the drop seen in the later part of the PFS curve is not representative of the treatment effect of epcoritamab, but rather due to the small number of patients at risk, and these data are subject to change with additional follow-up. This is further explained in response to Clarification Question B10.

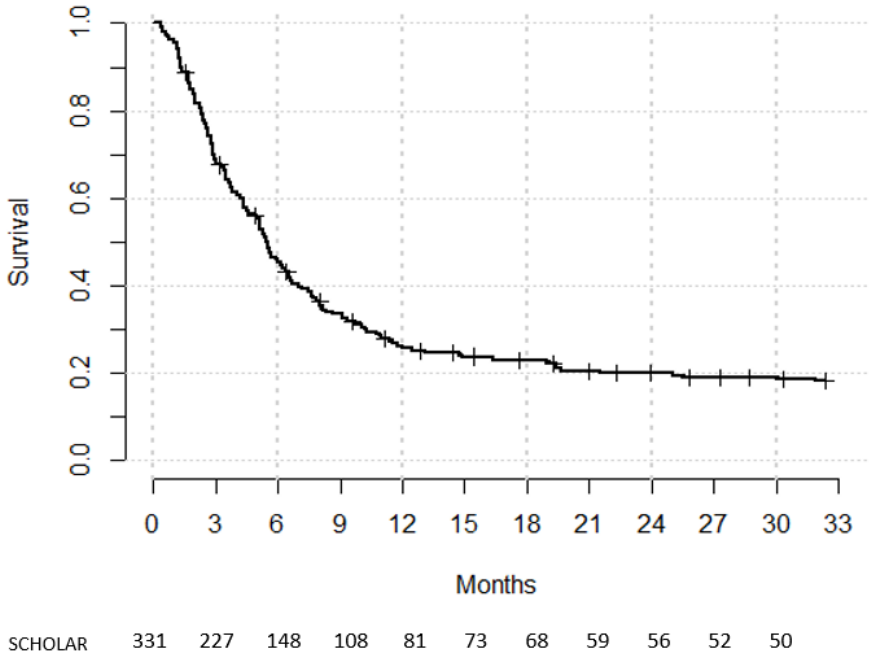
Regarding the differences observed in the PFS and TTD KM curves, this can be explained by the difference in the numbers at risk at the later timepoints of the curves which is due to differences in the censoring rules for PFS and TTD (CS, Section B.2.6.3, Figure 6). For PFS, patients who did not die or progress during the trial were censored on the date of their last evaluable tumour assessment, which corresponds with target visit days. In contrast, for TTD, patients were censored at the date of the database lock. As such, patients may have a longer duration at risk for TTD when compared with PFS, as reflected in the smaller numbers at risk for PFS than TTD. This difference in PFS and TTD is an artefact of the censoring rules in the clinical trial so would not be anticipated to be observed in UK clinical practice.

Population A

B7. Priority question. For R-CIT, please provide the SCHOLAR-1 OS KM data underlying the ITC conducted by the company, in an Excel spreadsheet (plotted and with the underlying data given), with numbers at risk.

The OS KM data from SCHOLAR-1 utilised in the MAIC are provided in an Excel spreadsheet in the reference pack accompanying these responses. The curve with the numbers at risk is presented in Figure 17.

Figure 17: Digitised OS KM curve based on SCHOLAR-1 used in the MAIC analyses



Abbreviations: KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.

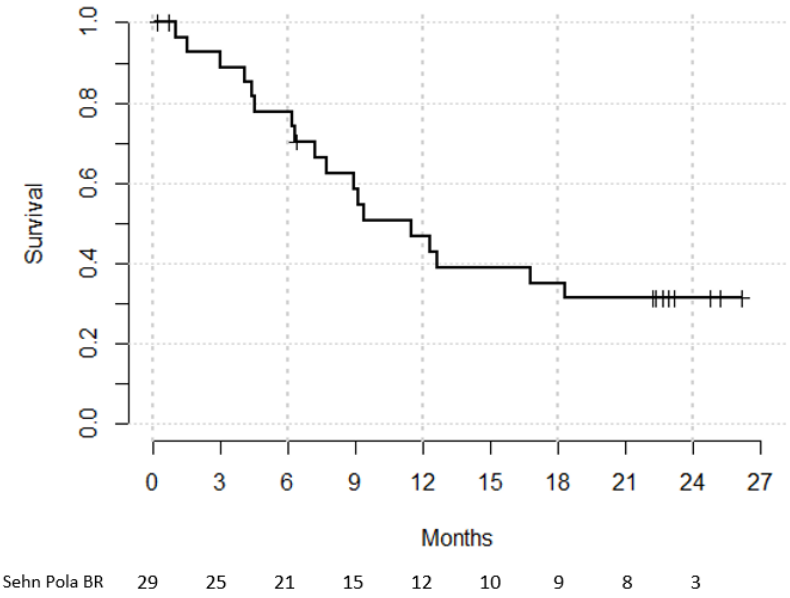
The curve was digitised from the study by Neelapu *et al.* comparing ZUMA-1 and SCHOLAR-1. However, the censoring in this study was not marked on the reported curves. As such, pseudo-IPD for R-based CIT were created with the assumptions of censoring information based on the curves shown in the Crump *et al.* study.

Assuming that the censoring distribution for SCHOLAR-1 would be consistent between the studies by Neelapu *et al.* and Crump *et al.,* it was assumed that the estimated number of censorings for the Neelapu *et al.* study was proportional to that observed in the Crump *et al.* study. From the Crump *et al.* study, a total of 505 out of 603 patients with an event were reported during the follow-up period up to 180 months (i.e. 98 patients were censored), and the censoring marks were mostly observed between 20 months to 120 months on the survival curve. A similar assumption was then applied to how the censoring may be distributed in the patient group of N=331 from Neelapu *et al: f*or the curve in Neelapu *et al*, it was assumed that there will be overall (505/603)*331 = 277 events. Using the Guyot algorithm to distribute the number of events and censored times in the absence of detailed information of N at risk, it was indicated that the best fit to the digitised KM curve was one with 66 censoring and 265 events.

B8. Priority question. For POLA+BR, please provide the Sehn OS and PFS (and TTD if available) KM data underlying the ITC conducted by the company, in an Excel spreadsheet (plotted and with the underlying data given), with numbers at risk.

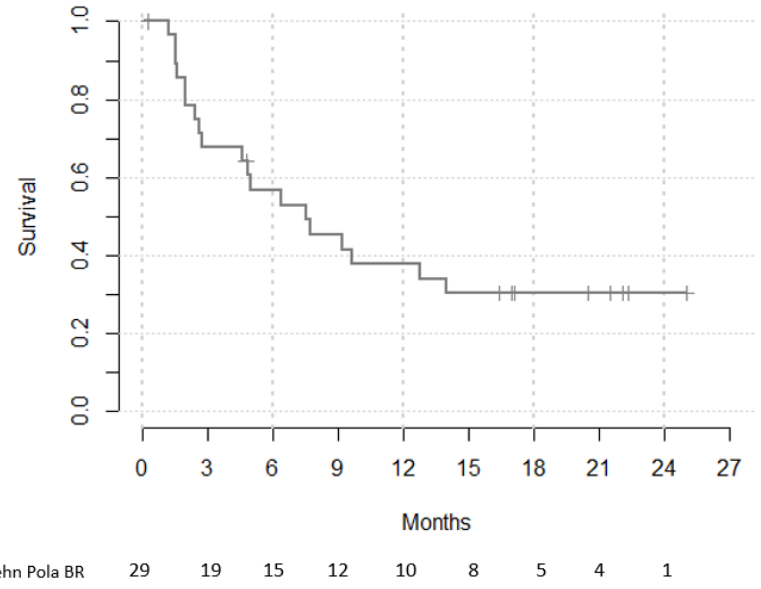
The OS and PFS KM data from Sehn *et al.* utilised in the MAIC are provided in an Excel spreadsheet in the reference pack accompanying these responses. The OS and PFS curves with the numbers at risk are presented in Figure 18 and Figure 19, respectively.

Figure 18: Digitised OS KM curve based on Sehn *et al.* used in the MAIC analyses



Abbreviations: KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; Pola BR: polatuzumab with bendamustine and rituximab.

Figure 19: Digitised PFS KM curve based on Sehn *et al.* used in the MAIC analyses



Abbreviations: KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; Pola BR: polatuzumab with bendamustine and rituximab.

B9. Priority question. Please include a scenario analysis in the model where the analysis requested in questions A7 and A8 is used to estimate treatment

effectiveness in the model for epcoritamab vs R-CIT; and for epcoritamab vs POLA+BR, respectively.

As outlined in Clarification Question A7 in response to the request from the EAG, AbbVie have conducted a MAIC in which the epcoritamab DLBCL, no prior CAR-T population is adjusted to match the R-based CIT population from SCHOLAR-1.[4] AbbVie have subsequently updated base case analysis A so that the comparative efficacy and epcoritamab reference curve are informed by the MAIC conducted in response to Clarification Question A7.

An overview of the updated survival analysis is presented in Appendix A; a summary of the extrapolations selected to model OS, PFS and TTD for epcoritamab in the updated base case analysis A is presented in Table 32. The updated base case results (population A and population B) are presented at the end of this response document (Table 39–Table 50) with the incremental impact of each change presented in Table 38.

Table 30: Base case extrapolations to model OS, PFS and TTD for epcoritamab in the updated base case analysis A

Endpoint	Base case extrapolation
OS	Lognormal
PFS	Generalised gamma
TTD	Generalised gamma

Abbreviations OS: overall survival; PFS: progression-free survival; TTD; time to treatment discontinuation.

As stated in response to Clarification Question A8, the analysis requested in Clarification Question A8 has not been conducted as AbbVie maintain that the variables adjusted for in the submitted MAICs provide the most robust estimates for the efficacy of epcoritamab versus Pola + BR.

B10. Priority question. The EAG is concerned that all of the company's base case parametric survival curves for epcoritamab PFS provide a considerably bad visual fit to the end of the KM PFS curves. Furthermore, the KM PFS data suggest that [redacted] of patients are progression-free at 21 months, with all patients having progressed by then, whereas the company is assuming that about [redacted] of patients are progression-free at the same point in time in the model. The EAG appreciates the small number of patients at risk in the KM curve from about month 17, however, it has not seen any evidence to substantiate the company's assumption. Therefore, can the company please:

a) **Provide any evidence available to substantiate the assumption that [redacted] of patients on epcoritamab would be progression-free at 21 months.**

AbbVie acknowledge that based on the PFS KM curves from EPCORE™ NHL-1 included in the CS, PFS is [redacted] at 21 months for patients receiving treatment with epcoritamab. This point on the PFS KM curve are driven by two patients only. However, at the time of the EPCORE™ NHL-1 [redacted] data cut, the median follow-up for PFS was [redacted]. As such, information presented towards the tail-end of the curve after the time of median follow-up is subject to change as the data are immature. For example, at Month 18, [redacted] of patients in the DLBCL, no prior CAR-T subgroup ([redacted]) were progression-free; at the time of the [redacted] data cut of EPCORE™ NHL-1, data were not yet available on whether these patients experience a PFS event. Furthermore, as highlighted

by the EAG, there are small numbers of patients at risk from approximately [redacted] onwards, resulting in large drops in the PFS KM curve, [redacted].

Regarding the timing of the drops observed in the PFS curve, the drops around [redacted] and [redacted] are due to the timing of assessments in the trial; these time points correspond to target visit days (CS, Section B.2.6.3). Due to the censoring rules for PFS, patients who did not progress or die during the trial period were censored at their last evaluable tumour assessment; this explains the concentration of censoring observed in the PFS KM curve, and associated drops, around [redacted] and [redacted].

With longer follow-up, information presented in the KM curve after the time of median follow-up ([redacted]), and particularly towards the tail-end of the curve, is subject to change. This pattern has been observed in earlier data cuts of the EPCORE™ NHL-1 trial. To conclude, the [redacted] in the PFS KM curve is not representative of the treatment effect of epcoritamab since there are currently no observed data with a 21-month follow-up.

Data from a more recent data-cut of EPCORE™ NHL-1 exist ([redacted]), which further support that the [redacted] is not representative of the treatment effect of epcoritamab. No formal clinical study report or analyses are being conducted on these data, however descriptive analyses are available and due to be presented at an upcoming conference.[23] At the time of the latest data cut, of the [redacted] patients who achieved a CR, [redacted] of patients with LBCL remained in complete response (CR) at 12 months; at 18 months, this figure was approximately [redacted] and the proportion of patients remaining in CR appears to be [redacted]. As there are small patient numbers at later points in the KM curve, individual events drive large changes in the KM curve, however it is clinically implausible to consider that all patients in CR would have progressed by [redacted]. This is supported by feedback from UK clinical experts who stated that it is clinically implausible for PFS with epcoritamab to be [redacted] based on extensive experience of disease biology for those in CR.

Considering the maturity of the PFS data from EPCORE™ NHL-1 and the low numbers of patients at risk at the later timepoints in the KM data, data from EPCORE™ NHL-1 were not deemed to be the most suitable by itself to validate the long-term extrapolations of the PFS data, including the [redacted] of patients progression-free at 21 months. As such, feedback from UK clinical experts, alongside assessment of the statistical fit and visual fit, was used to determine the most clinically plausible curves for selection in the base case (CS, Section B.3.3.2).

In order to robustly collect feedback from UK clinicians on the proportion of patients anticipated to be progression-free following treatment with epcoritamab, clinicians were asked to provide three proportions for each time point: one representing the lower plausible limit, one representing the most plausible value and a further value representing the upper plausible limit. As presented in the CS (Section B.3.3.3), the clinicians estimated a plausible range of 10–40% progression-free at two years and 5–35% progression-free at five years; considering the most likely value only, the clinicians estimated a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively.

Based on the feedback from UK clinicians that the most likely proportion of patients that would be progression-free at two years (24 months) is 30–35%, AbbVie maintain that [redacted] of patients progression-free at 21 months is clinically plausible; this represents a conservative estimate when compared to the feedback from UK clinical experts. When considering the wider range of estimates provided by UK clinical experts (10–40% of patients would be progression-free at two years), the estimate produced by the base case extrapolation falls comfortably within this range, lying closer to the lower limit than the upper limit.

b) Conduct a scenario analysis where all epcoritamab patients are assumed to have progressed at 24 months (i.e., please use the KM PFS data to model time to progression directly for epcoritamab in the model).

As outlined in response to part a of this Clarification Question, the [redacted] in the PFS KM curve is not representative of the treatment effect of epcoritamab and these data are subject to change with additional follow up. As such, these data should not be directly used in the model to estimate PFS for patients following treatment with epcoritamab.

The EAG's request to include a scenario analysis in which 100% of patients have progressed at 24 months is clinically implausible and does not align with the available data or feedback from UK clinical experts received by AbbVie. AbbVie conducted extensive clinical validation in advance of the submission to NICE, as outlined in the CS and in response to part a of this Clarification Question. As part of this validation, clinical experts were asked to provide the lowest plausible value for PFS of patients receiving epcoritamab at 24 months. The lowest value that was provided for this estimate by the clinicians was 10% (with the highest value being 30%). As such, the requested scenario analysis is clinically implausible and has not been conducted.

c) Please repeat the scenario analysis requested in part b when the PFS curve for epcoritamab is estimated as requested in question A7 in the comparison vs R-CIT.

As outlined in response to part b of this Clarification Question, a scenario analysis in which PFS for patients receiving epcoritamab is [redacted] at 24 months is clinically implausible. As such, the requested scenario analysis has not been conducted.

d) Please repeat the scenario analysis requested in part b when the PFS curve for epcoritamab is estimated as requested in question A8 in the comparison vs POLA+BR.

As outlined in response to part b of this Clarification Question, a scenario analysis in which PFS for patients receiving epcoritamab is [redacted] at 24 months is clinically implausible. As such, the requested scenario analysis has not been conducted.

e) In case the company has more mature PFS data since the submission date; or any alternative longer PFS data for epcoritamab, please consider using a more flexible modelling approach, in order to provide a better visual fit to the underlying shape of the PFS KM data.

Since the original submission, PFS data from the DLBCL, no prior CAR-T population of EPCORE™ NHL-1 from a [redacted] data cut have become available; these have been incorporated into an analysis comparing epcoritamab to axi-cel, based on ZUMA-1. These data are due to be presented by Salles *et al.* (2023) at the upcoming European Hematology Association (EHA) Annual Meeting (8–11 June 2023), which has been provided in the reference pack alongside this response.[24] The results from the unadjusted DLBCL, no prior CAR-T population are consistent with those from the [redacted] data cut (CS, Section B.2.8.2) and show that the drop in PFS observed in the [redacted] data cut is no longer present.

B11. Priority question. The clinical experts advising the EAG noted that the 2-year long-term responder assumptions made by the company for axi-cel; POLA+BR and R-CIT are reasonable for patients who are still progression-free 2 years after treatment has ended. Nonetheless, the company assumes this to be the case 2 years after treatment initiation. Please justify the assumption, in light of this.

As highlighted in the CS (Section B.3.2.2), it was assumed that patients remaining in the pre-progression health state for 24 months are in long-term remission, and this assumption was adopted in line with previous NICE submissions in R/R LBCL and based on feedback from UK clinical experts.[11, 25-27] Of the previous NICE submissions in R/R LBCL in which this assumption was adopted (including TA649, TA559 and TA567), it is unclear whether the assumption was applied from the point at which treatment ended or the point of treatment initiation.

Given that epcoritamab and the relevant comparators included in this appraisal have different lengths of treatment, it was assumed that the 24-month period starts from treatment initiation (i.e., the start of the model). Moreover, given that epcoritamab is received continuously until unacceptable toxicity or progression, whilst the comparator treatments are all received for a fixed duration, assuming that the 24-month period begins from treatment initiation allows for a consistent assumption to be applied across all treatments. If this assumption were to be changed to be 24 months from the end of treatment, an arbitrary timepoint would be required when applying this assumption to the epcoritamab arm.

In order to explore any uncertainty associated with this assumption, scenario analyses have been conducted in which the 24-month durable remission assumption begins after patients in the comparator arm have completed their treatment. As such, for the comparison of epcoritamab versus R-based CIT, patients who are progression-free 28 months after treatment initiation are assumed to be in long-term remission, rather than 24 months as used in the base case. For the comparison of epcoritamab versus axi-cel, no scenario analyses have been conducted as axi-cel is a one-time treatment so 24 months after treatment initiation and treatment ending are the same. The results of these scenario analyses are presented at the end of this response document (Table 51 and Table 52).

B12. Priority question. Please include a scenario analysis in the model where the HR between the OS and PFS KM curves for epcoritamab for the DLBCL population, no prior CAR-T unadjusted, is used to estimate the PFS curve for R-CIT. More specifically, please apply the estimated HR between the OS and PFS epcoritamab curves to the OS SCHOLAR-1 curve for R-CIT in order to estimate a PFS curve for R-CIT:

a) Please undertake the request above in the company's base case.

AbbVie previously considered the suggested approach for modelling PFS for SCHOLAR-1 and concluded that it was not appropriate due to a number of reasons. In particular, the relationship between OS and PFS is partly dependent on the treatment and the mechanism of action. It is therefore inappropriate to assume that the relationship between OS and PFS for epcoritamab is the same as that for R-based CIT. The EAG's suggested approach would be lending efficacy from epcoritamab to R-based CIT. Based on the data available on the efficacy of epcoritamab and R-based CIT, epcoritamab is considerably more effective at inducing complete response than R-based CIT so it is not appropriate to lend efficacy from epcoritamab to R-based CIT in this way. Validation conducted with UK clinical

experts confirmed that this would be an unreasonable assumption.[28] As such, the requested scenario analysis has not been conducted.

As such, the approach outlined in the CS (Section B.3.3.3), that the HR for PFS was assumed to be the same as the HR derived for OS, is maintained in the updated base case analysis A. This is consistent with the approach adopted in TA559 and has been validated as plausible by UK clinical and health economics experts.[11, 16]

b) Please undertake the request above when the OS and PFS curves for epcoritamab are derived through the EAG-preferred method, as requested in question A7

As stated in response to part a of this Clarification Question, the requested scenario analysis has not been conducted as it would be inappropriate to assume that the relationship between OS and PFS for epcoritamab is the same as that for R-based CIT.

B13. Priority question. Please investigate the viability of estimating a HR between the OS and PFS outcomes in the PIX30 trial (R-CIT arm) to then apply that HR to the OS R-CIT arm estimated in the model in order to obtain a PFS curve for R-CIT.

a) Please undertake the request above in the company's base case.

As outlined in the CS, a clinical SLR was conducted to identify data sources for comparator efficacy data for inclusion in the MAICs. The PIX30 trials (PIX301 and PIX306) highlighted by the EAG were both excluded from the SLR as they did not fulfil the inclusion criteria (CS Appendices, Appendix D.1); this is documented in the list of excluded studies from the clinical SLR provided in the reference pack alongside the submission.[29, 30]

More specifically, in the R-based CIT arm of the PIX306 trial, 3.8% and 63.7% of patients had received no or only one prior lines of therapy, respectively.[29] Furthermore, approximately 7.5% of patients either had subtypes of LBCL other than those specified in the inclusion criteria, or the data were missing. A similar pattern is observed in the PIX301 trial, in which approximately 18% of patients had subtypes of LBCL other than those specified in the inclusion criteria.[30] As such, the patient populations included in these trials do not align with the decision problem of this submission, and they are therefore not relevant to inform comparative efficacy estimates.

b) Please undertake the request above when the OS curve for epcoritamab is derived through the EAG-preferred method, as requested in question A7

As outlined in response to part a of this Clarification Question, the PIX301 and PIX306 trials were excluded from the clinical SLR as they did not fulfil the eligibility criteria. As such, they do not match the decision problem of this submission and are not suitable for informing comparative efficacy estimates.

B14. Priority question. The CS describes the assessment of PHs undertaken for OS and PFS data in population A analysis between epcoritamab and R-CIT. Can the company please explain the labelling in the model of "independent model" for OS,

when a HR is derived from fitting the survival curves together and applied to the epcoritamab arm in the company's base case.

AbbVie can confirm that this is simply a mislabelling error in the model and apologise for any confusion caused. The EAG's interpretation that efficacy is modelled by applying a HR to the epcoritamab arm is correct.

B15. The generalised gamma used to estimate OS leads to approximately [redacted] of patients on the epcoritamab arm being alive at 20 years in the model, when patients would be 83 years (with [redacted] of patients alive at 93 years). Considering the severity of r/r 3L+ LBCL, please comment on the plausibility of the long-term survival estimates for population A, made up of patients ineligible to intensive therapy.

As outlined in the CS (Section B.3.14), AbbVie conducted extensive validation with UK clinical experts, including validation of the most clinically plausible long-term survival extrapolations. The clinical experts commented that the Gompertz extrapolations produced clinically plausible long-term estimates, if background mortality was also considered. Based on the adjusted overall survival models, clinicians stated that the generalised gamma was one of the extrapolations which produced plausible long-term estimates for OS when general population mortality adjustment was not included.

As outlined in response to Clarification Question B9, AbbVie have updated base case analysis A and the extrapolation selected to model OS in the updated base case analysis A is the lognormal extrapolation. The Gompertz and generalised gamma extrapolations produce substantially higher survival estimates in the long-term based on patients alive in the progressed disease state, which was deemed implausible based on treatments currently recommended by NICE.

However, the long-term OS estimates produced by the lognormal extrapolation accounting for adjusted general population mortality are clinically plausible. Modelled OS converges with modelled PFS, which is consistent with clinical expert advice that patients that patients with LBCL who achieve a CR to treatment are at low risk of further events when the response is sustained. For patients with progressed disease, experts feedback indicates that current treatments options are only expected to provide palliative relief.

In conclusion, the economic model reflects that treatment with epcoritamab produces substantially greater probability of CR in third or later line of treatment and available data indicate that CR is durable. The estimated OS is therefore a reflection of the potential for epcoritamab to provide substantial health benefits for this population with few effective treatment options.

Population B

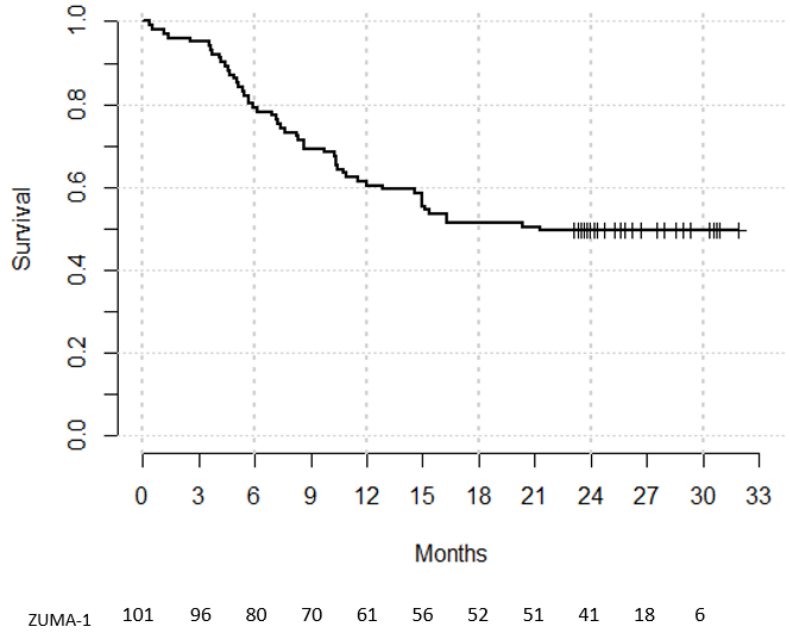
B16. Priority question. Please provide the KM data in an Excel spreadsheet with numbers at risk, underlying Figure 12 and Figure 13 in the CS for axi-cel.

a) Please provide the equivalent data for TTD from ZUMA-1, if available.

The OS and PFS KM data from ZUMA-1, based on Locke et al. 2019, utilised in the MAIC are provided in an Excel spreadsheet in the reference pack accompanying these responses. TTD data are not relevant for ZUMA-1 because it is a single infusion, and therefore have not been provided. However, AbbVie reiterates that, according to clinical experts, the ZUMA-1 data presented from the infused population strongly biases efficacy results in favour of axi-cel (see response to Clarification Question

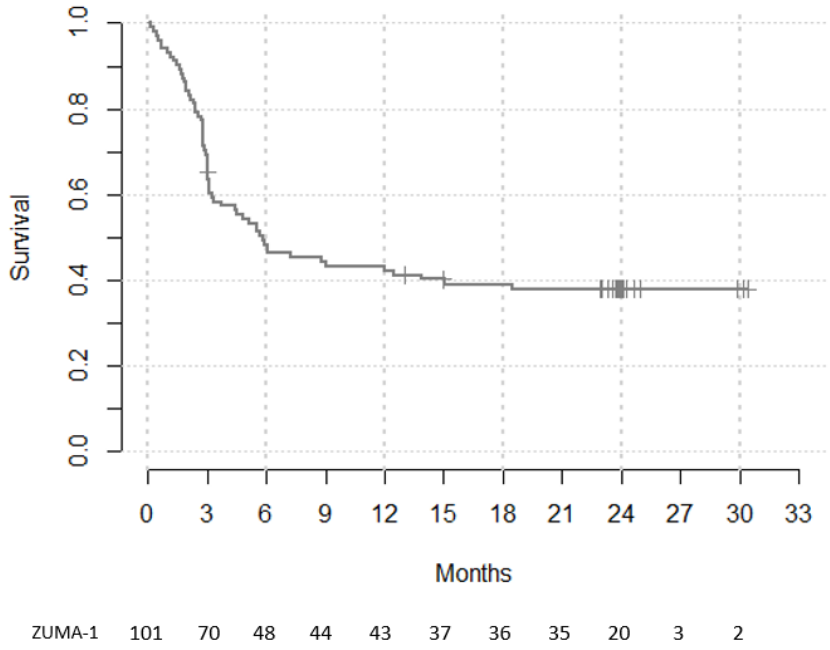
A9). The OS and PFS curves with the numbers at risk are presented in Figure 20 and Figure 21, respectively.

Figure 20: Digitised OS KM curve based on ZUMA-1 used in the MAIC analyses



Abbreviations: KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.

Figure 21: Digitised PFS KM curve based on ZUMA-1 used in the MAIC analyses



Abbreviations: KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival.

B17. Priority question. Please include a scenario analysis in the model where the analysis requested in question A10 is used to estimate treatment effectiveness in the model.

As outlined in response to Clarification Question A9, the cost-effectiveness model has been updated to incorporate the results of the adjusted MAICs informing population B (eligible for intensive therapies), in which the epcoritamab population is adjusted to match the ZUMA-1 population and compared with axi-

cel. In addition to the change from using the unadjusted to adjusted epcoritamab data, as outlined in response to Clarification Question A9, AbbVie have also updated the preferred efficacy assumptions in base case B to align with the EAG's preference for using the LBCL population from EPCORE™ NHL-1, rather than the DLBCL population.

A summary of the MAICs informing the original analyses, the updated base case analysis and new scenario analysis is provided in Table 31. The results of each these MAICs were presented in the CS (Section B.2.8.3). An overview of the updated survival analysis informing the updated base case B and new scenario analysis B.2 is presented in 0, and a summary of the extrapolations selected to model OS, PFS and TTD in the updated base case analysis B and scenario analysis B.2 is presented in Table 31. A summary of the results of the scenario analyses have been presented at the end of this response document (Table 51 and Table 52).

Table 31: Summary of the updated MAICs informing base case B and scenario analysis B.1

	Epcoritamab population	Epcoritamab versus comparator	Comparator population adjusted to
Updated base case analysis B: Eligible for intensive therapy	LBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Adjusted to match ZUMA-1[b]
Original base case B: Eligible for intensive therapy	DLBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Unadjusted to match ZUMA-1[b]
Scenario analysis B.1: Eligible for intensive therapy	LBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Unadjusted to match ZUMA-1[b]
Scenario analysis B.2: Eligible for intensive therapy	DLBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Adjusted to match ZUMA-1[b]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; MAIC: matching adjusted indirect comparisons.

Table 32: Base case extrapolations to model OS, PFS and TTD for epcoritamab in the updated base case analysis B and scenario analysis B.2

Endpoint	Selected extrapolation	
	Updated base case analysis B	Scenario analysis B.2
OS	Lognormal	Lognormal
PFS	Generalised gamma	Lognormal
TTD	Gompertz	Lognormal

Abbreviations OS: overall survival; PFS: progression-free survival; TTD; time to treatment discontinuation.

B18. Priority question. The EAG is concerned that all the company's parametric survival curves for epcoritamab PFS provide a considerably bad visual fit to the underlying KM PFS curves, particularly, from month 12 onwards. KM PFS data suggests that 0% of patients are progression-free at [redacted], with all patients having progressed by then, whereas the company is assuming that about [redacted] of patients are progression-free at the same point in time in the model, and that [redacted] of patients are long-term responders at 24 months. The EAG appreciates the small number of patients at risk in the KM curve from about month 16, however, has not seen any

evidence to substantiate the company's assumption. Therefore, can the company please:

a) **Provide any evidence available to substantiate the assumption that [redacted] of patients on epcoritamab would be progression-free at 24 months.**

As outlined in response to Clarification Question B10 (part a), information presented towards the tail-end of the PFS KM curve, is subject to change with additional follow-up and is not representative of the treatment effect associated with epcoritamab. This includes the [redacted] PFS observed at Month 20. The available data on the proportion of patients remaining in CR suggest that it is clinically implausible to consider that all patients in CR would have progressed by [redacted] and the proportion of patients in CR appears to be [redacted].[23]

Therefore, individual patient level data from EPCORE™ NHL-1 were used to generate parametric models for the long-term extrapolations of the PFS data. Feedback from UK clinical experts, alongside assessment of the statistical fit and visual fit, was used to determine the most clinically plausible curves for selection in the base case (CS, Section B.3.3.2).

As outlined in response to Clarification Question B10 (Part a), AbbVie maintain that [redacted] of patients progression-free at 24 months is clinically plausible and this represents a conservative estimate when compared to the feedback from UK clinical experts (most likely value: 30–35% of patients are progression-free at 24 months). When considering the wider plausible range of estimates provided by UK clinical experts (10–40% of patients would be progression-free at two years), the estimate produced by the base case extrapolation falls comfortably within this range, lying closer to the lower limit than the upper limit.

b) **Conduct a scenario analysis where all epcoritamab patients are assumed to have progressed at 24 months (i.e., please use the KM PFS data to model time to progression directly for epcoritamab in the model).**

As outlined in response to Clarification Question B10 (part b), a scenario analysis in which PFS for patients receiving epcoritamab is [redacted] at 24 months is clinically implausible. As such, the requested scenario analysis has not been conducted.

c) **Please repeat the scenario analysis requested in part b when the PFS curve for epcoritamab is estimated as requested in question A10.**

As outlined in response to Clarification Question B10 (part b), a scenario analysis in which PFS for patients receiving epcoritamab is [redacted] at 24 months is clinically implausible. As such, the requested scenario analysis has not been conducted.

d) **In case the company has more mature PFS data since the submission date; or any alternative longer PFS data for epcoritamab, please consider using a more flexible modelling approach, in order to provide a better visual fit to the underlying shape of the PFS KM data**

Since the original submission, PFS data from the DLBCL, no prior CAR-T, CAR-T eligible population of EPCORE™ NHL-1 from a [redacted] data cut have become available and an analysis has been

conducted comparing epcoritamab to axi-cel, based on ZUMA-1. These data are due to be presented by Salles *et al.* (2023) at the upcoming European Hematology Association (EHA) Annual Meeting (8–11 June 2023), which has been provided in the reference pack alongside this response.[24] The results are consistent with those from the MAICs conducted using data from the [redacted] data cut (CS, Section B.2.8.2) and show that the drop in PFS observed in the [redacted] data cut is no longer present.

B19. For population B, the generalised gamma used to estimate OS leads to approximately [redacted] of patients on the epcoritamab arm being alive at 20 years in the model, when patients would be 83 years (with [redacted] of patients alive at 93 years). Considering the severity of r/r 3L+ LBCL, please comment on the plausibility of the long-term survival estimates for population B.

As outlined in response to Clarification Question B15, the selection of the generalised gamma extrapolation to model OS in the base case analyses is aligned with feedback from UK clinical experts. As such, AbbVie maintain that the long-term OS estimates produced by the generalised gamma extrapolation are clinically plausible.

B20. For population B, the company's base case log-logistic TTD curve slightly tracks under the PFS curve throughout the models' time horizon. The company has not provided any rationale for why patients in population B would experience higher toxicity with epcoritamab than patients in population A (given that in the latter patients only discontinue due to toxicity over the first year of treatment, after which TTD and PFS curves converge). Therefore, can the company please discuss the clinical plausibility of this.

As stated in the CS (Section B.3.3.3 and Section B.3.3.4), UK clinical experts stated that they would expect the TTD curve to be similar in shape but repressed compared to the PFS curve, as patients would be likely to remain on treatment until they progress; the clinical experts stated that it was possible for patients to discontinue treatment due to toxicity rather than progression, but the available data suggests that epcoritamab is well-tolerated with only [redacted] of patients with DLBCL from EPCORE™ NHL-1 discontinuing due to AEs.

As different epcoritamab populations are included in population A (DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+) and population B (DLBCL, no prior CAR-T, CAR-T eligible), slightly different TTD KM curves were used to inform the extrapolation of TTD in the two populations. As such, the small differences in the relationship between TTD and PFS observed between the two populations is an artefact of the different KM curves and extrapolations selected to model TTD. However, AbbVie agree with the EAG that a difference in TTD and toxicity between the two populations is not anticipated to be observed in UK clinical practice; a small difference in TTD and PFS is expected in both populations, based on feedback from UK clinicians.

As outlined in response to Clarification Question A7 and Clarification Question A9, base case A and base case B have been updated. The extrapolations chosen to model PFS and TTD (and OS) in both updated populations are reported in response to Clarification Question B9 and Clarification Question B17, and the selected extrapolations mean that TTD is similar in shape but repressed compared to the PFS curve in both populations.

Adverse events

B21. Priority question. When using utilities from the EPCORE trial in the economic model, the costs associated with adverse events have been incorporated into total costs while the reciprocal disutilities have not been included in the total discounted QALYs. However, when using the ZUMA-1 utilities, the disutilities are incorporated. Please can the company confirm this is an error in the model and correct the model accordingly to include the disutility data when EPCORE utilities are used.

AbbVie can confirm that when the utility values derived from EPCORE™ NHL-1 are applied in the model, disutilities associated with AEs are not applied. This is an error and has been updated accordingly in the cost-effectiveness model. This update has been incorporated into the updated base case analyses (population A and population B). The updated base case results are presented at the end of this response document (Table 39–Table 50) with the incremental impact of each change presented in Table 38.

B22. Priority question. The EAG's clinical experts questioned the incidence of grade ≥3 adverse events for axi-cel treatments in the economic model (Table 55 in the CS), noting that in the ZUMA-1 study, 78% of patients suffered from neutropenia, 43% from anaemia, and 38% thrombocytopenia:

a) **Please can the company explain the difference between the ZUMA-1 incidence of grade ≥3 adverse events and those used in the economic model for axi-cel.**

As outlined in the CS, the AEs for axi-cel included in the base case analyses are based on those included in TA559. As outlined in TA559, the cost of all AEs (excluding CRS and B-cell aplasia) assume the cost of one excess bed day. The administration of axi-cel requires hospitalisation and this cost is accounted for separately in the submitted cost-effectiveness model (and TA559). As such, costing each AE individually would result in double-counting between the hospitalisation cost associated with administration of axi-cel and the individual AE costs, assuming that the costs of AEs are covered by the length of stage for axi-cel patients associated with administration. As such, only cytokine release syndrome (CRS) and B-cell aplasia were required to be costed individually; neutropenia, anaemia and thrombocytopenia were not costed to avoid double-counting, as due to the reasons documented above.

In the submitted cost-effectiveness model, the costs associated with ICANS were included in addition to CRS and B-cell aplasia, with the incidence per TA559, as it was reported in TA559 that neurotoxicity is one of the most dangerous side effects of axi-cel and can result in the need for hospitalisation.

b) **Please can the company conduct a scenario using the incidence of adverse events from the ZUMA-1 trial data for axi-cel**

As outlined in part a of this Clarification Question, the incidence of AEs included in the cost-effectiveness model differed from those reported in ZUMA-1 to avoid double-counting. Regardless, as requested by the EAG, a scenario analysis has been conducted whereby the incidence of AEs for the axi-cel treatment arm based on the ZUMA-1 publication by Neelapu *et al.* (2017) (Table 33).

The results of this scenario analysis are presented at the end of this response document; the probabilistic results are presented in Table 51 and the deterministic results are provided in Table 52.

Table 33: Incidence of AEs in the axi-cel treatment arm based on ZUMA-1 trial (Neelapu *et al.*, 2017)

Adverse event	Incidence (axi-cel)	
	Based on TA559	Based on Neelapu *et al.* (2017)
Anaemia	0.00%	42.57%
B-cell aplasia[a]	11.00%	0.00%
CRS	13.00%	12.87%
Febrile neutropenia	0.00%	30.69%
Hypokalaemia	0.00%	5.94%
ICANS	28.00%	0.00%
Leukopenia	0.00%	0.00%
Lymphopenia	0.00%	0.00%
Neutropenia	0.00%	77.23%
Neutrophil count decreased	0.00%	0.00%
Pneumonia	0.00%	0.00%
Rash	0.00%	0.00%
Thrombocytopenia	0.00%	37.62%
Source	TA559	Neelapu *et al.*, 2017

[a] B-cell aplasia includes only grade 1 and 2 AEs; [b] The incidence of CRS in the axi-cel arm is based on the proportion of patients experiencing grade 3 or higher CRS events in line with TA559; this approach was taken to reflect the impact of CRS associated with axi-cel on quality of life.
Abbreviations: AE: adverse events; axi-cel: axicabtagene ciloleucel; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

B23. Priority question. Can the company provide a justification for the inclusion of the incidence of grades 1 and 2 B-cell aplasia for axi-cel in the economic model.

This approach is aligned with the approach adopted in TA559 following the EAG Clarification Questions, in which grade 1 and 2 B-cell aplasia was included as this adverse event often requires treatment and is associated with potentially significant resource use consumption.[11]

B24. Priority question. When validating the incidence of grade ≥3 adverse events from the EPCOR CSR against the economic model, the EAG identified a number of inconsistencies. For example, the incidence in the economic model as described in Table 55 for neutropenia is [redacted]% while this value in the CSR is [redacted]% for DLBCL patients and [redacted]% for LBCL patients. Similar discrepancies have been identified for hypokalemia and leukopenia. Please can the company update the adverse events incidence in the economic model to reflect the values in the CSR and check the

other adverse events in Table 55 for similar errors. Adversely could the company explain the difference between the CSR and incidence used in the economic model.

The AE values used in Table 55 of the CS, and included in the cost-effectiveness model, were based on the January 2022 data cut for EPCORE™ NHL-1 (as indicated by the source beneath Table 55). However, for consistency with the other presented results in the CS the model has been updated with AE data from the [redacted] data cut for EPCORE™ NHL-1.

Whilst updating the data cut on which the AE incidence is based, an error was identified in the submitted model whereby the incidence of AEs in the epcoritamab arm were based on the incidence of serious AEs rather than AEs of grade 3 or higher. Therefore, in addition to updating the data cut, the AEs in the epcoritamab arm have been updated to be based on the incidence of grade 3 or higher AEs. Both of these changes have been incorporated into the updated base case analyses. The results of the updated base case analyses are presented at the end of this response document (Table 39–Table 50) with the incremental impact of each change presented in Table 38.

The updated AE incidence values for epcoritamab used in the cost-effectiveness model are presented in Table 19, alongside the values used in the original base case analyses.

Table 34: Incidence of AEs in the epcoritamab treatment arm

Adverse event	Incidence (epcoritamab)	
	January 2022 data cut	[redacted] data cut
Anaemia	[redacted]	[redacted]
B-cell aplasia	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
ICANS	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Source	EPCORE™ NHL-1, January 2022 DCO	EPCORE™ NHL-1, [redacted] DCO

Abbreviations: AE: adverse events; axi-cel: axicabtagene ciloleucel; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

B25. Please can the company provide an explanation as to why a different criterion has been used for CRS incidence between epcoritamab and axi-cel. As a scenario please can

the company use the inclusion criteria applied to axi-cel to derive the incidence of CRS for epcoritamab in the model.

The difference in criteria used to define CRS incidence for epcoritamab (based on EPCORE™ NHL-1) and for axi-cel (based on ZUMA-1) is due to the trials being conducted at different timepoints; both trials used the most recent CRS criteria at the time of conduct. As EPCORE™ NHL-1 was conducted after ZUMA-1, it uses a more recent CRS criterion compared with the ZUMA-1 trial.[2, 31]

It is not feasible to redefine the CRS incidence from EPCORE™ NHL-1 trial in line with the CRS criteria used in ZUMA-1; this would require the investigator to regenerate the CRS events with an older criterion which is not appropriate. As such, AbbVie are not able to conduct the EAG's request of a scenario analysis whereby the CRS criteria applied to axi-cel are applied to epcoritamab.

Furthermore, the incidence of CRS in the epcoritamab arm is based on the proportion of patients experiencing serious adverse event (SAEs) of CRS in the EPCORE™ NHL-1 trial, to best represent the cost of CRS associated with epcoritamab. In contrast, the incidence of CRS in the axi-cel arm is based on the proportion of patients experiencing grade 3 or higher CRS events in line with TA559. CRS for the epcoritamab arm was based on SAEs to reflect the cost impact of CRS for the epcoritamab arm, whilst CRS in the axi-cel arm was based on grade 3 or higher, as the tariff associated with axi-cel includes hospitalisation in the first 100 days.

B26. Given the similarities underpinning lymphopenia, leukopenia, neutropenia, and neutrophil count decrease, the EAG's clinical experts raised concerns that there were several inconsistencies in the incidence of these events per treatment arm in the model. Please can the company confirm the incidence rates used.

The incidence rates used in the economic model for lymphopenia, leukopenia, neutropenia and neutrophil count decrease are presented in Table 35. As outlined in response to Clarification Question B24, the incidence rates for the epcoritamab arm have been updated in the base case analyses to be based on the [redacted] data cut of EPCORE™ NHL-1.

Table 35: Incidence rates of lymphopenia, leukopenia, neutropenia and neutrophil count decrease used in the economic model

	Epcoritamab	R-based CIT	Axi-cel	Pola + BR
Lymphopenia	[redacted]	0.0%	0.0%	12.8%
Leukopenia	[redacted]	7.7%	0.0%	7.7%
Neutropenia	[redacted]	33.3%	0.0%	46.2%
Neutrophil count decrease	[redacted]	0.0%	0.0%	0.0%
Source	EPCORE™ NHL-1[32]	NICE TA649[26]	NICE TA559[11]	NICE TA649[26]

Abbreviations: CIT: chemoimmunotherapy; Pola + BR: polatuzumab with bendamustine and rituximab; R: rituximab.

Cost and resource use

B27. Priority question. Given that subsequent treatments following third line treatment will be dependent on eligibility to intense therapy, please justify using the same proportions of subsequent treatment for both populations A and B.

a) **As a scenario, please use the following proportions for patients receiving subsequent treatment.**

Treatment at entry	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	No active treatment
Epcoritamab (for population A)	30%	11%	25%	0.5%	3%	30%
Epcoritamab (for population B)	30%	30%	25%	0.5%	3%	11.5%
R-based CIT	30%*	8%	30%	0%	1.5%	30%
Axi-cel	9%	0%	32%	1%	5%	53%

*The EAG's clinical experts stated that after a previous treatment with R- based CIT additional chemotherapy would be palliative and not R-based

The proportion of subsequent treatments used in the submitted base case was informed by feedback from UK clinical experts. The clinical experts highlighted that subsequent treatments would vary based on the treatment received at third-line (as represented by the base case assumptions), and variability in the proportion expected to receive axi-cel as a subsequent treatment is acknowledged. Based on the clinical validation received, AbbVie maintain that the subsequent treatment assumptions used in the submitted base case are appropriate and AbbVie have not conducted a scenario analysis using the subsequent treatment proportions provided by the EAG.

In addition, data on subsequent treatments received after treatment with epcoritamab were collected in EPCORE™ NHL-1 and the proportions for the epcoritamab arm based on feedback from the EAG's clinical experts substantially differ from those reported in EPCORE™ NHL-1. In particular, the EAG's preferred estimates include a substantially higher proportion of patients receiving CAR-T therapy after treatment with epcoritamab than reported in EPCORE™ NHL-1 (11% [population A] and 30% [population B] versus [redacted] in the LBCL population of EPCORE™ NHL-1). This increased CAR-T usage would be associated with a clinical benefit which is not reflected in the efficacy data for epcoritamab currently used in the model. As such, any scenario analysis using the EAG's preferred subsequent treatment assumptions would need to be combined with efficacy data for epcoritamab that had been amended to reflect the alternative proportions of subsequent treatments, in particular the increased CAR-T therapy use, to minimise any bias in the analyses.

B28. Priority question. The EAG is concerned that the resources included in Table 66 of the CS might be double counting the care utilised by patients, particularly for residential care; day care; home care; hospice; nurse use; and palliative care. The residential care cost (referenced from PSSRU 2021) seems to refer to hospital specialist palliative care support (adults only). Please explain what this resource is capturing, and what unit is reflected in the £155 cost (i.e., hour, bed-day, etc.). The company also included time with a palliative care team and hospice care. Can the company please explain if there is overlap in these resources (therefore, double counting palliative care). If so, please reconsider the resource use included in the model as to not double count care.

AbbVie wish to highlight that all cost categories and cost sources used in the model are aligned with previous NICE appraisals in R/R LBCL (such as TA649, TA306 and TA559).[11, 26, 33] These were subsequently validated by UK clinical experts, following which AbbVie updated some of the resource use estimates to align more closely with UK clinical practice.

Regarding the EAG's queries about the residential care cost, the palliative care cost and hospice care:

- The residential care cost included in the model was sourced from Personal Social Services Research Unit (PSSRU) and covers resident day establishment costs for voluntary and private sector residential care home for adults requiring physical support. Specifically, this cost covers capital costs, land costs, and total expenditure (excluding capital costs).
- The palliative care cost included in the model is for hospital specialist palliative care for those aged 19 years and over, source from the National Schedule of Reference Costs 2019-20 (SD03A).
- The hospice cost is an end-of-life in hospice cost, which has been sourced from TA649 and inflated to 2021.

TA306, TA649 and TA559 all included the above three cost categories, and the inputs are originally based on a questionnaire conducted and presented in TA306.

a) **The day care cost (referenced from PSSRU 2021) seems to refer to 1 working hour of a band 7 nurse. The company also included time with a specialist nurse; district nurse; and nurse time. Can the company please explain if there**

is overlap in these resources (therefore, double counting nurse time). If so, please reconsider the resource use included in the model as to not double count care.

As highlighted in response to part a of this Clarification Question, the resource use categories included in the model are aligned with previous NICE technology appraisals in R/R LBCL.

Regarding the EAG's query about the day care, specialist nurse, district nurse and nurse time, day care is part of professional and social services, with the cost sourced from PSSRU. The district nurse resource use is considered to be community-based health care, whilst the specialist nurse and nurse resource use are hospital-based health care. However, the cost associated with the district nurse, specialist nurse and nurse time are all based on the National Schedule of Reference Costs 2019-20 (N02AF), in line with previous NICE TAs in R/R LBCL.

b) Please explain what is included in the home care and hospice care resource use.

As highlighted in response to part a of this Clarification Question, the resource use categories home care and hospice care are aligned with previous NICE TAs in R/R LBCL.

The cost sources for these inputs are aligned with TA649 and both are source from the National Audit Office 2008, which was then inflated to 2021 cost year. TA649 does not include a detailed explanation of what is included in these two resource use categories, but they are both part of professional and social services.

B29. Priority question. Please include a scenario analysis in the model where PFS patients continue to incur the resource use associated with being in the PFS state for 3, 4, and 5 years separately.

In the base case economic analysis, patients in the progression-free health state after 24 months are considered to be in long-term remission; as well as no longer following the PFS curve and instead experiencing an adjusted background mortality rate (SMR of 1.41) to reflect the additional risk of death due to long-term complications associated with cancer treatment (CS, Section B.3.2.2), these patients are assumed to incur no healthcare resources beyond those required for treatment administration after 24 months (CS, Section B.3.2.2). This approach aligns with prior NICE appraisals in R/R LBCL and is consistent with current clinical practise in UK according to clinical expert opinion.[11, 16, 25, 26]

AbbVie conducted extensive validation with UK clinical experts, during which clinicians stated that patients would be expected to be fully discharged after two years if progression-free. AbbVie conducted further validation with UK clinical experts to support development of response to these Clarification Questions, who reiterated that there is no clinical rationale for the PFS on-treatment resource use estimates to be applied to patients that are in complete response.[16] As such, assuming that patients in the PFS health state incur healthcare resource use for 3, 4 or 5 years is not aligned with UK clinical practice. Therefore, AbbVie have not provided scenario analyses in which patients in the PFS state continue to incur resource use for 3, 4 or 5.

B30. Priority question. Considering the SmPC for epcoritamab states that treatment should be given until progression or unacceptable toxicity, please can the company provide additional justifications for the use of [redacted] as a threshold after which

progression free epcoritamab patients are considered to switch to the "off-treatment" resource use in the model.

For patients in the epcoritamab arm, [redacted] is used as the timepoint for which patients are assumed to switch from the PFS *on*-treatment resource use estimates to the PFS *off*-treatment resource use estimates. It is not assumed that patients in the epcoritamab arm incur *no* resource use estimates after [redacted], but rather the resource use decreases.

AbbVie acknowledge that the dosing of epcoritamab differs from currently available treatments as patients would receive epcoritamab via a subcutaneous (SC) injection until progression or unacceptable toxicity, rather than for a fixed duration infusion. As such, patients in the epcoritamab arm will always be on-treatment according to modelled TTD whilst progression-free, but the resource use of patients receiving epcoritamab is anticipated to decrease over time, as stated by UK clinical experts.[16] It was therefore necessary for AbbVie to explore the most appropriate timepoint at which the resource use of patients would be expected to decrease and [redacted] was selected for this timepoint.

As outlined in the CS, the timepoint of [redacted] was selected as this is the median PFS for patients with DLBCL in partial response (PR), based on the [redacted] data cut of EPCORE™ NHL-1. Therefore, patients who are progression-free beyond this point have surpassed the median PFS for patients receiving epcoritamab who are in PR and most progression-free patients beyond this timepoint are in CR. This is further supported by data from EPCORE™ NHL-1, as of the [redacted] patients with LBCL who achieved CR, an estimated [redacted]% of patients remained in CR at 9 months (based on the [redacted] data cut from EPCORE™ NHL-1). Furthermore, based on the January 2022 data cut, after the Week 36 tumour assessment, 9 patients who had previously achieved a PR (based on the first or second assessment) subsequently converted to a CR, suggesting a deepening and durable response to epcoritamab for those in PR.[34]

The timepoint of reducing the intensity of resource use, based on decreasing follow-up, for patients receiving treatment with epcoritamab is uncertain. However, feedback from UK clinical experts confirmed that the timepoint by which most patients are in CR represents an appropriate timepoint for the resource use associated with epcoritamab to decrease. The clinical experts stated that patients in CR are unlikely to require resource use beyond injection service, blood tests, interpretation of blood tests by nurse or pharmacist, and occasional consultant lead contacts.[16] As such, assuming that patients receiving epcoritamab continue to incur the resource use associated with the PFS on-treatment health state for their duration of treatment is a substantial overestimation of the healthcare resource use of these patients. The model has therefore not been updated to allow for patients receiving epcoritamab to continue to incur resource use associated with the PFS health state whilst remaining on treatment. Instead, the model continues to assume a lower (but not zero) resource use for epcoritamab beyond [redacted] (until 2 years).

AbbVie wish to reiterate that epcoritamab is the first and only SC treatment available for patients with R/R LBCL after two or more prior lines of systemic therapy. As outlined in the CS, the SC administration enables quick administration across different practice settings when compared with currently available intravenous therapies. Therefore, the resource use of patients in the progression-free health state receiving epcoritamab is not anticipated to be the same as the resource use of patients who are receiving currently available treatments.

a) **In order to be consistent with the company's assumption of long-term remission at 2 years for the model comparators, please include a scenario in the model where progression-free epcoritamab patients at 2 years do not incur any resource use from that point forward.**

The assumption of long-term remission at two years (after which patients do not incur any resource use) is applied to all treatment arms in the model, including the epcoritamab treatment arm. For the epcoritamab treatment arm however, costs for treatment administration continue to be incurred after two years; as epcoritamab is received continuously until disease progression or unacceptable toxicity, it would be inappropriate for patients receiving epcoritamab to not incur costs associated with treatment administration after two years, but no further resource use is considered. As such, the scenario requested by the EAG is already aligned with the assumptions used in the original and updated base case analyses and no additional scenario analyses have been conducted.

b) Clinical expert opinion provided to the EAG indicated that epcoritamab patients would be followed while on treatment. Therefore, please include an option in the model where the "on-treatment" resource use estimated for PFS for epcoritamab is used while patients remain on treatment.

As outlined in response to part a of this Clarification Question, although epcoritamab is received continuously until progression or unacceptable toxicity, the resource use of patients receiving epcoritamab is anticipated to decrease over time. For patients in long-term PFS, it is anticipated that patients will only routinely incur resource use associated with administration of epcoritamab (which is captured separately in the administration costs) and a blood test.[16] As such, assuming that patients receiving epcoritamab continue to incur the resource use associated with the PFS on-treatment health state is a substantial overestimation of the healthcare resource use of these patients. As such, the model has not been updated to allow for patients receiving epcoritamab to continue to incur resource use associated with the PFS health state whilst remaining on treatment. Instead, the model continues to assume a lower (but not zero) resource use for epcoritamab beyond [redacted].

B31. Priority question. Clinical expert opinion provided to the EAG reflected that R-CIT patients often discontinue treatment due to toxicity (before the end of the fixed duration of treatment). The EAG also found a study indicating that about 10% of patients discontinued treatment with R-CIT (Cazelles et al. 2021[35]). Nonetheless, the company assumed that patients did not discontinue treatment for reasons other than progression or end of treatment period. Therefore, can the company please conduct an exploratory scenario analysis where patients also discontinue treatment due to toxicity (i.e., where time to treatment discontinuation is not assumed to be the same as PFS for R-CIT).

Based on feedback from UK clinical experts, the vast majority of patients that receive treatment with R-based CIT will remain on treatment for as long as possible, as there are no other treatment options available once a patient has discontinued treatment with R-based CIT. As such, for the vast majority of patients, they will only discontinue treatment with R-based CIT upon progression. AbbVie maintain that few patients would discontinue R-based CIT for reasons other than progression or reaching the end of the fixed duration treatment period, so the scenario analysis requested by the EAG has not been conducted. As current CIT options are generic or biosimilar, the expected impact on cost-effectiveness is minimal.

In addition, AbbVie wish to highlight that there is not sufficient information in available literature to conduct a scenario analysis varying the TTD for patients receiving R-based CIT; information on the proportion and timing of discontinuation would be required to conduct this scenario analysis.

B32. Priority question. For the scenario which compares epcoritamab against POLA+BR can the company please outline the assumptions made to estimate the costs of treatment POLA+BR as these are not clearly described in the CS (or the appendix).

All information relating to the costs associated with treatment with Pola + BR are presented in the CS and CS appendices. All inputs are aligned with those used in the base case analyses versus R-based CIT and axi-cel; where specific inputs are required for Pola + BR, these are presented in Appendix P.

Specifically, information relating to the drug dosage inputs, drug acquisition costs, treatment administration/monitoring costs, subsequent treatment proportions and AE incidence for the Pola + BR arm are presented in the CS Appendices (Appendix P.5 and Appendix P.6). The subsequent treatment costs, resource use and AE unit costs used in the comparison of epcoritamab versus Pola + BR are aligned with the base case analyses, as presented in the CS (Section B.2.5.2 and Section B.3.5.3).

B33. Priority question. The EAG finds that the administration cost for axi-cel assumed in the model lacks clarity. The company's model reports this cost to be £41,101, to which the company deducted £3,560 to prevent double counting the cost of CRS in the model. Can the company please:

a) **Provide a detailed description of all the resources included in the £41,101 overall cost of administration.**
b) **Point the EAG to where in the TA872 documents (referred to as the source for the £41,101), the cost is reported.**

AbbVie can confirm that the cost of £41,101 for axi-cel was taken from Slide 4 of the Public Committee Slides from the third appraisal committee meeting for TA872, and confirmed by the budget impact template from NHS England.[36] AbbVie's understanding from these slides is that NHS England had agreed with the submitting Company that this value is an appropriate total cost for the first 100 days following CAR-T use and should be used in all ongoing and future appraisals that capture CAR-T therapies.

As part of this using this total cost in TA872, a number of cost categories were subsequently set to zero. Whilst the costs are redacted, these cost categories included the following, which have been interpreted as the relevant costs and resources which feed into the £41,101 overall cost:

- Axi-cel leukapheresis costs
- Hospitalisation costs for conditional chemotherapy
- Weighted average cost of CRS
- Hospitalisation costs for axi-cel administration
- Axi-cel costs for weighted average cost of allogenic SCT
- Training costs
- Medical resource use costs for the first three months (~100 days)

- Hypogammaglobulinemia costs for the first three months (~100 days)

As a result of this list, to prevent any double counting, the cost of CRS has been removed from the one-time administration cost of axi-cel in the epcoritamab model. However, having looked into this further as part of AbbVie's response to this question, an error was identified in how this had been calculated. Incidence of CRS is still considered within the model to enable the disutility of this AE and costs of CRS for other comparators to still be captured. In the original model however, the total cost of a CRS event was incorrectly removed from the administration cost of axi-cel (by inadvertently assuming that all patients experience a CRS event), rather than weighting this cost reduction based on the incidence. This therefore resulted in an over-adjustment and reduction of for the cost of axi-cel when attempting to remove the double-counting. This has been corrected in the model base case, such that the one-time administration cost of axi-cel is calculated as £41,101 – (cost of CRS × incidence of CRS for axi-cel).

B34. The EAG has identified less expensive costs for bendamustine (£21.29 per 100mg, £28.75 per 5x25mg) and oxaliplatin (£13.49 per 50mg and £21.52 per 200mg) and a bigger pack size for bendamustine (£77.70 per 5x100mg) within the eMIT database (July 2022 -Dec 2022) than those used by the company in the model. Please can the company provide a scenario analysis using these costs.

The base case analyses (population A and population B) have been updated to include the EAG's preferred costs for bendamustine and oxaliplatin from the eMIT database (July 2022–Dec 2022). The updated base case results are presented at the end of this response document (Table 39–Table 50) with the incremental impact of each change presented in Table 38.

B35. Please can the company explain the use of cost code XD31Z from the NHS reference cost 2015/16 for costing CRS in addition to XC01Z from NHS references costs 2019/20.

The cost of CRS used in the cost-effectiveness model is aligned with the approach adopted in TA559. As stated in TA559, the cost of CRS is based on an assumption that patients with grade 3 or higher CRS require management with cytokine inhibitor drugs and intensive care unit (ICU) hospitalisation. As such, the cost of cytokine inhibitor drugs was derived from the cost code XD31Z from NHS reference cost 2015/16 (inflated to cost year 2020/21) and the cost of ICU hospitalisation is derived from XC01Z from NHS reference costs 2019/20 (inflated to cost year 2020/21).[11]

B36. The EAG's clinical experts noted that in clinical practice only CT scans of three or three or more areas with contrast would be used. As such please provide a scenario in which only cost codes RD26Z and RD27Z are used to cost CT scans.

As requested by the EAG, a scenario analysis has been conducted for both base case A and base case B whereby computed tomography (CT) scans are costed using the cost codes RD26Z and RD27Z. The results of these scenario analyses are provided at the end of this response document (Table 51 and Table 52) and demonstrate that this assumption has a minimal impact on the cost-effectiveness results.

B37. Opinion provided by the EAG's independent clinical experts is that in clinical practice the proportion of patients receiving a MUGA on disease progression is likely to be

negligible. As such, please provide a scenario where the proportion receiving MUGA is 0%.

As stated in the CS (Section B.3.5.2), the frequency of resource use in all health states was aligned with previous NICE TAs in R/R LBCL (TA649, TA306 and TA559), which all used the same resource use inputs. These resource use inputs were subsequently validated by UK clinical experts.

However, in response to the request from the EAG, a scenario analysis has been conducted where the resource use for a multiple-gated acquisition (MUGA) scan is set to 0%, rather than 33% used in the submitted base case. The results of this scenario analysis conducted for base case A and base case B are presented at the end of this response document (Table 51 and Table 52) and demonstrate that this assumption has a minimal impact on the cost-effectiveness results.

B38. Opinion provided by the EAG's independent clinical experts is that in UK clinical practice patients are likely to see only a haematologist and not an oncologist. As such, please provide a scenario where oncologist visits are removed from resource use.

As stated in response to Clarification Question B37, the frequency of resource use in all health states was aligned with previous NICE TAs in R/R LBCL (TA649, TA306 and TA559).

However, as requested by the EAG, a scenario analysis has been conducted for base case A and base case B in which the resource use for an oncologist in all health states is set to zero. The results of these scenario analyses are presented at the end of this response document (Table 51 and Table 52) and demonstrate that this assumption has a minimal impact on the cost-effectiveness results.

B39. Please can the company justify the monthly frequency of radiologists for those PF on-treatment. Opinion provided by the EAG's clinical experts is that radiologists would only be needed to interpret imaging results which would already be part of test costs.

As stated in response to Clarification Question B37, the frequency of resource use in all health states was aligned with previous NICE TAs in R/R LBCL (TA649, TA306 and TA559), which all used the same resource use inputs. These resource use inputs were subsequently validated by UK clinical experts. During this validation, one clinician commented that resource use in the PFS on-treatment health state should be set to 0, based on clinical practice in their region. However, this was inconsistent with feedback from the other clinical experts. In order to align with the majority of clinicians, AbbVie maintained the resource use estimates for radiologists as aligned with TA306, TA649 and TA559 (PFS on-treatment: 1.33, PFS off-treatment: 0.33; CS, Section B.2.5.2).

However, during subsequent clinical validation to develop this response document, UK clinical experts confirmed that the cost of interpreting image results is included in the cost of a scan, so the resource use for a radiologist should set to zero in the PFS health state (on-treatment and off-treatment). This change has been incorporated into the updated base case analyses. The results of the updated base case analyses are presented at the end of this response document (Table 39–Table 50) with the incremental impact of each change presented in Table 38.

Section C: Textual clarification and additional points

C1. Please provide the deterministic and probabilistic ICERs for epcoritamab vs POLA+BR.

The deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) for epcoritamab vs Pola + BR (scenario analysis A.1) have been provided in Table 36 and Table 37, respectively. All relevant changes to base case analysis A that have been made in response to the EAG Clarification Questions (Table 38) are included in the results for epcoritamab versus Pola + BR.

Table 36: Scenario analyses: epcoritamab versus Pola + BR – deterministic results (epcoritamab PAS price)

Parameter	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis A.1	Comparator efficacy informed by Sehn *et al.* 3L+ (epcoritamab population: DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+)	[redacted]	[redacted]	£6,172	[redacted]	[redacted]
Scenario analysis A.2	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: DLBCL unadjusted)	[redacted]	[redacted]	£7,583	[redacted]	[redacted]
Scenario analysis A.3	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: LBCL unadjusted)	[redacted]	[redacted]	£10,811	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; RWE: real world evidence; NHB: net health benefit; QALY: quality adjusted life year.

Table 37: Scenario analyses: epcoritamab versus Pola + BR – probabilistic results (epcoritamab PAS price)

Parameter	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis A.1	Comparator efficacy informed by Sehn *et al.* 3L+ (epcoritamab population: DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+)	[redacted]	[redacted]	£4,077	[redacted]	[redacted]
Scenario analysis A.2	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: DLBCL unadjusted)	[redacted]	[redacted]	£11,811	[redacted]	[redacted]
Scenario analysis A.3	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: LBCL unadjusted)	[redacted]	[redacted]	£9,358	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; RWE: real world evidence; NHB: net health benefit; QALY: quality adjusted life year.

C2. In Table 32 of the CS, should the number of CRS events in the LBCL population be [redacted] rather than [redacted] (as in the CSR table 14.3.1.1.1 provided)?

Table 31 states CSR AESI number of patients with ≥1 therefore this data value is correct. This value was taken from Table 14.3.2.4 of the EPCORE™ NHL-1 Data Tables, [redacted] provided.[1]

C3. Please can the company provide the deterministic results of the additional scenario analyses reported in Table 85 of the CS conducted to allow the EAG to validate these values in the economic model.

As detailed throughout this response document, AbbVie have made a number of updates to the base case analyses and numerous new scenario analyses have been conducted. As such, AbbVie have provided the updated base case results and new scenario analyses (run on the updated base case) at the end of this response document (Table 39–Table 52). In line with the NICE Methods Guide, all results have been run probabilistically.

Updated base case cost-effectiveness analysis

As detailed throughout the responses above, a number of assumptions have been updated in the base case economic analyses in response to the requests from the EAG. An overview of the updated assumptions is presented in Table 38.

Table 38: Assumptions updated in the base case, and associated incremental ICER (deterministic – epcoritamab PAS price)

Submitted base case assumption	Updated base case assumption (related Clarification Question)	ICER incremental (£/QALY)
Original base case analysis A		**£26,160**
Epcoritamab DLBCL, no prior CAR-T population adjusted to Sehn et al. 3L+	Epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1 (B9)	£15,608
AE disutilities not applied when utility values from EPCORE™ NHL-1 are applied	AE disutilities are applied when utility values from EPCORE™ NHL-1 are applied (B21)	£15,604
AE incidence for the epcoritamab arm based on January 2022 data cut of EPCORE™ NHL-1	AE incidence for the epcoritamab arm based on [redacted] data cut of EPCORE™ NHL-1 (B24)	£15,605
Error associated with calculation of the administration cost for axi-cel	Axi-cel administration cost derived from TA872 (with the cost of CRS removed, accounting for CRS incidence; B33)	£15,567
Original costs for oxaliplatin and bendamustine included	EAG's preferred costs for oxaliplatin and bendamustine included (B34)	£15,589
Frequency of radiologist resource use aligned with TA306	Radiologist resource use set to zero (B39)	£15,498
Updated base case analysis A (deterministic)		**£15,498**
Original base case analysis B		**Epcoritamab is dominant**
Epcoritamab DLBCL, no prior CAR-T, CAR-T eligible unadjusted population	Epcoritamab LBCL, no prior Car-T, CAR-T eligible adjusted to ZUMA-1 (B17)	Epcoritamab is dominant
AE disutilities not applied when utility values from EPCORE™ NHL-1 are applied	AE disutilities are applied when utility values from EPCORE™ NHL-1 are applied (B21)	Epcoritamab is dominant
AE incidence for the epcoritamab arm based on January 2022 data cut of EPCORE™ NHL-1	AE incidence for the epcoritamab arm based on [redacted] data cut of EPCORE™ NHL-1 (B24)	Epcoritamab is dominant
Error associated with calculation of the administration cost for axi-cel	Axi-cel administration cost derived from TA872 (with the cost of CRS removed, accounting for CRS incidence; B33)	Epcoritamab is dominant

Original costs for oxaliplatin and bendamustine included	EAG's preferred costs for oxaliplatin and bendamustine included (B34)	Epcoritamab is dominant
Frequency of radiologist resource use aligned with TA306	Radiologist resource use set to zero (B39)	Epcoritamab is dominant
Updated base case analysis B (deterministic)		**Epcoritamab is dominant**

Abbreviations: AE: adverse event; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; EAG: External Assessment Group; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; PAS: patient access scheme; QALY: quality-adjusted life year.

Base-case cost-effectiveness analysis results

Base-case results

Base case analysis A: Patients ineligible for, or chose not to receive, intensive therapies

As outlined in the CS (Section B.2.6), the shortfall for base case population A meets the threshold for applying a severity modifier of 1.2 to the incremental QALYs. As such, this modifier is applied in the base case results for analyses considering the population of patients who are ineligible for, and choose not to receive, intensive therapy. Results of the base case analysis A without a severity modifier applied, and subsequently with the 1.2 severity modifier applied to the QALYs, are presented in the following sections.

No severity modifier applied

For patients ineligible for, or choose not to receive, intensive therapies, the results of the probabilistic analysis at epcoritamab patient access scheme [PAS] price are presented in Table 39. The probabilistic net health benefit (NHB) associated with epcoritamab at epcoritamab PAS price is presented in Table 40. The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Deterministic results are also provided in Table 41 (at epcoritamab PAS price). The deterministic NHB associated with epcoritamab is presented in Table 42 (at epcoritamab PAS price).

Table 39: Base-case probabilistic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£85,507 (£64,895, £116,478)	[redacted]	1.024 (0.412, 1.985)	[redacted]	[redacted]	[redacted]	£19,005

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 40: Net health benefit (probabilistic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£85,507	1.024	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 41: Base-case deterministic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£82,610	[redacted]	0.900	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 42: Net health benefit (deterministic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£82,610	0.900	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Severity modifier applied

Equivalent probabilistic and deterministic results cost-effectiveness results and NHB are presented in able 43–Table 46 (at epcoritamab PAS price).

able 43: Base-case probabilistic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£85,507 (£64,895, £116,478)	[redacted]	1.024 (0.412, 1.985)	[redacted]	[redacted]	[redacted]	£15,837

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 44: Net health benefit (probabilistic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£85,507	1.024	[redacted]	[redacted]	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 45: Base-case deterministic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
R-based CIT	£82,610	[redacted]	0.900	[redacted]	[redacted]	[redacted]	£15,498

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 46: Net health benefit (deterministic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
R-based CIT	£82,609.65	0.900	[redacted]	[redacted]	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Base case analysis B: Patients eligible for intensive therapies

For patients eligible for intensive therapies, the results of the probabilistic analysis are presented in Table 47 (at epcoritamab PAS price). The probabilistic NHB associated with epcoritamab is presented in Table 48 (at epcoritamab PAS price). The PSA was run for 1000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Deterministic results are also provided in Table 49 (at epcoritamab PAS price). The deterministic NHB associated with epcoritamab is presented in Table 50 (at epcoritamab PAS price).

Table 47: Base-case probabilistic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-

Axi-cel	£376,740 (£360,348, £428,360)	[redacted]	3.814 (2.001, 5.606)	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 48: Net health benefit (probabilistic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
Axi-cel	£376,740	3.814	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 49: Base-case deterministic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£370,344	[redacted]	3.842	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 50: Net health benefit (deterministic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]	-	-	-	-
Axi-cel	£370,344	3.842	[redacted]	[redacted]	[redacted]	[redacted]

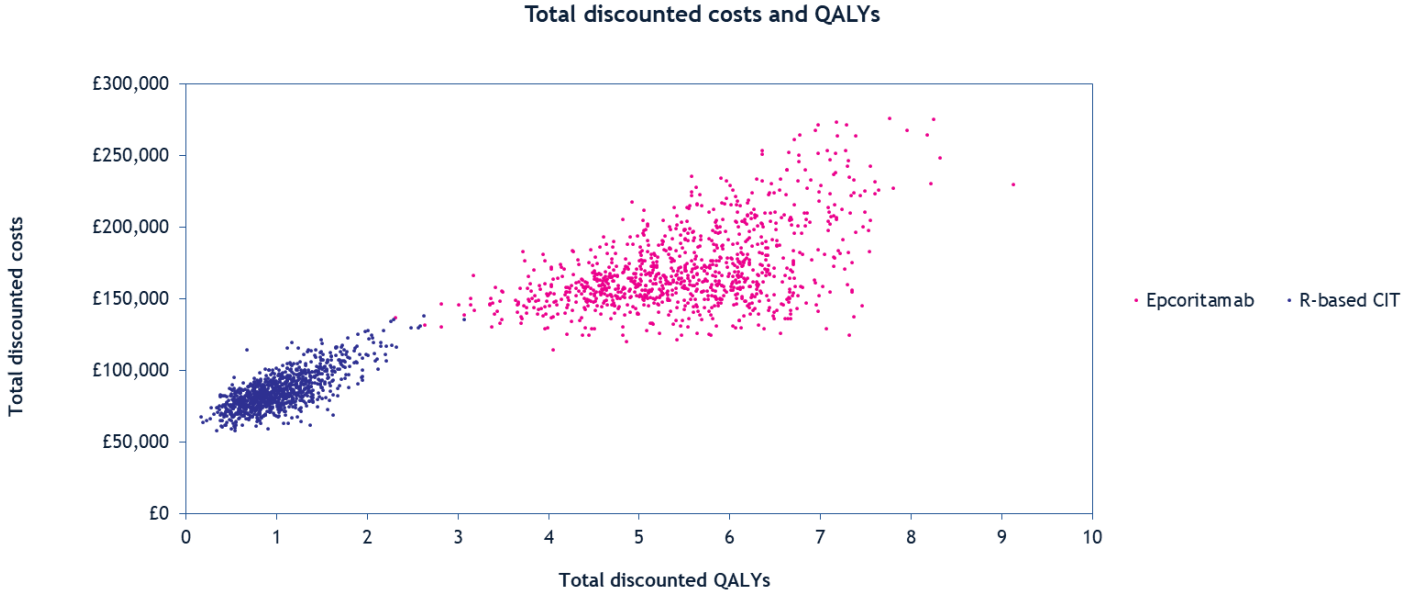
Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Probabilistic sensitivity analysis

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for epcoritamab versus R-based CIT for patients who are ineligible for, or choose not to receive, intensive therapies are presented in Figure 22 and Figure 23, respectively. The equivalent figures for epcoritamab versus axi-cel for patients eligible for intensive therapies are presented in Figure 24 and Figure 25.

Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

Figure 22: Cost-effectiveness scatter plot for epcoritamab versus R-based CIT (epcoritamab PAS price)



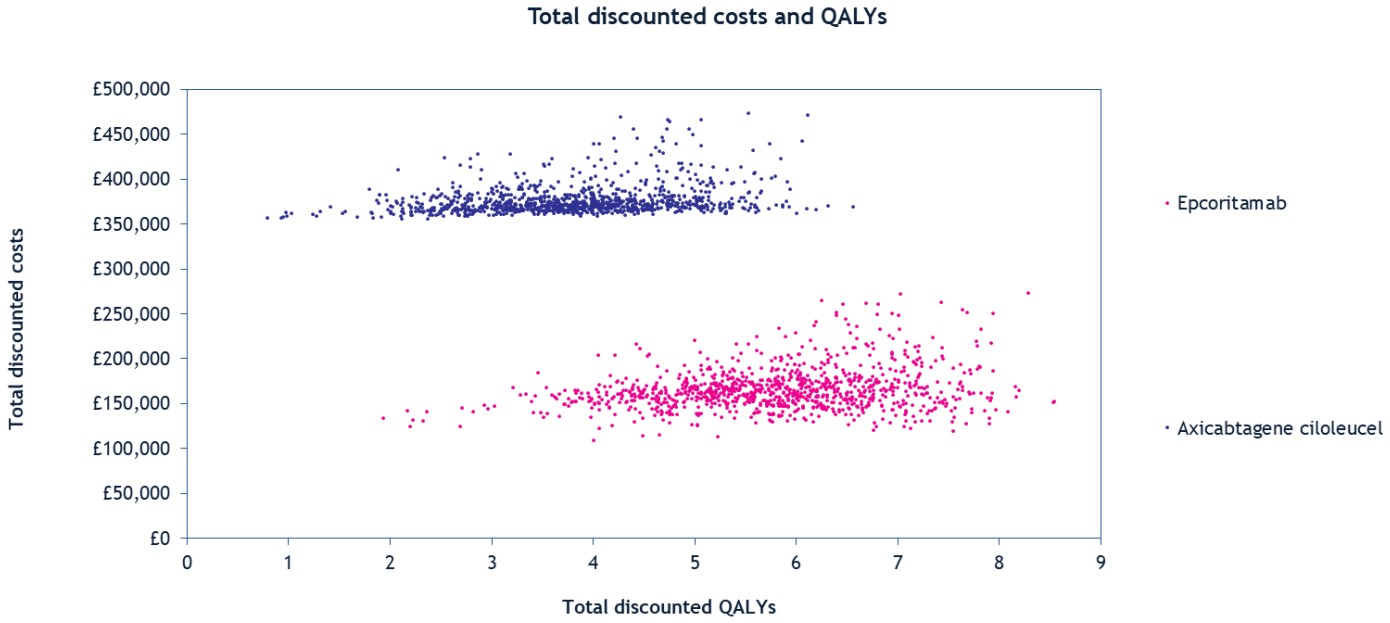
Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

Figure 23: Cost-effectiveness acceptability curve for epcoritamab versus R-based CIT (epcoritamab PAS price)

Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

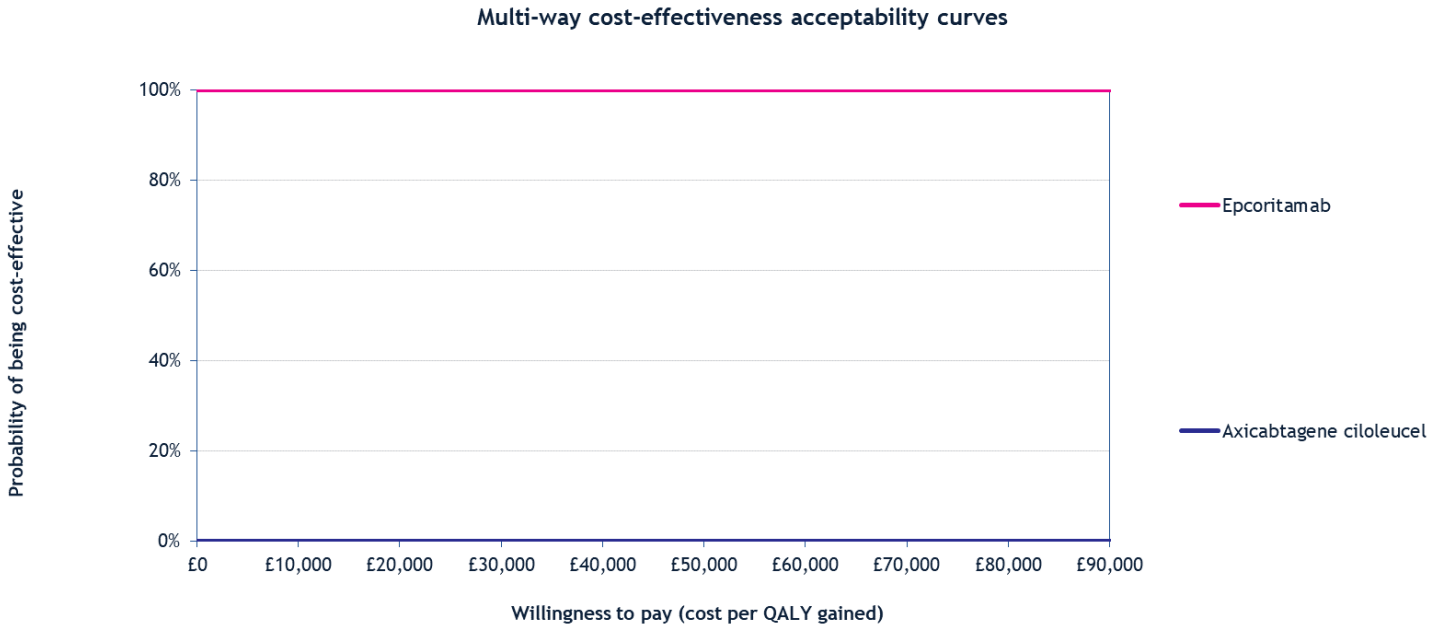
Base case analysis B: Patients eligible for intensive therapies

Figure 24: Cost-effectiveness scatter plot for epcoritamab versus axi-cel (epcoritamab PAS price)



Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 25: Cost-effectiveness acceptability curve for epcoritamab versus axi-cel (epcoritamab PAS price)



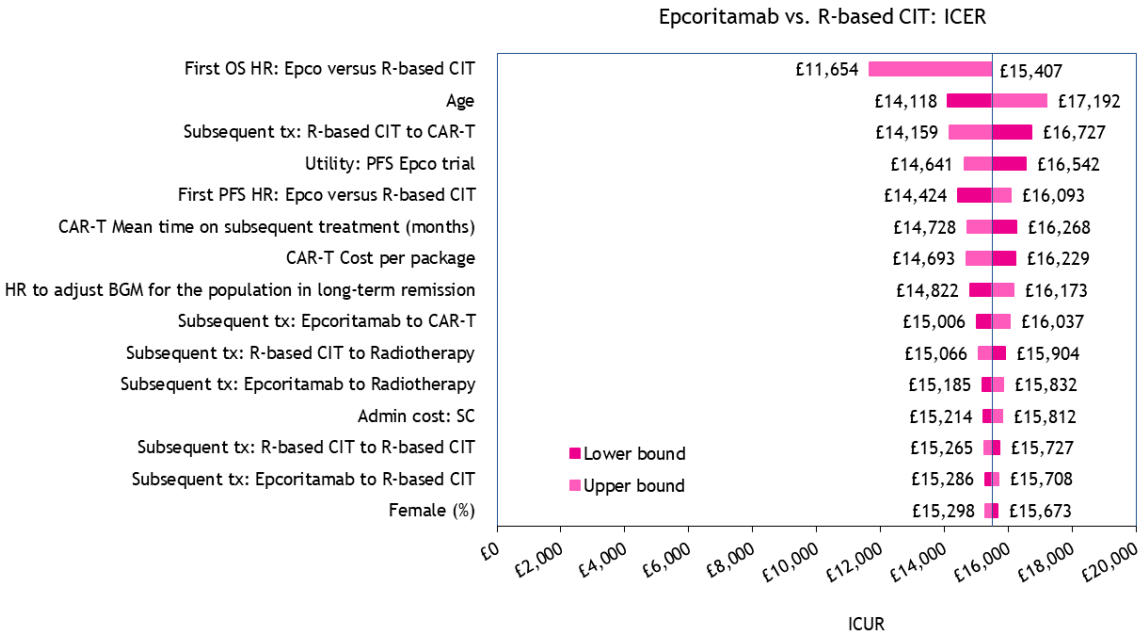
Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis was conducted. Where available, each parameter was varied by 95% CIs. For parameters where CIs were not available the input was varied by ±10% of their mean value.

Patients ineligible for, or choose not to receive, intensive therapies

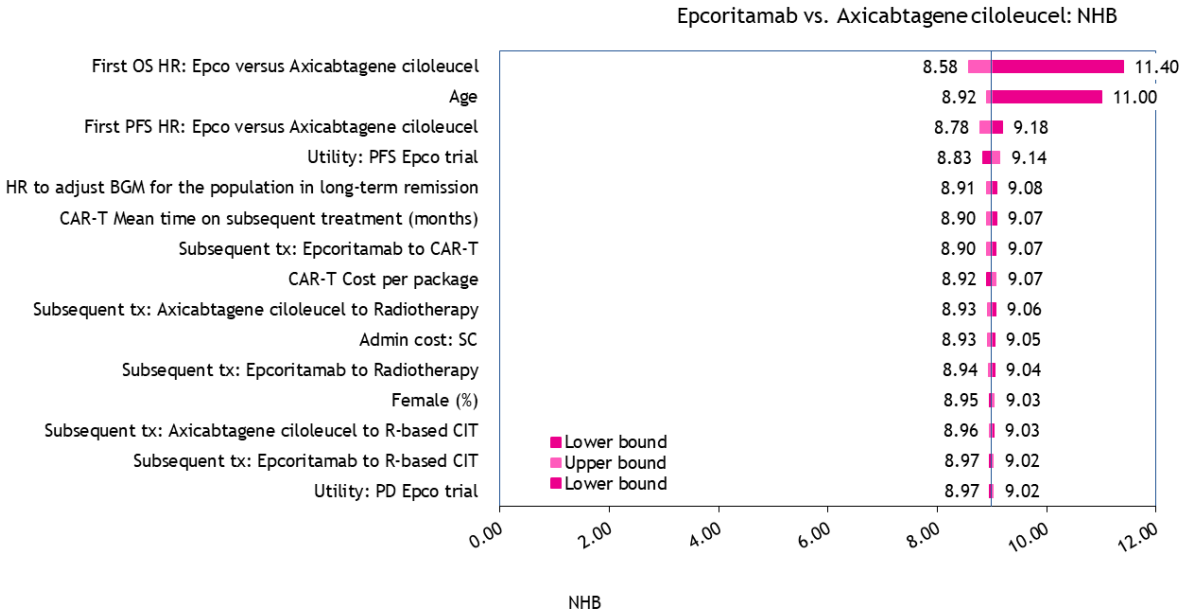
Figure 26: DSA tornado plot for epcoritamab versus R-based CIT (epcoritamab PAS price)



Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

Patients eligible for intensive therapies

Figure 27: DSA tornado plot for epcoritamab versus axi-cel (epcoritamab PAS price)



Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; DSA: deterministic sensitivity analysis; epco: epcoritamab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy; SC: subcutaneous.

Scenario analyses

Probabilistic results at epcoritamab PAS price for all scenario analyses run in response to the EAG Clarification Questions are present in Table 51.

Table 51: Scenario analyses probabilistic results (epcoritamab PAS price)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A vs CIT			[redacted]	[redacted]	£15,837	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic	[redacted]	[redacted]	£15,751	[redacted]	[redacted]
	Lognormal	Weibull	[redacted]	[redacted]	£15,513	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
B11: Time-point of durable remission assumption	24 months after treatment initiation	28 months after treatment initiation	[redacted]	[redacted]	£16,508	[redacted]	[redacted]
B36: Cost of CT scans	CT costed as the average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z	CT scans are costed using the cost codes RD26Z and RD27Z	[redacted]	[redacted]	£15,738	[redacted]	[redacted]
B37: Resource use – diagnostic tests	MUGA scans 33%	MUGA scans 0%	[redacted]	[redacted]	£15,926	[redacted]	[redacted]
B38: Resource use	Resource use aligned with previous NICE appraisals in R/R LBCL	Oncologist resource use set to zero in all health states	[redacted]	[redacted]	£15,849	[redacted]	[redacted]
Base case population B vs Axi-cel			[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B17: Epcoritamab population	LBCL, no prior CAR-T adjusted to ZUMA-1	DLBCL, no prior CAR-T adjusted to ZUMA-1 (Scenario B.2)	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Weibull	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B22: Incidence of AEs for axi-cel	Incidence of AEs for axi-cel removes though that may be double-counting	Incidence of AEs for axi-cel aligns with Neelapu et al.	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
B36: Cost of CT scans	CT costed as the average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z	CT scans are costed using the cost codes RD26Z and RD27Z	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B37: Resource use – diagnostic tests	MUGA scans 33%	MUGA scans 0%	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B38: Resource use	Resource use aligned with previous NICE appraisals in R/R LBCL	Oncologist resource use set to zero in all health states	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: AE: adverse event; axi-cel: axicabtagene ciloleucel; CT: computed topography; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; NHB: net health benefit; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PET: positron emission tomography; PFS: progression-free survival; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy; TA: technology appraisal.

Table 52: Scenario analyses deterministic results (epcoritamab PAS price)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A vs CIT			[redacted]	[redacted]	£15,498	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic	[redacted]	[redacted]	£15,398	[redacted]	[redacted]
	Lognormal	Weibull	[redacted]	[redacted]	£15,278	[redacted]	[redacted]
B11: Time-point of durable remission assumption	24 months after treatment initiation	28 months after treatment initiation	[redacted]	[redacted]	£15,982	[redacted]	[redacted]
B36: Cost of CT scans	CT costed as the average of RD20A, RD21A,	CT scans are costed using the cost codes RD26Z and RD27Z	[redacted]	[redacted]	£15,510	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z						
B37: Resource use – diagnostic tests	MUGA scans 33%	MUGA scans 0%	[redacted]	[redacted]	£15,504	[redacted]	[redacted]
B38: Resource use	Resource use aligned with previous NICE appraisals in R/R LBCL	Oncologist resource use set to zero in all health states	[redacted]	[redacted]	£15,462	[redacted]	[redacted]
Base case population B vs Axi-cel			[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B17: Epcoritamab population	LBCL, no prior CAR-T adjusted to ZUMA-1	DLBCL, no prior CAR-T adjusted to ZUMA-1 (Scenario B.2)	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Weibull	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B22: Incidence of AEs for axi-cel	Incidence of AEs for axi-cel removes though that may be double-counting	Incidence of AEs for axi-cel aligns with Neelapu et al.	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B36: Cost of CT scans	CT costed as the average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z	CT scans are costed using the cost codes RD26Z and RD27Z	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
B37: Resource use – diagnostic tests	MUGA scans 33%	MUGA scans 0%	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]
B38: Resource use	Resource use aligned with previous NICE appraisals in R/R LBCL	Oncologist resource use set to zero in all health states	[redacted]	[redacted]	Epcoritamab is dominant	[redacted]	[redacted]

Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: AE: adverse event; axi-cel: axicabtagene ciloleucel; CT: computed topography; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LBCL: large B-cell lymphoma; NHB: net health benefit; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PET: positron emission tomography; PFS: progression-free survival; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy; TA: technology appraisal.
CCC

Appendix A Time-to-event analyses

Updated base case analysis A: DLBCL, no prior CAR-T adjusted to the SCHOLAR-1 population

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the SCHOLAR-1 population is provided in Figure 28.

Figure 28: KM plot of PFS, OS and TTD used in updated base case analysis A ([redacted] data cut-off)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival

Assessment of the PH assumption

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus R-based CIT are presented in Figure 29 and Figure 30. Assessment of the log-cumulative hazard curve and Schoenfeld residual curve suggest that the PH assumption is not violated. This is consistent with the Grambsch and Therneau test of OS as the p-value of [redacted] suggests that the PH assumption cannot be rejected.

Figure 29: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 30: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to SCHOLAR-1, and evaluated based on AIC and BIC values, which are presented in Table 53.

The exponential and log-normal distributions performs best in terms of AIC and BIC. However, all distributions could be considered viable on the basis of goodness of fit statistics due to minimal differences in the AIC/BIC values.

Table 53: Goodness of fit statistics for OS (AIC and BIC; updated base case analysis A)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Distribution	AIC	BIC
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 31. The corresponding survival estimates at several landmarks are presented in Table 54. As highlighted in the CS (Section B.3.3.3), the clinicians estimated a plausible range of 10–50% alive at two years and 5–45% alive at five years; considering the most likely value only, the clinicians estimated a range of 30–46% and 20–37% of patients alive at two and five years, respectively. Considering the survival estimates provided by each extrapolation at these timepoints, all extrapolations overestimate OS at two years. The exponential extrapolation is the only extrapolation that aligns with the five-year survival estimates provided by the clinicians.

In order to balance visual and statistical fit with the feedback received from UK clinical experts, the lognormal extrapolation was chosen to model OS in the updated base case analysis A.

Figure 31: Long-term OS extrapolations for epcoritamab (updated base case analysis A)

Abbreviations: OS: overall survival.

Table 54: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption[a] (updated base case analysis A)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis A. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]). [a] Estimates are provided when using the base case PFS curve (generalised gamma).
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to SCHOLAR-1. These were evaluated based on AIC and BIC values, which are presented in Table 55.

The generalised gamma model performs best both in terms of AIC and BIC, and the log-normal model could also be considered in terms of goodness of fit.

Table 55: Goodness of fit statistics for PFS (AIC and BIC; updated base case A)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in **Figure 32**. The corresponding survival estimates at several landmarks are

presented in Table 56. As outlined in the CS (Section B.3.3.3), UK clinical experts estimated a plausible range of 10–40% progression-free at two years and 5–35% progression-free at five years; considering the most likely value only, the clinicians estimated a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively. Based on these estimates, the generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case A as it demonstrates the best statistical fit, in terms of AIC and BIC, and produces clinically plausible long-term PFS estimates.

Figure 32: Long-term PFS extrapolations for epcoritamab (updated base case analysis A)

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A.
Abbreviations: PFS: progression-free survival.

Table 56: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (updated base case analysis A)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Month					
	12	24	48	60	120	180
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted DLBCL population from EPCORE™ NHL-1 are presented in Table 57.

The Gompertz distribution performs best in terms of AIC and BIC followed by the log-normal and log-logistic models. The other models are likely not the best fitting models based on the AIC and BIC.

Table 57: Goodness of fit statistics for TTD (AIC and BIC; updated base case analysis A)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model TTD for epcoritamab in the updated base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 33. The corresponding TTD estimates at several landmarks are presented in Table 58.

As outlined in the CS (Section B.3.3.3), UK clinical experts stated that they would expect the TTD curve to be similar in shape but repressed compared with the PFS curves, as patients would be likely to remain on treatment until they progress; the clinical experts stated that it was possible for patients to discontinue treatment due to toxicity rather than progression, but the available data suggests that epcoritamab is well-tolerated with only [redacted] of patients with DLBCL from EPCORE™ NHL-1 discontinuing due to AEs. As such, the generalised gamma extrapolation was selected to model TTD for epcoritamab in the updated base case analysis A.

Figure 33: Long-term TTD extrapolations for epcoritamab (updated base case analysis A)

Abbreviations: TTD: time to treatment discontinuation.

Table 58: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (updated base case analysis A)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model TTD for epcoritamab in the updated base case analysis A. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the R-based CIT arm in the cost-effectiveness model is presented in Table 59.

Table 59: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (updated base case A)

Outcome	HR (95% CI)
Updated base case A (modelled population: DLBCL, no prior CAR-T adjusted to SCHOLAR-1)	
OS	[redacted]
Source of comparator efficacy	SCHOLAR-1[4]

Abbreviations: CI: confidence interval; CIT: chemoimmunotherapy; HR: hazard ratio; OS: overall survival; R: rituximab.

Updated base case analysis B: LBCL, no prior CAR-T, CAR-T eligible adjusted to axi-cel

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the LBCL, no prior CAR-T, CAR-T eligible EPCORE™ NHL-1 population adjusted to the ZUMA-1 population is provided in in Figure 34.

Figure 34: KM plot of PFS, OS and TTD used in updated base case analysis B ([redacted] data cut-off)

[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS IRC: progression-free survival-Independent Review Committee; TTD: time to treatment discontinuation.

Overall survival

Assessment of the PH assumption

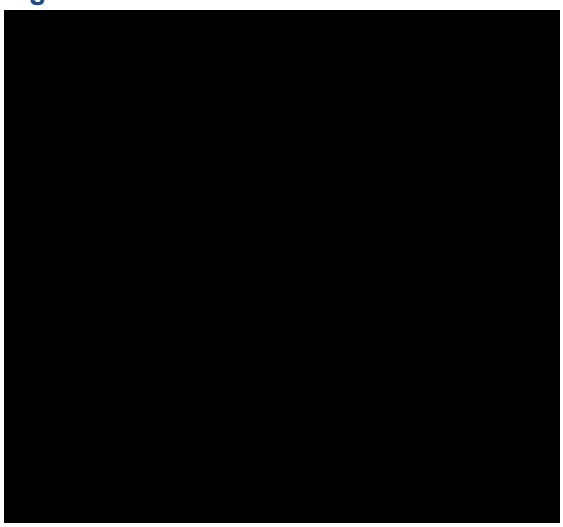
The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus R-based CIT are presented in Figure 35 and Figure 36. Assessment of the log-cumulative hazard curve and Schoenfeld residual curve suggest that the PH assumption is violated. This is

consistent with the Grambsch and Therneau test of OS as the p-value of [redacted] suggests that the PH assumption is violated.

Figure 35: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 36: Schoenfeld residual curve – OS (epcoritamab versus axi-cel)



Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the adjusted LBCL population from EPCORE™ NHL-1 trial, and evaluated based on AIC and BIC values, which are presented in Table 60.

The generalised gamma model performs the best in terms of AIC and the exponential distribution performs best in terms of BIC, and the Gompertz and log-normal models could also be considered in terms of goodness of fit.

Table 60: Goodness of fit statistics for OS (AIC and BIC; updated base case B)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 37. The corresponding survival estimates at several landmarks are presented in Table 61. As highlighted in the CS (Section B.3.3.3), the clinicians estimated a plausible range of 10–50% alive at two years and 5–45% alive at five years; considering the most likely value only, the clinicians estimated a range of 30–46% and 20–37% of patients alive at two and five years, respectively.

However, the plausibility of the OS estimates produced by each extrapolation for axi-cel (after application of the HR derived from the MAIC) must also be considered. Through comparison with the OS estimates for axi-cel in R/R LBCL (TA842), it is apparent that the log-logistic and log-normal extrapolations would produce implausibly low OS estimates for axi-cel. In the base case cost-effectiveness analysis of axi-cel in R/R LBCL, approximately 50% of patients were estimated to be alive at 60 months.

As such, after consideration of statistical and visual fit, feedback from UK clinical experts, and in order to produce clinically plausible results for both epcoritamab and axi-cel, the lognormal extrapolation was selected to model OS for epcoritamab in base case analysis B.

Figure 37: Long-term OS extrapolations for epcoritamab (updated base case B)

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.
Abbreviations: OS: overall survival.

Table 61: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption[a] (updated base case B)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis B. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]). [a] Estimates are provided based on the base case PFS curve (generalised gamma).
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reported; OS: overall survival.

Progression-free survival

Assessment of the PH assumption

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus axi-cel are presented in Figure 38 and Figure 39. Assessment of the log-cumulative hazard curve

and Schoenfeld residual curve suggest that the PH assumption is violated. However, this is not consistent with the Grambsch and Therneau test of OS as the p-value of [redacted] suggests that the PH assumption is not violated.

Figure 38: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; R: rituximab.

Figure 39: Schoenfeld residual curve – OFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; R: rituximab.

Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the adjusted LBCL population from EPCORE™ NHL-1 trial. These were evaluated based on AIC and BIC values, which are presented in Table 62.

The generalised gamma model performs best both in terms of AIC and BIC, and the Gompertz could also be considered in terms of the BIC.

Table 62: Goodness of fit statistics for PFS (AIC and BIC; updated base case B)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 40. The corresponding survival estimates at several landmarks are presented in Table 63. As outlined in the CS (Section B.3.3.3), UK clinical experts estimated a plausible range of 10–40% progression-free at two years and 5–35% progression-free at five years; considering the most likely value only, the clinicians estimated a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively.

In line with the reasoning detailed above when selecting the base case extrapolation for OS, after consideration of statistical and visual fit, feedback from UK clinical experts, and in order to produce clinically plausible results for both epcoritamab and axi-cel, the generalised gamma extrapolation was selected to model PFS for epcoritamab in base case analysis B.

Figure 40: Long-term PFS extrapolations for epcoritamab (updated base case B)

Abbreviations: PFS: progression-free survival.

Table 63: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (updated base case B)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reported; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted LBCL population from EPCORE™ NHL-1 are presented in Table 64.

Table 64: Goodness of fit statistics for TTD (AIC and BIC; updated base case B)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model TTD for epcoritamab in the updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 41. The corresponding TTD estimates at several landmarks are presented in Table 65. As outlined in the CS (Section B.3.3.3), UK clinical experts stated that they would expect the TTD curve to be similar in shape but repressed compared with the PFS curves, as patients would be likely to remain on treatment until they progress; the clinical experts stated that it was possible for patients to discontinue treatment due to toxicity rather than progression, but the available data suggests that epcoritamab is well-tolerated with only [redacted] of patients with

DLBCL from EPCORE™ NHL-1 discontinuing due to AEs. As such, the Gompertz extrapolation was selected to model TTD for epcoritamab in the updated base case analysis B.

Figure 41: Long-term TTD extrapolations for epcoritamab (updated base case B)

Abbreviations: TTD: time to treatment discontinuation.

Table 65: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (updated base case B)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model TTD for epcoritamab in the updated base case analysis B. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the axi-cel arm in the cost-effectiveness model is presented in Figure 41.

Table 66: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – Updated base case B

Outcome	HR (95% CI)
OS	[redacted]
PFS	[redacted]
Source of comparator efficacy	ZUMA-1[22]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

Scenario analysis B.2: DLBCL, no prior CAR-T, CAR-T eligible adjusted to axi-cel

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T, CAR-T eligible EPCORE™ NHL-1 population adjusted to the ZUMA-1 population is provided in Figure 42.

Figure 42: KM plot of PFS, OS and TTD used in scenario analysis B.1 ([redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS IRC: progression-free survival-Independent Review Committee; TTD: time to treatment discontinuation.

Overall survival

Assessment of PH assumption

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus axi-cel are presented in Figure 43 and Figure 44. Assessment of the log-cumulative hazard curve and Schoenfeld residual curve suggest that the PH assumption is violated. This is consistent with the Grambsch and Therneau test of OS as the p-value of [redacted] suggests that the PH assumption is violated.

Figure 43: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 44: Schoenfeld residual curve – OS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the adjusted DLBCL population from EPCORE™ NHL-1 trial, and evaluated based on AIC and BIC values, which are presented in Table 67.

The generalised gamma distribution performs best in terms of AIC and BIC, and the exponential, log-normal and Gompertz models could also be considered in terms of goodness of fit.

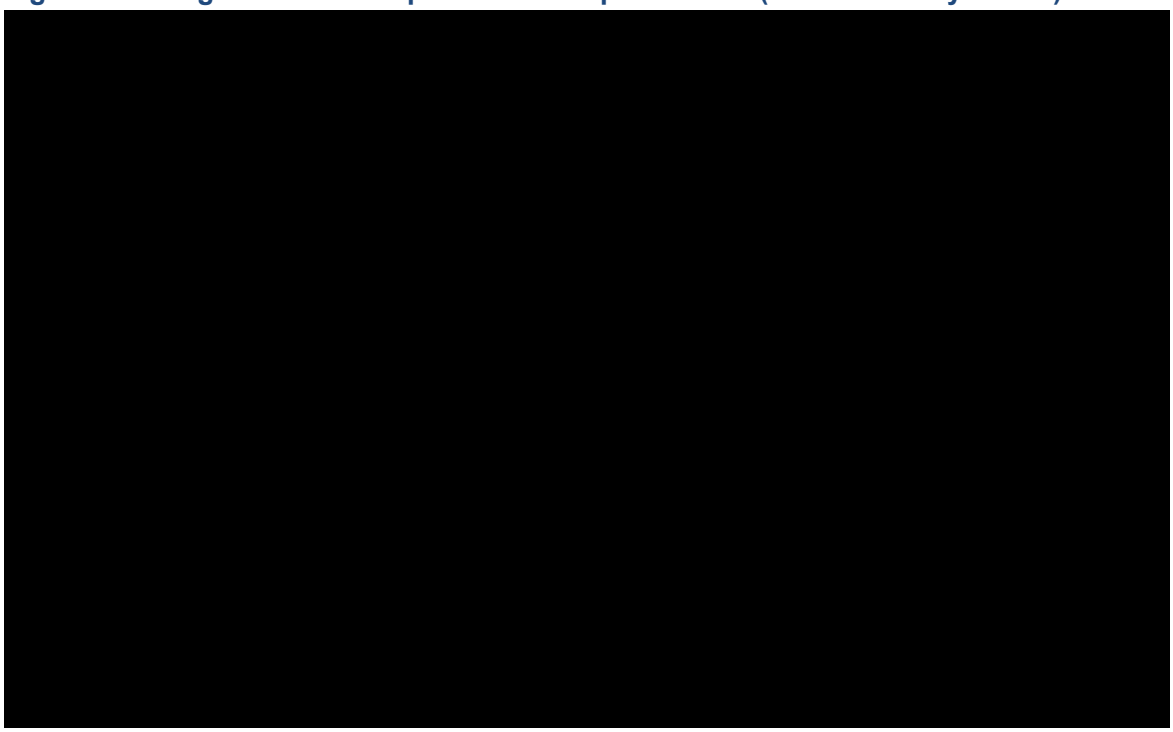
Table 67: Goodness of fit statistics for OS (AIC and BIC; scenario analysis B.2)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The exponential extrapolation was selected to model OS for epcoritamab in the scenario analysis B.2.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 45. The corresponding survival estimates at several landmarks are presented in Table 68. In line with the approach taken for the updated base case analysis B, the lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis B.2. Further details on the justification for the selection of this extrapolation are provided in the section above (Updated base case analysis B).

Figure 45: Long-term OS extrapolations for epcoritamab (scenario analysis B.2)



Abbreviations: OS: overall survival.

Table 68: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption[a] (scenario analysis B.2)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the scenario analysis B.2. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]). [a] Estimates are provided based on the base case PFS curve (lognormal).
Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival

Assessment of PH assumption

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus axi-cel are presented in Figure 46 and Figure 47. Assessment of the log-cumulative hazard curve and Schoenfeld residual curve suggest that the PH assumption is violated. This is consistent with the Grambsch and Therneau test of OS as the p-value of [redacted] suggests that the PH assumption is not violated.

Figure 46: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 47: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the adjusted DLBCL population from EPCORE™ NHL-1 trial. These were evaluated based on AIC and BIC values, which are presented in Table 69.

The generalised gamma model performs best both in terms of AIC and BIC, with none of the other models looking plausible in terms of the goodness of fit statistics.

Table 69: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis B.2)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis B.2.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 48. The corresponding survival estimates at several landmarks are presented in Table 70. As outlined in the CS (Section B.3.3.3), UK clinical experts estimated a plausible range of 10–40% progression-free at two years and 5–35% progression-free at five years; considering the most likely value only, the clinicians estimated a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively.

Considering these estimates, the gamma, Weibull, lognormal and loglogistic extrapolations all align most closely with the clinicians estimates of PFS at two years. Of these extrapolations, after consideration of statistical and visual fit, feedback from UK clinical experts, and in order to

produce clinically plausible results for both epcoritamab and axi-cel, the lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis B.2.

Figure 48: Long-term PFS extrapolations for epcoritamab (scenario analysis B.2)

Abbreviations: PFS: progression-free survival.

Table 70: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (scenario analysis B.2)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis B.2. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted LBCL population from EPCORE™ NHL-1 are presented in Table 71.

The Gompertz distribution performs best in terms of AIC and BIC followed by the generalised gamma and the log-normal distribution. The other models are likely not the best fitting models based on the AIC and BIC.

Table 71: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis B.2)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 49. The corresponding TTD estimates at several landmarks are presented in Table 72.

As outlined above, and in the CS (Section B.3.3.3), the UK clinical experts stated that they would expect the TTD curve to be similar in shape but repressed compared to PFS curves, as patients would be likely to remain on treatment until they progress. As such, the lognormal extrapolation was selected to model TTD for epcoritamab in scenario analysis B.2.

Figure 49: Long-term TTD extrapolations for epcoritamab (scenario analysis B.2)

Abbreviations: TTD: time to treatment discontinuation.

Table 72: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (scenario analysis B.2)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the axi-cel arm in the cost-effectiveness model is presented in Table 73.

Table 73: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – scenario analysis B.2

Outcome	HR (95% CI)
OS	[redacted]
PFS	[redacted]
Source of comparator efficacy	ZUMA-1[22]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

References

1. AbbVie Data on File. EPCORE™ NHL-1 CSR. January 2022. .
2. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-638.
3. Phillippo DM, Ades AE, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE., 2016.
4. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood advances 2021;5:4149-4155.
5. Maloney DG, Kuruvilla J, Liu FF, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol 2021;14:140.
6. Avivi I, Perry C, Segman Y, et al. Polatuzumab-based regimen or CAR T cell for patients with refractory/relapsed DLBCL-a matched cohort analysis. Ann Hematol 2022;101:755-762.
7. NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. Report by the Decision Support Unit. Available at: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD19-Partitioned-Survival-Analysis-final-report.pdf [Accessed: 14 February 2023].
8. AbbVie Data on File. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). UK Medical Advisory Board – Meeting Report. 14 July 2022.
9. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808.
10. AbbVie Advisory Board. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). 14 July 2022.
11. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. Final appraisal document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document [Accessed: 1 November 2022].
12. AbbVie Data on File. Catherine Thieblemont, at al. Efficacy of Subcutaneous Epcoritamab vs Axi-cel in R/R DLBCL CAR T-naive and CAR T-eligible Patients: An Indirect Comparison European Hematology Association Annual Meeting Poster P1154. .
13. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood Adv 2021;5:4149-4155.
14. Woods B, Sideris E, Palmer S, et al. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review., 2017.
15. NICE DSU Technical Support Document 14: Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation With Patient-Level Data. Available at: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD14-Survival-analysis.updated-March-2013.v2.pdf [Accessed: 1 June 2023].
16. AbbVie Data on File. Epcoritamab in Large B-Cell Lymphoma: Clinical Validation Interviews. December 2022–May 2023.
17. Neelapu SS, Jacobson CA, Ghobadi A, et al. 5-Year Follow-Up Supports Curative Potential of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1). Blood 2023:blood.2022018893.
18. EUnetHTA. PTJA06 – Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. Available at: https://www.eunethta.eu/ptja06/ [Accessed: 09 December 2022].
19. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-165.
20. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 2016;128:2489-2496.
21. Connors JM. Is the lymphoma better? Not easy to determine. Blood, The Journal of the American Society of Hematology 2016;128:2481-2482.

22. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
23. AbbVie Data on File. Yasmin Karimi, at al. Effect of follow-up time on the ability of subcutaneous epcoritamab to induce deep and durable complete remissions in patients with relapsed/refractory large B-cell lymphoma: Updated results from the pivotal EPCORE NHL-1 trial. American Society of Clinical Oncology Annual Meeting Poster 7525. .
24. AbbVie Data on File. Catherine Thieblemont, at al. Efficacy of Subcutaneous Epcoritamab vs Axi-cel in R/R DLBCL CAR T-naive and CAR T-eligible Patients: An Indirect Comparison. American Society of Clinical Oncology Annual Meeting Poster P1154. .
25. NICE. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. Available at: https://www.nice.org.uk/guidance/TA567 [Accessed: 18 November 2022].
26. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Available at: https://www.nice.org.uk/guidance/ta649/resources/polatuzumab-vedotin-with-rituximab-and-bendamustine-for-treating-relapsed-or-refractory-diffuse-large-bcell-lymphoma-pdf-82609146587077 [Accessed: 10 October 2022].
27. AbbVie Data on File. Epcoritamab for Treating Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL). UK Medical Advisory Board – Meeting Report. 22 February 2023.
28. Hess LM, Brnabic A, Mason O, et al. Relationship between Progression-free Survival and Overall Survival in Randomized Clinical Trials of Targeted and Biologic Agents in Oncology. J Cancer 2019;10:3717-3727.
29. Pettengell R, Długosz-Danecka M, Andorsky D, et al. Pixantrone plus rituximab versus gemcitabine plus rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation: a phase 3, randomized, multicentre trial (PIX306). Br J Haematol 2020;188:240-248.
30. Pettengell R, Coiffier B, Egorov A, et al. Long-Term Response and Remission with Pixantrone in Patients with Relapsed or Refractory Aggressive Non-Hodgkin Lymphoma: Post-Hoc Analysis of the Multicenter, Open-Label, Randomized PIX301 Trial. Clin Drug Investig 2018;38:527-533.
31. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
32. AbbVie Data on File. EPCORE™ NHL-1 Data Tables. .
33. NICE. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma [TA306]. Available at: https://www.nice.org.uk/guidance/ta306 [Accessed: 18 November 2022].
34. Thieblemont C, Phillips T, Ghesquieres H, et al. ABCL-422 Subcutaneous Epcoritamab in Patients With Relapsed or Refractory Large B-Cell Lymphoma (EPCORE NHL-1): Pivotal Results from a Phase 2 Study. Clinical Lymphoma Myeloma and Leukemia 2022;22:S379.
35. Cazelles C, Belhadj K, Vellemans H, et al. Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation. Leuk Lymphoma 2021;62:2161-2168.
36. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA872]. Available at: https://www.nice.org.uk/guidance/ta872 [Accessed: 31 March 2023].

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Blood Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Blood Cancer UK is the UK's biggest blood cancer research charity. We fund world-class research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has ~100 employees and is funded primarily through donations and legacies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We have received £10,450 from AbbVie for projects including our Health Information Transformation Project and for our Support Services team. We have also received £35,000 from BMS to support the development of our 'Blood Cancer Action Plan' – a state of the nation report on experiences and outcomes for patients in the UK.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information for this appraisal was gathered from insights derived through our communications with the clinical, research and patient community, particularly those personally affected by the various subtypes of large B-cell lymphoma. We also spoke to a few patients who have had Epcoritamab and to those who have experience caring for the patient group of interest. Blood Cancer UK has close relationships and maintains regular contact with the haemato-oncology community. We do this through our Healthcare Professional Advisory Panel (HPAP), Nurses Working Group (NWG), our patient ambassador network etc. We additionally maintain relationships with many other blood cancer specialists – from research nurses to academic researchers – through our Information and Support, Research, and Policy, Campaigns and Engagement teams. We specifically reached the patient group of interest for this appraisal through our social media channels and our clinical networks who put us in touch with patients willing to share their experiences of the technology with us. We have also included information based on our previous conversations with people who have large B-cell lymphoma. These conversations built our understanding of the experiences of those affected by the issues of interest for this appraisal.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Large B-cell lymphoma (LBCL) covers a few subtypes including DLBCL, PMBCL, and follicular lymphoma. Although the different subtypes largely fall under the umbrella of LBCL, patients experience differing symptoms of varying intensity, even within a subtype. There is a heavy burden borne by patients and carers who experience refractory / relapse disease in both managing symptoms of disease combined with the toxicity of treatment. In most cases, there is no time to process what is happening when someone receives a diagnosis of large B-cell lymphoma as they often and rapidly commence treatment. At first, the focus is on physically getting through the disease. Post treatment, there can be marked and long-term psychological effects. One patient spoke about having PTSD following the diagnosis and undergoing chemotherapy. Treatment for LBCL usually involves frequent and extended hospital stays - a lonely experience. Patients express the difficulties to keep occupied and maintain a positive mood. Social isolation can continue outside of the hospital. This can be owing to a loss of confidence, or concerns about the risk of infection (especially since the Covid-19 pandemic) or both. Financial worries are common as many people are unable to work during or after treatment and sick pay may not be enough. Many mourn the loss of the life they had thought they would live. Carers play a critical role in patients' disease and treatment journey and caring for someone with large B-cell lymphoma is often challenging and burdensome. Carers are fundamental to a patient's day to day wellbeing, helping with everything from transportation, managing appointments to their nutritional needs. One patient with follicular lymphoma explained that his wife, who is his main carer, has 'given up an awful lot.' He explained that both his wife and daughter sought and are receiving counselling and treatment from the NHS as a direct result of his cancer and the stress it has 'forced' on them. He later expressed he is dealing with the reality that he 'cannot be the dad [he] wanted to be.' A carer explained how since hearing the news of her husband's refractory lymphoma, she felt 'inescapable guilt' if she ever went out to 'escape the constant reminder that [her] husband was dying.'

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Both the disease itself and its treatments can significantly affect quality of life with treatment experiences varying. Although patients are grateful for the available options, existing treatments can be hard to tolerate, bringing a range of side effects and late effects. There is, therefore, a need for kinder treatments. Initial lines of treatment can "wreck" the body and make it harder to tolerate further treatment. People experience debilitating side effects on a treatment that is their only remaining option for survival. Therefore, more options would be a great positive step forward. Many existing treatments have harsh side effects and cause changes to one's appearance (weight loss or gain, hair loss, skin changes, scarring etc.) which are distressing and can reduce confidence. Additionally, people are living with late effects from chemotherapy including nerve damage, fatigue, brain fog, bone pain, persistent blood clots, which can affect them for the rest of their lives. Current treatments for LBCL can also increase the risk of neutropenic sepsis and therefore the risk of dying while on treatment. This is a considerable mental burden to bear. The intensity of this was brought to life by the experiences of a man who, due to the effects of treatment, was left needing the assistance of a wheelchair for two to three weeks with no improvements in his lymphoma. Carers find themselves devoting "everything" to caring for their sick, loved ones, constantly monitoring them for any changes and spend 'excruciating amounts of time' waiting through appointments and check-ups, fearing the worst. One patient expressed that there isn't anybody around them that their cancer hasn't impacted. He explained that his wife is constantly confronted with questions about updates relating to his health and deals with the pain of reliving and retelling the bad news of another futile treatment. Time is often perceived as particularly limited for many with aggressive and unresponsive cancers. Patients often feel like they have lost this precious time battling LBCL instead of spending it with their loved ones.

8. Is there an unmet need for patients with this condition?	Our conversations with clinicians, a research nurse and patients themselves have highlighted and bared the huge unmet need at the third line setting of relapsed/refractory LBCL. It is important to highlight that these are patients who have undergone intensive therapies but are multiply refractive, and therefore especially challenging to treat. At this line, they now face limited or no options and consequently have poor prognosis. A patient told us 'there was nothing more on the NHS, that's why it was clinical trial time.' The investigation of new therapies through clinical trials and the transition of existing therapies into earlier lines of treatment are introducing new and bigger gaps in the third line space. Epcoritamab in this line could be a beneficial option for this rapidly progressing, highly refractory group of patients. Patients with relapsed / refractory disease stressed that the most important factor to them when it comes to treatments is its curative potential. One patient went onto explain 'if not a cure, I want something that buys me more time. If it can buy me that, the longer, the better.' There's also a need for kinder treatments which provide long-term benefit. One patient expressed that although the treatments available are 'harsh and put me through hell,' he had no option but to go through them as it is 'either that or I die without trying.'

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients who are ineligible to receive highly intensive therapies or those who relapse following, have limited options, poor prognosis, and survival. This means Epcoritamab as an option for them would be advantageous and beneficial on many fronts. Epcoritamab addresses some of the highly important factors for patients with regards to what they want and value from new treatments. It is largely well-tolerated, particularly compared to the majority of existing treatment options. One patient who received Epcoritamab described it as being 'not intrusive', and 'compatible' with his body and stated that, unlike the previous treatments, he had no 'negative associations with it.' This bispecific antibody is also relatively easy to administer and is more readily available than options like CAR-T. As it does not require a manufacturing period, like CAR-T does, it is particularly beneficial for patients with rapidly progressing disease. Furthermore, as CAR-T has transitioned into the second line, its efficacy for CAR-T refractory patients is also advantageous. This was emphasised by a patient who had Epcoritamab following CAR-T therapy. The subcutaneous method of administration and its tolerability means there is space to explore how, in the longer term, patients can access this treatment in the most effective way possible, including local and home delivery. This would be a real benefit for both patients, clinicians, and the NHS in the long-term. The factors beyond physical fitness which determine uptake of CAR-T among patients (including socioeconomic status, geography etc.) may be less of an issue for Epcoritamab. This gives patients and clinicians room to discuss which therapy could be more suitable for a patient. Additionally, the rarer subtypes of LBCL, often excluded from trials due to the smaller patient groups, can also benefit from the efficacy of Epcoritamab.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage described by patients is that Epcoritamab is not curative. Other factors, which contribute towards a negative patient experience, such as intolerable and persisting side effects and prolonged stays away from home, were not an issue with Epcoritamab. However, the time required to reach the intended dose, due to step-up dosing intended to mitigate the risk of cytokine release syndrome, can be a long, difficult time for patients. Initially, Epcoritamab may need to be delivered in larger, transplant or CAR-T centres. In the long run however and as patients get through the first cycle, it is possible Epcoritamab will not be restricted to those centres. There is a need for investment into providing additional facilities and support for smaller hospitals to manage potential side effects such as CRS, ICANS and TLS. If these efforts do not happen, it could cause prolonged inequities in access.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why	Patients with high-risk comorbidities can be more challenging to manage with bispecific antibodies such as Epcoritamab and could potentially mean they benefit less from it. Elderly patients and those less able to manage stem cell transplants or more intensive treatments could benefit more from this treatment. Lastly, its off-the-shelf accessibility means Epcoritamab would be a good treatment for patients living further away from transplant and CAR-T centres.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	At the outset, Epcoritamab may need to be delivered at larger, transplant or CAR-T centres. This could result in short-lived inequities in access as small local hospitals may not be able to embrace Epcoritamab straight away post license. This could pose challenges for patients who live further from centres and cannot afford, for financial or logistical reasons, to travel longer distances. However, this issue should become less significant as it becomes more widely accessible through increased efforts. On the other hand, there is a possibility that this potential inequity in access, although expected to be temporary, could be prolonged if the right measurements to increase training and support for smaller centres are not in place.

Other issues

13. Are there any other issues that you would like the committee to consider?	Careful consideration should be given to ensure early planning of the resources required to prepare wider clinicians and community medical professionals, with no prior experience of bispecific antibodies or CAR-T (which have similar side effects), to equip them with the skills needed to deliver and monitor the use of Epcoritamab so that it can be as widely accessible as possible.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A significant proportion of patients will fail to respond to first two lines of therapy or will relapse after an initial response. These patients with highly R/R disease live with the challenges associated with the disease itself combined with treatment toxicities, as well as the psychological impacts of ineffective and harsh treatments. This has significant effects on the quality of life of both patients and carers. • A treatment's ability to improve a patient's quality and length of life is hugely important to them and their loved ones. • Epcoritamab is relatively easy to administer, well tolerated, is more readily available than options like CAR-T therapy and can provide long term benefit. • The ongoing changes in the treatment landscape of lymphoma, including the transition of existing treatments into earlier lines of therapy, introduces new unmet needs which Epcoritamab can help meet. It is also effective in CAR-T refractory patients and those with rarer subtypes of LBCL. • Epcoritamab offers a treatment option for a population of patients who have exhausted other options. Even if not curative, additional life years gained through this treatment is hugely valuable for patients and their loved ones.

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Funding received in 2022: Abbvie £10,000 Celgene/BMS £11,000 Incyte £22,750 Gilead £45,870 Pfizer £300 Roche £26,000
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We reached out to our patient community for their experience of living with and receiving treatment for refractory or relapsed DLBCL. We also used information obtained from our prior experience of working with those affected by DLCBL, or their carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	DLBCL is a high grade (aggressive) form of lymphoma. Most people with DLBCL first notice enlarging painless lumps. These can be in the neck, groin or armpit and are enlarged lymph nodes. They tend to grow very rapidly, over a few weeks. In some cases, about 4 in 10, the cancer develops outside of the lymph nodes, this is extra nodal disease. Extra nodal DCLBL in the chest can cause a cough and shortness of breath. One of our patients described their initial symptoms – "*I had a cough for about 4 weeks that did not seem to be attributed to anything – no cold, virus or illness. It did not even feel like a proper cough and I could not understand why I even felt the need to cough. My chest felt a bit tight at times and a short walk would leave me feeling breathless. I then randomly felt a lump on my collar bone".* Due to its aggressive nature the symptoms from DLBCL often progress incredibly quickly, *"The disease appeared very quickly and progressed fast", "Symptoms came on quickly – stomach pain, night sweats, fatigue'.* Patients also described the *"psychological impact of diagnosis" as being "enormous." '* 1 in 3 people with DLCBL have B symptoms when they are diagnosed, examples of these are night sweats, weight loss and fatigue. From our patient responses fatigue is particularly debilitating and difficult to live with for DLBCL patients. When asked about what it is like to live with DLBCL, one patient said "I found it quite hard. The fatigue was the main one for me." DLBCL is treated with the aim of cure; however up to 45% are refractory to treatment, or relapse after the initial round of treatment. The prognosis for these people is poor, and the current treatment regimens available only confer a median survival of twelve months. Due to the aggressive nature of these lymphomas and their treatment patients often need to spend weeks in hospital isolated from their support network, and unable to work. This often leads to a financial strain on the family – "*Finances were a struggle, but my husband was able to support me financially".* Another patient described the psychological impact this can have – *"I had to spend weeks on end in hospital and leave my teenage children at home. Whilst in hospital I was very lonely and felt isolated from my family. I had fantastic care, but I was very anxious about relapse; this was more severe around the time my chemo finished and I was no longer being treated"*. The side effects from the disease and the treatment can last for months, or even years. This can be fatigue, peripheral neuropathy or depression/anxiety amongst others. One of our patients described the ongoing

	symptoms – *"I finished treatment a year ago and still struggle physically and mentally. Day to day life is as pre DLBCL but it is a constant reminder in my head and body".* Another patient described the long-term impact immobility during treatment can have on the body – "*When I was discharged, I was very weak, and it took me many months to get my physical strength back; the effects of being immobile during treatment should not be underestimated – this led to mobility issues, e.g. needing to use a wheelchair at times. I suffered from fatigue for several years after treatment."* These prolonged side effects are even worse in patients with refractory or relapsed disease because they may require more treatment as well as having the ongoing mental strain of not being in remission. This is how one patient who unfortunately relapsed described it – "*second time round my anxiety was high during the early weeks; I struggled to sleep and felt very low. Once treatment started I was able to focus on it, and I felt more in control of my treatment; the research I had done earlier was really helpful. Time in hospital for chemo and the stem cell transplant (SCT) meant I was away from work again, this time for about 10 months. Recovery from SCT was easier physically, because I had maintained my fitness up to SCT, but the fatigue remained for several years. Other symptoms included brain fog and memory problems, and ongoing bowel issues".* One other patient questioned described how that impact of relapse can lead to longer term psychological problems – "*I relapsed about 12 months after my first treatment ended. I spent the early days in a complete emotional state Each R-ICE round took a week as an inpatient – I was semi-conscious for much of it. Work was impossible at this time, despite my best intentions. Luckily my employers were very supportive. Time during recovery was bittersweet. The relief of coming home and getting back into some kind of normal life is marred by the anxiety of relapse and the worry that your body will somehow let you down. This fades with time, but it can be a roller-coaster of emotions."* Due to these symptoms and the impact of treatment, patients with DLBCL require large amounts of support from their carers. It can be time consuming, for example taking the patient to various hospital appointments, emotionally draining and they often take on the financial burden for the family. *"My husband and daughter looked after me well, but both struggled with it emotionally."* DLBCL tends to be a disease of middle age which means that many of the patients may still have children to look after. This can put an additional strain on their partner, but in addition can impact on the child. One of our patients described the affect her diagnosis of DLBCL had on her son- *"My eldest was starting his A levels and for the first year of his studies he struggled. He didn't even tell his friends about my diagnosis. He used school to escape from it. Now, almost as soon as I got the all clear, his grades have picked back up again."*

	Having both a high grade B cell lymphoma and children is also very difficult for the patient – *'….. and had to tell my 17- and 14-year-old that I now had cancer. I had to be strong for them, so they could see that if I was not going to let this beat me, or get me down, then they would be able to stay positive too."* These thoughts and feelings were also reflected by another patient – "*The children were also affected by my diagnosis and treatment, which coincided with GCSE and A level exams. I wasn't able to be there for them to support them practically or emotionally. They had to see me at my lowest ebb, and it must have been a frightening time. It brought us all closer together as a family, but it left its mark, particularly with health-related anxiety."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Whilst there are a number of treatment options available for relapsed or refractory DLBCL, options are limited when it comes to 3rd line treatment, and the conversation often goes to CAR T.
8. Is there an unmet need for patients with this condition?	Patients feel that there are multiple treatment options currently available, but a more targeted therapy in refractory or relapsed DLBCL with potentially fewer side effects would be beneficial. Having more viable treatment options available is also desirable to patients, one patient said – *"R-CHOP doesn't work for everyone and DLBCL can recur so it's important to have a range of second and third-line treatment options that are effective, widely available and well tolerated."* People eligible for CAR T would also benefit from this.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	There are limited options when you get to 3rd line and therefore this could provide people, especially those that are ineligible for CAR T, with a lifeline.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients who would be offered this treatment would have had multiple treatments before this, as well as experiencing relapse or their disease being refractory. It is possible some may not be able to tolerate it.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who are either ineligible for CAR T or who have difficulties accessing it.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Refractory or relapsed DLBCL can be very difficult to treat with limited treatment options. • The current treatments available have a significant physical and mental burden on patients and their carers. Having alternative treatment options for those patients unable to tolerate this would be welcomed. • There remains an unmet need for those who have had 2+ systemic treatments and are ineligible for CAR T.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? A specialist in the clinical evidence base for this condition or technology? Other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of the treatment is to achieve a complete remission (CR) from lymphoma, for as long as possible, and PFS
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In terms of response as measured in a Ph2 study, there are well established response assessments eg Lugano criteria Key outcome measures are CR/sustained PR
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Currently there is no standard of care of relapsed high grade B NHL post failure of CAR-T cell therapy, or in patients in whom CAR-T cell treatment is not possible/indicated after failure of initial treatment. This represents an area of unmet need as there is a lack of available treatments which will lead to durable responses.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is no current standard of care for relapsed high grade B NHL post CAR-T or in patients ineligible for CAR-T treatment. Patients are given several palliative chemotherapy regimens, or entered into clinical trials
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	National (BSH and NICE) and international guidelines. New BSH guidelines are in progress, as are ESMO guidelines Guidelines are being updated in view of rapid changes in availability of new therapies such as recently approved 1st line polatuzumab etc
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is well defined. There is some geographical variation around the country in terms of access to CAR-T services, as CAR-T treatment is commissioned at a small number of centres
9c. What impact would the technology have on the current pathway of care?	This technology would not substantially alter the overall treatment pathway for 1st line treatment, but would give treatment options to patients where there are currently no good options
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology would be used instead of palliative chemotherapy. It would provide an extra treatment option for patients unable to receive any suitable treatment currently. In patients unwilling or unable to travel for CAR-T therapy this technology would offer another effective treatment option

10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist haematology clinics in centres experienced in delivery of lymphoma anti-cancer treatment
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Some training around management of CRS (cytokine release syndrome) and ICANs (immune effector cell associated neurotoxicity syndrome) in non-CAR-T centres. These are side effects of cellular therapy which are seen with CAR-T therapy, and less commonly with epcoritamab, but are straightforward to treat with some education and experience
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The reported rates of CR and PFS are very impressive in this very heavily pre-treated group of patients, who have a dire prognosis with currently available treatments. This is a highly innovative technology that represents a novel treatment approach in this group of patients
11a. Do you expect the technology to increase length of life more than current care?	Yes. Currently available treatment options in this heavily pretreated group of patients are extremely limited and none lead to the CR rates or PFS rates reported using this epcoritamab. The durability of responses in patients who achieve a CR is very impressive indeed and there are no other agents which could be expected to lead to comparable outcomes.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, it is a very easy treatment to deliver, and the toxicity profile appears favourable in comparison to commonly used chemotherapy regimens

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is easier to give epcoritimab than standard chemotherapy regimens, but there are some toxicities that some (non-CAR-T) centres may require education around, such as management of cytokine release syndrome and ICANS, which they may not be familiar with. Trial data suggests that these toxicities are usually low grade and relatively easy to manage.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing. Treatment is to progression
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes - this is an innovative technology. It represents a new class of treatment available for patients with relapsed/refractory high grade B NHL and has the potential to induce durable remissions in a group of patients with no clear treatment options currently
16a. Is the technology a 'step-change' in the management of the condition?	This technology represents a paradigm shift in the management of R/R DLBCL, particularly post CAR-T cell relapses and in patients unsuitable for CAR-T treatment.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, there is a significant unmet need in that most patients who are given CAR-T cell treatment will ultimately relapse, and there is no currently available effective treatment option for them.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the trial data reflect UK practice
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, the trial reported CR rates, PFS and OS
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA306, TA559 and TA649?	
21. How do data on real-world experience compare with the trial data?	Not aware of any current real-world evidence using this technology

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There is currently no standard of care for patients with R/R high grade B NHL post CAR-T relapse or in patients unsuitable for CAR-T • This is a novel, innovative technology that leads to sustained complete responses in a significant number of these patients. • This therapy represents a paradigm shift in this disease area, offering many patients the possibility of durable remission and good quality of life in a situation that would usually be palliative and life-limiting. • It would be straightforward to add to current treatment pathways and would be deliverable in all centres currently able to give standard chemotherapy regimens for lymphoma.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135903.

Title:	Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Nicole Downes, Senior Clinical Evidence Analyst, BMJ-TAG, London Mariana Bacelar, Principal Health Economist, BMJ-TAG, London Victoria Wakefield, Clinical Evidence Manager, BMJ-TAG, London Archie Walters, Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	29/06/2023
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135903.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Mary Gleeson (Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust, London) and Dr Robert Lown (Consultant Haematologist, University Hospital Southampton, Southampton) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report. The EAG would also like to thank Dr Paul Kerr, Consultant Haematologist, Royal Devon University Hospitals Trust for providing clinical advice prior to the company submission.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Downes N, Bacelar M, Wakefield V, Walters A. Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments: A Single Technology Appraisal. BMJ Technology Assessment Group, 2023.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Nicole Downes	Critical appraisal of the company's submission and the clinical evidence; drafted clinical sections including summary, introduction and background, and critique and results of the trials and indirect comparisons. Reviewed the critique of the methods review.
Victoria Wakefield	Critical appraisal of the company's submission and of the clinical evidence; drafted the critique of the methods review.
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; and drafted the economic sections.

All authors read and commented on draft versions of the EAG report.

Table of Contents

Table of Contents 4

List of Tables 7

List of Figures 12

List of Abbreviations 15

1 Executive summary 19

1.1 Overview of the EAG's key issues 19

1.2 Overview of key model outcomes 20

1.3 Summary of the EAG's key issues 21

1.4 Summary of EAG's preferred assumptions and resulting ICER 42

2 Introduction and background 48

2.1 Introduction 48

2.2 Background 48

2.2.1 Position of epcoritamab in the UK treatment pathway 49

2.3 Critique of the company's definition of the decision problem 51

2.3.1 Population 58

2.3.2 Intervention 66

2.3.3 Comparators 67

2.3.4 Outcomes 68

3 Clinical effectiveness 69

3.1 Critique of the methods review 69

3.2 Critique of trials of the technology of interest 72

3.3 Critique of the clinical effectiveness analysis 77
3.3.1 Survival and response outcomes 77
3.3.2 Health-related quality of life 79
3.3.3 Adverse events 81
3.3.4 Subgroups 89
3.4 Critique of trials identified and methods used in the indirect comparisons (MAICs) 95
3.4.1 Identification of trials and critique of general methods 95
3.4.2 Critique of methods specific to each comparison 98
3.5 Results of the indirect comparisons (MAICs) 112
3.5.1 Epcoritamab vs R-based CIT 112
3.5.2 Epcoritamab vs Pola + BR 114
3.5.3 Epcoritamab vs axi-cel 118
3.6 Conclusions of the clinical effectiveness section 121
4 Cost effectiveness 123
4.1 EAG comment on the company's review of cost effectiveness evidence 125
4.2 Summary and critique of company's submitted economic evaluation by the EAG 127
4.2.1 NICE reference case checklist 127
4.2.2 Modelling approach and model structure 128
4.2.3 Perspective, time horizon and discounting 132
4.2.4 Treatment effectiveness 133
4.2.5 Health-related quality of life 166
4.2.6 Resource use and costs 169

5 Cost effectiveness results 181

5.1 Company's cost effectiveness results 181

5.2 Company's sensitivity analyses 183

5.2.1 Probabilistic sensitivity analysis 183

5.2.2 Deterministic sensitivity analysis 184

5.2.3 Scenario analysis 184

6 Additional economic analysis undertaken by the EAG 185

6.1 Model corrections 186

6.2 Exploratory and sensitivity analyses undertaken by the EAG 187

6.3 Conclusions of the cost effectiveness sections 192

7 Severity modifier 197

7.1.1 EAG critique 198

8 References 199

List of Tables

Table 1. Summary of key issues 19

Table 2. Issue 1. The population in the decision problem may be broader than that covered by the trial 21

Table 3. Issue 2. Issues associated with the paper used to inform data for SCHOLAR-1 in the MAIC vs R-based CIT 21

Table 4. Issue 3. Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used 24

Table 5. Issue 4. The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population 25

Table 6. Issue 5. Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment 25

Table 7. Issue 6. It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments 26

Table 8. Issue 7. Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons 27

Table 9. Issue 8. All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1 28

Table 10. Issue 9. Limitations of Sehn *et al.* for the MAIC vs Pola + BR 30

Table 11. Issue 10. Limitations of ZUMA-1 for the MAIC vs axi-cel 30

Table 12. Issue 11. Implementation of when the long-term remission assumption starts in the model 31

Table 13. Issue 12. Estimation of overall survival in the model 33

Table 14. Issue 13. Estimation of progression-free survival in the model 34

Table 15. Issue 14. Estimation of time to treatment discontinuation in the model 37

Table 16. Issue 15. Utilities used in the model 38

Table 17. Issue 16. Treatment and administration costs of comparators in the model 38

Table 18. Issue 17. Subsequent treatments in the model 40

Table 19. Issue 18. Disease follow-up costs in the model 40

Table 20. Results of the EAG's exploratory analyses – R-based CIT 45

Table 21. Results of the EAG's exploratory analyses – Pola + BR 46

Table 22. Results of the EAG's exploratory analyses – axi-cel 46

Table 23. Summary of decision problem 52

Table 24. Dosing schedule for epcoritamab (reproduced from Table 3 of the CS) 66

Table 25. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to this appraisal 71

Table 26. Quality assessment of EPCORE™ NHL-1 (adapted from Table 13 of the CS) 74

Table 27. Mean FACT-Lym total score and FACT-LymS while on treatment (FAS – LBCL population, N=157; [redacted] data cut-off) – adapted from Table 80 of the CS appendices 80

Table 28. Mean scores for EQ-5D-3L health utility while on treatment (various analysis populations) [redacted] data cut-off) – adapted from Table 82 of the CS appendices and the company's response to CQ A4 81

Table 29. Summary of AEs in EPCORE™ NHL-1 – full LBCL population (adapted from Tables 32, 34 and 35 of the CS, Table 14.3.1.5.1 of the CSR tables provided for [redacted] and the company's response to CQs A2 and A4) 85

Table 30. AE rates for epcoritamab and comparators used in the cost-effectiveness model – adapted from Table 55 of the CS, Table 157 of the CS appendices and Table 34 of the company's response to CQ B22 87

Table 31. Summary of baseline mean age and proportion female used for the epcoritamab population in the economic model for each comparison and comparison with overall EPCORE™ NHL-1 population 98

Table 32. Baseline characteristics for updated base case analysis A (ECPORE™ NHL-1 DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) – reproduced from Table 18 of the company's response to CQ A7 101

Table 33. Baseline characteristics for scenario analysis A.1 (ECPORE™ NHL-1 DLBCL, no prior CAR-T population adjusted to Sehn *et al.*) – adapted from Table 26 of the CS 107

Table 34. Baseline characteristics for updated base case analysis B (ECPORE™ NHL-1 LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – reproduced from Table 28 of the CS..... 111

Table 35. Unadjusted and adjusted outcomes for epcoritamab vs R-based CIT (updated base case analysis A – epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) – adapted from Table 19 of the company's response to CQ A7 113

Table 36. Unadjusted and adjusted outcomes for epcoritamab vs Pola + BR (scenario A.1 – epcoritamab DLBCL, no prior CAR-T population adjusted to Sehn *et al.*) – adapted from Table 96 of the CS appendices 116

Table 37. Unadjusted and adjusted outcomes for epcoritamab vs axi-cel (updated base case analysis B – epcoritamab LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – adapted from Table 31 of the CS 119

Table 38. Company's base case probabilistic results – epcoritamab vs R-based CIT 124

Table 39. Company's base case deterministic results – epcoritamab vs R-based CIT..... 124

Table 40. Company's probabilistic scenario analysis – epcoritamab vs Pola + BR 124

Table 41. Company's deterministic scenario analysis – epcoritamab vs Pola + BR..... 125

Table 42. Company's base case probabilistic results – epcoritamab vs axi-cel..... 125

Table 43. Company's base case deterministic results – epcoritamab vs axi-cel 125

Table 44. Assessment of company conducted systematic literature review. 126

Table 45. NICE reference case checklist..... 127

Table 46. Landmark OS estimates for R-based CIT compared with SCHOLAR-1 OS data..... 137

Table 47: Landmark OS estimates for R-based CIT compared with Sehn *et al.* OS data 139

Table 48: Landmark OS estimates for axi-cel compared with ZUMA-1 OS data 141

Table 49. Landmark PFS estimates for Pola + BR compared with Sehn PFS data..... 151

Table 50: Landmark PFS estimates for axi-cel compared with ZUMA-1 PFS data 153

Table 51. Utility values derived from EPCORE NH-1 using linear mixed models (adapted from Table 56 in the CS). 166

Table 52. Adverse event-related utility decrements applied in the cost-effectiveness model. Reproduced from Table 58 in the CS. 168

Table 53. Drug dosage inputs applied in the cost-effectiveness model (adapted from table 60 in the CS). 170

Table 54. Drug acquisition costs (adapted from Table 61 in the CS.) 171

Table 55. Administration costs in the model 171

Table 56. Other drug administration costs (reproduced from Table 63 in the CS). 172

Table 57. Proportion of patients receiving subsequent treatments for each preceding treatment (reproduced from Table 64 in the CS)..... 174

Table 58. Costs and administrations of subsequent treatments. 174

Table 59. EAG preferred subsequent treatment proportions. 175

Table 60. Disease management health care resource use and cost by health state and treatment discontinuation. Reproduced from Table 66 in the CS). 177

Table 61. Resource use and unit cost of disease follow up for patients with progressive disease (reproduced from Table 67 in the CS)..... 178

Table 62. Terminal care related resource use and cost. Reproduced from Table 68 in the CS..... 178

Table 63. AE costs in the economic model. Reproduced from Table 69 in the CS. 181

Table 64. Company's base case probabilistic results – epcoritamab vs R-based CIT 182

Table 65. Company's base case deterministic results – epcoritamab vs R-based CIT 182

Table 66. Company's probabilistic scenario analysis – epcoritamab vs Pola + BR 182

Table 67. Company's deterministic scenario analysis – epcoritamab vs Pola + BR 183

Table 68. Company's base case probabilistic results – epcoritamab vs axi-cel 183

Table 69. Company's base case deterministic results – epcoritamab vs axi-cel 183

Table 70. Company's base case deterministic results – epcoritamab vs R-based CIT 186

Table 71. Company's deterministic scenario analysis – epcoritamab vs Pola + BR 187

Table 72. Company's base case deterministic results – epcoritamab vs axi-cel 187

Table 73. Results of the EAG's exploratory analyses – R-based CIT 189

Table 74. Results of the EAG's exploratory analyses – Pola + BR 191

Table 75. Results of the EAG's exploratory analyses – axi-cel 191

Table 76. QALY weighting for severity 197

Table 77. Summary of preferred assumptions for general population QALY shortfall estimates 197

Table 78. Company's QALY shortfall analysis 197

Table 79. EAG's QALY shortfall calculation 198

List of Figures

Figure 1. Company's summary of the current clinical pathway of patients with LBCL in the UK, including the proposed positioning of epcoritamab (reproduced from Figure 2 of the CS)[3, 4] 50

Figure 2. KM plot of OS[a] in LBCL overall, DLBCL and other LBCL types (FAS; [redacted] data cut-off) – reproduced from Figure 8 of the CS 78

Figure 3. KM plot of PFS[a] in LBCL overall, DLBCL and other LBCL types (FAS; [redacted] data cut-off) – reproduced from Figure 8 of the CS 78

Figure 4. KM plot of OS in EPCORE™ NHL-1 LBCL patients by prior CAR-T use (FAS; [redacted] data cut-off) – reproduced from Figure 2 of the company's response to CQ A1 91

Figure 5. KM plot of PFS in EPCORE™ NHL-1 LBCL patients by prior CAR-T use (FAS; [redacted] data cut-off) – reproduced from Figure 4 of the company's response to CQ A1 92

Figure 6. KM plot of OS in EPCORE™ NHL-1 LBCL patients by number of prior lines of therapy (FAS; [redacted] data cut-off) – reproduced from Figure 6 of the company's response to CQ A1..... 94

Figure 7. KM plot of PFS in EPCORE™ NHL-1 LBCL patients by number of prior lines of therapy (FAS; [redacted] data cut-off) – reproduced from Figure 8 of the company's response to CQ A1..... 94

Figure 8. Unadjusted and adjusted OS for epcoritamab vs R-based CIT (updated base case analysis A – DLBCL, no prior CAR-T population adjusted to SCHOLAR-1[a]) – reproduced from Figure 10 of the company's response to CQ A7 114

Figure 9. Unadjusted and adjusted OS for epcoritamab vs Pola + BR (scenario A.1 – DLBCL, no prior CAR-T population adjusted to Sehn *et al.*[a]) – reproduced from Figure 14 of the CS appendices 116

Figure 10. Unadjusted and adjusted PFS for epcoritamab vs Pola + BR (scenario A.1 – DLBCL, no prior CAR-T population adjusted to Sehn *et al.*[a]) – reproduced from Figure 15 of the CS appendices 117

Figure 11. Unadjusted and adjusted OS for epcoritamab vs axi-cel (updated base case analysis B – LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – reproduced from Figure 16 of the company's response to CQ A14..... 120

Figure 12. Unadjusted and adjusted PFS for epcoritamab vs axi-cel (updated base case analysis B – LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – reproduced from Figure 15 of the CS 120

Figure 13. Company's model (reproduced from Figure 16 CS) 128

Figure 14. Implementation error in OS and PFS curves used in the company's base case for epcoritamab (population A, for the comparison with R-based CIT). 132

Figure 15. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to Pola + BR with two or more prior lines of therapy (reproduced from Figure 14 of the CS appendices) 135

Figure 16. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, no prior CAR-T therapy epcoritamab population (reproduced from Figure 16 of the company's response to clarification question A14) 136

Figure 17. OS curves used in the company's base case for epcoritamab and Pola + BR 139

Figure 18. OS curves used in the company's base case for epcoritamab and Pola + BR (corrected) . 140

Figure 19. OS curves used in the company's base case for epcoritamab and axi-cel 142

Figure 20. OS curves used in the company's base case for epcoritamab and axi-cel (corrected for crossing of OS and PFS curves) 143

Figure 21. Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (reproduced from Figure 15 in the CS appendixes). 145

Figure 22. Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population (reproduced from Figure 13 of the CS) 146

Figure 23. Updated long-term PFS extrapolations for epcoritamab: population A, for the comparison against R-based CIT 147

Figure 24. Updated long-term PFS extrapolations for epcoritamab: population A, for the comparison against Pola + BR 147

Figure 25. Updated long-term PFS extrapolations for epcoritamab: population B 148

Figure 26. Long-term PFS extrapolations for R-based CIT 150

Figure 27. PFS curves used in the company's base case for epcoritamab and Pola + BR (corrected) 151

Figure 28. Long-term PFS extrapolations for axi-cel - corrected 153

Figure 29. EAG exploratory analysis for PFS extrapolations for epcoritamab: population A, for the comparison against R-based CIT 156

Figure 30. EAG exploratory analysis for PFS extrapolations for epcoritamab: population B 157

Figure 31. Population A, example of the company's different TTD curves fitted..... 159

Figure 32. Population A, TTD and PFS fitted curves, together with TTD and PFS KM data 161

Figure 33. Population B, TTD and PFS KM data 162

Figure 34. Population B, TTD (Gompertz) and PFS (generalised gamma) fitted curves for epcoritamab 163

Figure 35. Population B, TTD (Gompertz) and PFS (lognormal) fitted curves for epcoritamab 163

Figure 36. KM PFS and TTD curves for epcoritamab – population A, vs R-based CIT..... 164

Figure 37. KM PFS and TTD curves for epcoritamab – population A, vs Pola + BR..... 164

Figure 38. KM PFS and TTD curves for epcoritamab – population B 165

List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
Allo-SCT	Allogenic stem cell transplantation
aNHL	Aggressive B-cell non-Hodgkin lymphoma
ASCT	Autologous stem cell transplant
Axi-cel	Axicabtagene ciloleucel
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine and rituximab
CAR-T	Chimeric antigen receptor T-cell
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CIT	Chemoimmunotherapy
CQ	Clarification question
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CTLS	Clinical tumour lysis syndrome
CXDX	Cycle X Day X
DHAP	Dexamethasone, cytarabine, cisplatin
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMTREE	Embase subject headings
eMIT	Electronic market information tool
EPCO	Epcoritamab
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
ESMO	European Society for Medical Oncology
ESS	Effective sample size

EU	European
FACT-Lym	The Functional Assessment of Cancer Therapy
FACT-LymS	Functional Assessment of Cancer Therapy – Lymphoma Subscale
FAS	Full analysis set
FL	Follicular lymphoma
FL Gr 3B	Follicular lymphoma grade 3B
GDP	Gemcitabine, dexamethasone and cisplatin
GEP	Gene expression profiling
GP	General practitioner
HGBCL	High-grade B-cell lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Appraisals
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio
ID	Identification
IPD	Individual patient data
IPI	International Prognostic Index
IRC	Independent Review Committee
IVE	Ifosfamide, etoposide and epirubicin
IWG	International Working Group
KM	Kaplan–Meier
LBCL	Large B-cell lymphoma
LDH	Lactate dehydrogenase
LLM	Linear mixed models
LTR	Long-term remission
LYG	Life years gained
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MAIC	Matching-adjusted indirect comparisons
MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
N/A	Not applicable
n^{eff}	Effective sample size
NHB	Net health benefit
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NHSEI	National Health Service England and National Health Service Improvement

NICE	National Institute for Health and Care Excellence
NR	Not reached or not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD	Disease progression
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PMBCL	Primary mediastinal B-cell lymphoma
Pola	Polatuzumab vedotin
Pola + BR	Polatuzumab vedotin with rituximab and bendamustine
Pola + R-CHP	Polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone
PR	Partial response
PS	Performance score
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
R	Rituximab
R-based CIT	Rituximab-based chemoimmunotherapy
R-Gem	Rituximab and gemcitabine
R-GemOx	Rituximab, gemcitabine and oxaliplatin
R/R	Relapsed or refractory
R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
RCT	Randomised controlled trial
RWE	Real-world evidence
SC	Subcutaneous
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
STA	Single technology appraisal
TA	Technology appraisal
TE	Technical engagement
TEAE	Treatment-emergent adverse event
TFL	Transformed follicular lymphoma
ToT	Time on treatment

TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
UK	United Kingdom
US	United States
WHO	World Health Organisation
3L+	Third line and beyond

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of The National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	The population in the decision problem may be broader than that covered by the trial	Table 2 and Section 2.3.1.1
2	Issues associated with the paper used to inform data for SCHOLAR-1 in the MAIC vs R-based CIT	Table 3 and Sections 2.3.1.2 and 3.4.2.1
3	Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used	Table 4 and Sections 2.3.1.2 and 3.4.2.1
4	The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population	Table 5 and Sections 2.3.1.2 and 3.4.2.2
5	Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment	Table 6 and Sections 2.3.1.2, 3.3.4.2 and 3.4.2
6	It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments	Table 7 and Sections 2.3.1.2, 3.4.2.1 and 3.4.2.2
7	Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons	Table 8 and Sections 2.3.1.2, 3.4.1 and 3.4.2
8	All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1	Table 9 and Section 2.3.4
9	Limitations of Sehn *et al.* for the MAIC vs Pola + BR	Table 10 and Section 3.4.2.2
10	Limitations of ZUMA-1 for the MAIC vs axi-cel	Table 11 and Section 3.4.2.3
11	Implementation the long-term remission assumption in the model.	Table 12 and Section 4.2.2.
12	Estimation of overall survival in the model.	Table 13 and Section 4.2.4.1 and Section 4.2.4.2.
13	Estimation of progression-free survival in the model.	Table 14 and Section 4.2.4.2 and Section 4.2.4.3.

14	Estimation of time to treatment discontinuation in the model.	Table 15 and Section 4.2.4.5 and Section 4.2.4.6.
15	Utilities used in the model.	Table 16 and Section 4.2.5.
16	Treatment and administration costs of comparators in the model.	Table 17 and Section 4.2.6.1 and Section 4.2.6.2.
17	Subsequent treatments in the model.	Table 18 and Section 4.2.6.3 and Section 4.2.6.4.
18	Disease follow-up costs in the model.	Table 19 and Section 4.2.6.5 and Section 4.2.6.6.

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; NHL, Non-Hodgkin lymphoma; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, in the company's base case, the technology is modelled to affect QALYs by:

- Directly increasing the proportion of patients who remain in the overall survival and progression-free survival states, which in its turn leads to better survival and better quality of life.

Overall, in the company's base case, the technology is modelled to affect costs by:

- Its higher unit cost compared to rituximab-based chemoimmunotherapy (R-based CIT) and polatuzumab vedotin with rituximab and bendamustine (Pola + BR), and lower unit costs compared to axicabtagene ciloleucel (axi-cel).
- Decreasing the probability of patients progressing, therefore leading to lower follow-up costs associated with disease progression.

The modelling assumptions that have the greatest effect on the ICER are:

- The assumption that epcoritamab patients enter long-term remission (LTR) at 2 years and therefore stop incurring follow-up costs in the NHS at that point in the model. The EAG notes that the impact of this assumption on survival was not explored in the EAG's analysis

but it will only magnify the impact on the ICER once the company allows for this to be changed in the model.

- The assumption that epcoritamab patients start incurring the "PFS off-treatment" follow-up costs from [redacted] up to 2 years while assuming that follow-up costs for comparator treatments are the "PFS on-treatment" costs for 2 years.
- The distribution of subsequent treatments in the model.

1.3 Summary of the EAG's key issues

Table 2. Issue 1. The population in the decision problem may be broader than that covered by the trial

Report section	2.3.1.1
Description of issue and why the EAG has identified it as important	The EAG highlights a number of slight differences between the decision problem population and the population included in the EPCORE™ NHL-1 trial used to inform the CS for epcoritamab, which may be important to consider in terms of the wording of any recommendations. The EPCORE™ NHL-1 trial limited the population to: • those that had failed (or were ineligible for) prior ASCT; • and those with ECOG scores 0-2. This is not the case in the NICE final scope or the decision problem. While this may not exclude many in UK practice, the EAG considers that these may be important factors to consider given no evidence for epcoritamab is available in these groups.
What alternative approach has the EAG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	N/A

Abbreviations: ASCT, autologous stem cell transplant; CS, company submission; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; NHL, Non-Hodgkin lymphoma; N/A, not applicable; NICE, National Institute for Health and Care Excellence; UK, United Kingdom.

Table 3. Issue 2. Issues associated with the paper used to inform data for SCHOLAR-1 in the MAIC vs R-based CIT

Report section	2.3.1.2 and 3.4.2.1
Description of issue and why the EAG has identified it as important	The EAG has concerns about the paper used to inform SCHOLAR-1 data for the MAIC vs R-based CIT. The Neelapu *et al.* paper rather than the Crump *et al.* paper has been used, which the EAG considers is associated with the following limitations: 1. the SCHOLAR-1 population presented in Neelapu *et al.* represents a population that is more comparable to ZUMA-1 as propensity score matching has been performed. ZUMA-1

represents a CAR-T eligible population and, therefore, the EAG does not consider this to be very representative of the population that the comparison of epcoritamab vs R-based CIT is relevant to (those ineligible or that choose not to have intensive treatments; population A). The ZUMA-1 study will not have included patients that are ineligible for CAR-T and matching SCHOLAR-1 to this study may therefore have excluded (or reduced the weighting) of the patients that are relevant to population A in the CS, which will subsequently affect the weighting of epcoritamab patients in EPCORE™ NHL-1 when the MAIC is performed using this study and the adjusted KM curve obtained for epcoritamab. The EAG notes that 100% of patients from SCHOLAR-1 in the Neelapu *et al.* paper had ECOG score 0-1 (an important factor for CAR-T eligibility and prognosis) and it has fewer proportions with disease severity measures such as disease stage III-IV and IPI score ≥3 compared to the analysed EPCORE™ NHL-1 population and the population in Crump *et al.* and this may be a result of the population being more like a CAR-T eligible group when this paper is used;

2. KM curves for OS in this paper do not contain information on censoring; the company have had to make the assumption that the pattern of censoring is the same as that observed in the Crump *et al.* paper, despite the populations being different between these papers as a result of the comparison vs ZUMA-1 in Neelapu *et al.* This introduces additional uncertainty;
3. despite being matched for this, the proportion with disease stage III-IV still appears to be imbalanced between Neelapu *et al.* and EPCORE™ NHL-1;
4. while the company states that the Neelapu *et al.* paper was limited to DLBCL, the EAG could not confirm this and considers that the population may actually be LBCL; if this is true, the exclusion of DLBCL from EPCORE™ NHL-1 is unnecessary and adds to uncertainties, as this will have introduced a difference between EPCORE™ NHL-1 and SCHOLAR-1 for this population factor that could impact outcomes;
5. while the company assert that using Neelapu *et al.* limits inclusion to those with at least two prior treatments in SCHOLAR-1, the EAG could not confirm this and notes that it is possible that some with only one prior treatment remain in this paper, which cannot be adjusted for; the EAG agrees that this would remain an issue if the Crump *et al.* paper is used, but highlights that the rationale provided for using Neelapu *et al.* may not be accurate and, therefore, the EAG's argument against the introduction of the limitations described above and an alternative source of data may provide a more robust comparison with R-based CIT.

Given the uncertainty associated with unanchored MAICs, the EAG considers that the Neelapu *et al.* paper introduces additional uncertainty, which could impact conclusions in terms of clinical and cost-effectiveness, and is not appropriate as a source of SCHOLAR-1

	data for the MAIC vs R-based CIT. In addition, the EAG considers it may not have been appropriate to limit the EPCORE™ NHL-1 population to DLBCL for this analysis, as the EAG could not confirm that the Neelapu *et al.* paper limited to DLBCL patients. If so, this will have introduced additional uncertainty in the analysis as the two studies will differ with regards to their inclusion.
What alternative approach has the EAG suggested?	The EAG acknowledges that other sources of data for R-based CIT may also be limited and that sufficient data may not be available to perform more robust analyses; however, the EAG has listed some options below (in order of preference) with the aim of reducing uncertainty in the MAIC for epcoritamab vs R-based CIT: 1. consider whether there are any other studies reporting on R-based CIT that could be used in an indirect comparison to resolve the issues described above (if these also resolve issues described below in Table 4, this would provide further rationale to avoid using SCHOLAR-1 at all); 2. ideally, IPD for SCHOLAR-1 or CORAL (one of the four studies that make up SCHOLAR-1 and highlighted as potentially useful by the EAG in Section 3.4.2.1) would be available to the company. This would mean propensity score methods (as described in NICE DSU TSD17) could be used to match EPCORE™ NHL-1 to the comparator study using IPD from each and may resolve the concern about not including people with only one prior treatment, as well the EAG's concern about how applicable the SCHOLAR-1 population from Neelapu *et al.* is. While this was available to the authors of Neelapu *et al.*; the EAG notes that this is likely because Kite (a Gilead company) was involved in SCHOLAR-1 and ZUMA-1. While this would be the EAG's preferred second option, the EAG considers that it is unlikely IPD for either of these studies would be available to the company; 3. consider performing the MAIC using the Crump *et al.* paper for SCHOLAR-1 and acknowledging the limitation of including some with only one prior treatment. In addition, if an LBCL population is covered for the comparator trial, the analysis population from EPCORE™ NHL-1 should be updated in line with this to avoid differences in populations with regards to this factor. Additional limitations of SCHOLAR-1, regardless of which paper is used, are described in Table 4 below. See also the EAG's concerns (and suggested alternative approach) about jointly fitting survival curves for epcoritamab and the comparator in Issues 12 and 13.
What is the expected effect on the cost-effectiveness estimates?	The EAG is unclear how and to what extent the current use of Neelapu *et al.* impacts the clinical and cost-effectiveness estimates but considered its use to be a major source of uncertainty. The possible impact of any difference in terms of LBCL inclusion for EPCORE™ NHL-1 and SCHOLAR-1 is also unclear.

What additional evidence or analyses might help to resolve this key issue?	As described above in order of preference, identification of other studies that may resolve these issues as well as those in Table 4 below, use of IPD data if available for SCHOLAR-1 or CORAL (although unlikely), or use of the Crump *et al.* paper for SCHOLAR-1 with acknowledgement of limitations. Ensuring that non-DLBCL subtypes of LBCL are included for EPCORE™ NHL-1 (rather than excluding them) if the comparator trial has included them would reduce concerns about how aligned the trials are in terms of this population.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CS, company submission; DLBCL, diffuse large B-cell lymphoma; DSU, Decision Support Unit; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; IPD, individual patient data; IPI, International Prognostic Index; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; NICE, National Institute for Health and Care Excellence; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy; TSD, technical support document.

Table 4. Issue 3. Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used

Report section	2.3.1.2 and 3.4.2.1
Description of issue and why the EAG has identified it as important	In addition to those specific to the use of the Neelapu *et al.* paper described in Table 3 above, the EAG highlights additional limitations associated with the SCHOLAR-1 study regardless of which paper is used: • SCHOLAR-1 only includes those with refractory disease (rather than a mix of relapsed and refractory disease); this might underestimate survival outcomes for R-based CIT compared to if a mixed population was included; • the types of CIT used in SCHOLAR-1 (and proportions with each) is not reported. This means it is unclear whether all or most patients received R-based CIT and the EAG notes that estimates for R-based CIT from this study may be underestimated if a large proportion did not receive R-based CIT. The Crump *et al.* paper does, however, describe one of the advantages of SCHOLAR-1 as being that it represents a large number of patients treated in the "modern rituximab era"; • the inclusion of 28% of patients with only one prior treatment in the Crump *et al.* paper for SCHOLAR-1, which is not the case for EPCORE™ NHL-1 (only those with at least two prior treatments included) and it would not be possible to adjust for this unless IPD were available (see Table 3 above) These are limitations that would apply even if the Crump *et al.* paper for SCHOLAR-1 is used for matching (and also apply when the Neelapu *et al.* paper is used, although there are potentially fewer patients with one prior treatment in the latter). The first two limitations may bias against R-based CIT, while the latter might have the opposite effect. For this reason, the EAG notes above in Table 3 that other sources of data for R-based CIT that could resolve issues described here and above would be preferable but acknowledges that SCHOLAR-1 may be the best available despite limitations and have provided alternatives.
What alternative approach has the EAG suggested?	If SCHOLAR-1 remains the source of data for R-based CIT after considering the EAG's points above in Table 3, the EAG notes that these are unresolvable limitations of this study.

What is the expected effect on the cost-effectiveness estimates?	The inclusion of only refractory disease and the uncertainty around how many patients used R-based CIT in SCHOLAR-1 may underestimate survival for R-based CIT, improving ICERs for epcoritamab vs R-based CIT. The opposite effect may be expected for the inclusion of those with only one prior treatment in SCHOLAR-1 but not in EPCORE™ NHL-1.
What additional evidence or analyses might help to resolve this key issue?	N/A

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; MAIC, matching-adjusting indirect comparison; N/A, not applicable; NHL, Non-Hodgkin lymphoma; R-based CIT, rituximab-based chemoimmunotherapy.

Table 5. Issue 4. The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population

Report section	2.3.1.2 and 3.4.2.2
Description of issue and why the EAG has identified it as important	For the MAIC vs Pola + BR, the EPCORE™ NHL-1 population has been limited to those with DLBCL to bring it in line with the population in Sehn *et al.;* only one patient in Sehn *et al.* had a type of LBCL that was not DLBCL and it is unclear if this was FL Gr 3B covered in EPCORE™ NHL-1. The EAG highlights that this analysis population does not cover the full LBCL population detailed in the decision problem and NICE final scope, so it may be slightly less applicable to the overall population; however, given that other subtypes of LBCL are rare in practice and differences in treatment pathway and [redacted] may be small, the EAG considers that the DLBCL population may be sufficient for informing outcomes in the whole LBCL population.
What alternative approach has the EAG suggested?	The EAG considers this to be an unresolvable limitation when the Sehn *et al.* study is used for Pola + BR and highlights it as a potential limitation in terms of applicability to the full LBCL population.
What is the expected effect on the cost-effectiveness estimates?	Given other subtypes of LBCL are rare in practice and differences in the treatment pathway and [redacted] may be small, the EAG considers that inclusion of these patients (if they had been reported in the comparator study as well and could be adjusted for) may not have a large impact on results.
What additional evidence or analyses might help to resolve this key issue?	N/A

Abbreviations: DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; FL Gr 3B, follicular lymphoma grade 3B; LBCL, large B-cell lymphoma; MAIC, matching-adjusting indirect comparison; N/A, not applicable; NHL, Non-Hodgkin lymphoma; NICE, National Institute for Health and Care Excellence; Pola + BR, polatuzumab vedotin with rituximab and bendamustine.

Table 6. Issue 5. Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment

Report section	2.3.1.2, 3.3.4.2 and 3.4.2
Description of issue and why the EAG has identified it as important	Given the EPCORE™ NHL-1 populations analysed in MAICs do not include those with prior CAR-T use, and as survival results from EPCORE™ NHL-1 [redacted], the EAG considers that the results of the MAICs and economic model may not be applicable to the group with prior CAR-T use.

	This is a limitation of the analyses that was required to align studies in MAICs and the EAG does not consider this to be resolvable. The EAG notes this as a limitation for comparisons vs R-based CIT and Pola + BR (as there may be some in practice that have had prior CAR-T if they were previously eligible, e.g. patients that might have epcoritamab as an option for fourth or later line treatment, as currently CAR-T is used at third line). However, for the comparison vs axi-cel, the EAG does not consider this to be an issue given patients would not be retreated with CAR-T and for this comparison to be applicable, would therefore not have a history of CAR-T treatment.
What alternative approach has the EAG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	Survival outcomes in those with prior CAR-T use in EPCORE™ NHL-1 appear to [redacted]. Their inclusion in MAICs may, therefore, [redacted] ICERs. It is unclear what the impact would be if comparator trials had included those with prior CAR-T use and matching could then be performed for this, without the need to exclude them to bring populations in line.
What additional evidence or analyses might help to resolve this key issue?	N/A

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; N/A, not applicable; NHL, Non-Hodgkin lymphoma; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy.

Table 7. Issue 6. It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments

Report section	2.3.1.2, 3.4.2.1 and 3.4.2.2
Description of issue and why the EAG has identified it as important	For comparisons vs R-based CIT and Pola + BR, the company defines the population that are ineligible for intensive treatments (or choose not to have them) as the population of interest (population A). The company describes the population from EPCORE™ NHL-1 analysed in the MAICs for these comparisons as "DLBCL, no prior CAR-T", with [redacted] included. There is no mention of the requirement for patients to be ineligible for intensive treatments and the EAG is, therefore, unclear how well this analysed population matches that set out for population A in the CS. If the population analysed is substantially different from the group that were deemed ineligible for intensive treatments, the EAG anticipates that this has the potential to affect the results of the MAICs and economic model.
What alternative approach has the EAG suggested?	Further clarification on eligibility for intensive treatments in the [redacted] analysed, as well as exploring the potential impact on results of the MAIC and economic model if this group consists of a large proportion that would be considered eligible for intensive treatments would help to assess the potential impact.
What is the expected effect on the cost-effectiveness estimates?	If the analysed group does contain a substantial proportion of patients that are eligible for intensive treatments (rather than only including those ineligible), the EAG anticipates that this may improve the outcomes for epcoritamab compared to a population that is not eligible for intensive treatments, given it may be a population with worse prognostic factors.
What additional evidence or analyses might help to resolve this key issue?	To reduce uncertainty, the EAG considers that the following would be useful to first clarify how the analysed population may differ from a group ineligible for intensive treatments:

	• provide details of whether the [redacted] patients currently analysed from EPCORE™ NHL-1 included in the MAICs vs R-based CIT and Pola + BR includes some that would be eligible for intensive treatments and how many patients this applied to; • provide information on the criteria used to conclude that an individual would be eligible for intensive treatments in the EPCORE™ NHL-1 study; If there are patients included that would be classified as eligible for intensive treatments, the following would be useful to assess the impact of using an MAIC with them excluded for comparisons in population A: • provide baseline characteristics for the subgroup considered ineligible for intensive treatments (no prior CAR-T); • provide the following outcomes for the subgroup considered ineligible for intensive treatments with no prior CAR-T (relevant to the economic model): o OS, PFS and TTD, including KM curves; o AE rates for those used in the economic model (Table 55 of the CS); o EQ-5D-3L results as applied in the economic model (Table 56 of the CS). • perform scenarios for the MAICs vs R-based CIT and Pola + BR where the subgroup ineligible for intensive treatments from EPCORE™ NHL-1 (no prior CAR-T) is matched to the comparator studies – the EAG notes that it would be preferable for these scenarios to be performed once the limitations described for current MAICs covering these comparisons have been addressed (Table 3, Table 4, Table 10 and Table 11). See also the EAG's concerns (and suggested alternative approach) about jointly fitting survival curves for epcoritamab and the comparator in Issues 12 and 13.

Abbreviations: AE, adverse event; CAR-T, chimeric antigen receptor T-cell; CS, company submission; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; KM, Kaplan-Meier; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; OS, overall survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; PFS, progression-free survival; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

Table 8. Issue 7. Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons

Report section	2.3.1.2, 3.4.1 and 3.4.2
Description of issue and why the EAG has identified it as important	Some baseline characteristics reported for EPCORE™ NHL-1 and comparator studies used for MAICs have not been adjusted for as part of MAIC analyses. This is despite some remaining in imbalance between arms and adjustment for factors being particularly important for unanchored MAICs regardless of the impact on ESS, as described in NICE DSU TSD 18.
What alternative approach has the EAG suggested?	The EAG requested at clarification (CQ A6) that MAICs be updated to include all baseline characteristics reported in the comparator trials in the matching process. No additional adjustments were included in the company's response to clarification. The EAG maintains that inclusion of all reported baseline characteristics would be preferable and would reduce uncertainty. While the EAG acknowledges that ESS may reduce further with adjustment of more

	baseline characteristics, it notes that this in itself indicates a lack of comparability between EPCORE™ NHL-1 and the comparator trial used for each MAIC. Therefore, it is inappropriate to conclude that results without adjustments for further characteristics are more suitable than those with further adjustments; while the precision would likely reduce, the EAG consider less precise and potentially more accurate estimates to be preferable to more precise estimates that are likely to be less accurate. The EAG highlights the following factors for each MAIC as particularly important, given they remain in imbalance in the current MAICs or were highlighted by the EAG's clinical experts as being potential prognostic factors: • Epcoritamab vs R-based CIT (see Section 3.4.2.1): ○ ≥3 lines of chemo and ASCT ○ SCT any time after refractory disease • Epcoritamab vs Pola + BR (see Section 3.4.2.2): ○ Refractory to last anti-lymphoma treatment ○ IPI score ≥3 ○ ≥3 lines of chemo and ASCT • Epcoritamab vs axi-cel (see Section 3.4.2.3): ○ IPI score ≥3 ○ ≥3 prior treatment lines See also the EAG's concerns (and suggested alternative approach) about jointly fitting survival curves for epcoritamab and the comparator in Issues 12 and 13.
What is the expected effect on the cost-effectiveness estimates?	The exact impact of adjusting for these additional factors is unclear.
What additional evidence or analyses might help to resolve this key issue?	MAICs updated to include all reported baseline characteristics in the adjustment, particularly those highlighted above in this table, would provide more reliable results even if this results in reduced precision.
Abbreviations: ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CQ, clarification question; DSU, Decision Support Unit; EAG, External Assessment Group; ESS, effective sample size; IPI, International Prognostic Index; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; NICE, National Institute for Health and Care Excellence; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy; SCT, stem cell transplant; TSD, technical support document.	

Table 9. Issue 8. All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1

Report section	2.3.4
Description of issue and why the EAG has identified it as important	The data provided in the CS and additional analyses requested at clarification are based on data from the [redacted] data-cut of EPCORE™ NHL-1. A more recent data-cut ([redacted]) was mentioned in response to CQ B9. It is important that all data used in the appraisal is based on the most recently available data-cut. The EAG notes that by technical engagement, the latest data-cut may no longer be [redacted].

What alternative approach has the EAG suggested?	At technical engagement, data within the CS should be updated with data from the most recent data-cut, including clinical outcomes, MAICs and economic modelling. This should be performed for data provided in the original CS and in response to CQs. Updated CSR tables for this data-cut should also be provided. The EAG highlights the following as particularly important: • data for any outcomes (including KM curves and tabulated results) included in this EAG report in Section 3.3, including any subgroups requested as part of CQs; • data for any additional analyses requested as part of CQs (clinical and economic); • data for MAICs as a result of updated analyses (i.e. any changes in baseline characteristics for those analysed [if applicable] and updated results); • economic model data as requested in Issue 12, 13 and 14.
What is the expected effect on the cost-effectiveness estimates?	The impact on ICERs is unclear.
What additional evidence or analyses might help to resolve this key issue?	As above, data within the CS should be updated to reflect the most recent data-cut.

Abbreviations: CS company submission; CSR, clinical study report; CQ, clarification question; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; NHL, Non-Hodgkin lymphoma.

Table 10. Issue 9. Limitations of Sehn *et al.* for the MAIC vs Pola + BR

Report section	3.4.2.2
Description of issue and why the EAG has identified it as important	In addition to lack of adjustment for all reported baseline characteristics described above in Table 8, a number of other uncertainties associated with the MAIC vs Pola + BR are highlighted by the EAG: 1. estimates for Pola + BR in Sehn *et al.* were not in line with those from a paper based on UK RWE and may be an overestimate of results that would be seen in UK practice; 2. at least one potentially important prognostic factor highlighted by the EAG's clinical experts (primary refractoriness) was not reported in Sehn *et al.*, meaning it could not be adjusted for and it is unclear whether there are any important differences compared to EPCORE™ NHL-1 in the MAIC. Both of these factors have the potential to impact the clinical and cost-effectiveness outcomes.
What alternative approach has the EAG suggested?	The company did not use the UK RWE study cited in a scenario as data for those with at least two prior treatment could not be obtained. An alternative RWE study was used but this was considered to be limited by the EAG. The EAG considers this to be an unresolvable uncertainty that means use of Sehn *et al.* to inform Pola + BR may overestimate survival outcomes.
What is the expected effect on the cost-effectiveness estimates?	If it is true that results for Pola + BR in Sehn *et al.* are not reflective of UK practice, inclusion of data that is a more realistic estimate may reduce ICERs for epcoritamab. In terms of potential prognostic factors not reported and therefore not adjusted for, including primary refractoriness, it is unclear what impact this has on ICERs as it is unclear how these differ between studies.
What additional evidence or analyses might help to resolve this key issue?	If there was an alternative source of UK RWE for Pola + BR that could be used to perform a scenario, this may help to assess if and to what extent Sehn *et al.* may overestimate survival outcomes and the impact this has on ICERs. However, the EAG is not aware of such a paper that could be used. In addition, the EAG notes that use of RWE for Pola + BR but trial-based data for epcoritamab may be associated with more limitations than using data from Sehn *et al.* for Pola + BR. The lack of reporting for certain factors in Sehn *et al.* is an unresolvable uncertainty.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; RWE, real-world evidence; UK, United Kingdom.

Table 11. Issue 10. Limitations of ZUMA-1 for the MAIC vs axi-cel

Report section	3.4.2.3
Description of issue and why the EAG has identified it as important	In addition to lack of adjustment for all reported baseline characteristics described above in Table 8, a number of other uncertainties associated with the MAIC vs axi-cel are highlighted by the EAG: 1. The definition used for PFS (Lugano vs International Working Group criteria) differs between EPCORE™ NHL-1 and ZUMA-1; 2. The ZUMA-1 study appears to include only those that were infused with axi-cel, whereas in UK clinical practice some may become ineligible before they actually receive infusion of axi-cel, as the treatment has to be manufactured for each patient after cells are taken;

	3. At least one potentially important prognostic factor highlighted by the EAG's clinical experts (refractory to last anti-lymphoma treatment) was not reported in ZUMA-1 meaning it could not be adjusted for and it is unclear whether there are any important differences compared to EPCORE™ NHL-1 in the MAIC. All of these factors have the potential to impact the clinical and cost-effectiveness outcomes.
What alternative approach has the EAG suggested?	The EAG considers that the company could explore what impact the different definition has by applying the IWG criteria to IPD from the analysed EPCORE™ NHL-1 population. The latter two points are considered to be unresolvable limitations when ZUMA-1 is used to inform axi-cel in the MAIC. See also the EAG's concerns (and suggested alternative approach) about jointly fitting survival curves for epcoritamab and the comparator in Issues 12 and 13.
What is the expected effect on the cost-effectiveness estimates?	The extent of the potential impact is unclear, but the first two points could introduce bias against epcoritamab; the PFS definition appears to be more sensitive in terms of progression events for EPCORE™ NHL-1 and had patients that are due to receive axi-cel but deteriorate and become ineligible while waiting for the treatment been included in ZUMA-1, outcomes may be worse. In terms of potential prognostic factors not reported and therefore not adjusted for, including refractoriness to last anti-lymphoma treatment, it is unclear what impact this has on ICERs as it is unclear how these differ between studies.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers the last two points to be unresolvable uncertainties associated with the ZUMA-1 trial and is not aware of another study that would resolve these issues. For the different outcome definitions, this could be explored by applying the definition used in ZUMA-1 to analysed EPCORE™ NHL-1 IPD and assessing the impact.

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; IWG, International Working Group; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; PFS, progression-free survival; UK, United Kingdom.

Table 12. Issue 11. Implementation of when the long-term remission assumption starts in the model

Report section	Section 4.2.2.
Description of issue and why the EAG has identified it as important	All patients in the progression-free state 2 years after the beginning of the model are assumed to enter entering LTR which means that: 1. Patients experience no further progression events. 2. Patients experience an adjusted background mortality rate, where a standardised mortality ratio (SMR) of 1.41 is applied to the general population mortality matched for age and sex. 3. Patients do not use any healthcare resources associated with follow-up. 4. Patients experience the utility value associated with being in the PFS state while alive. The EAG notes that the company's LTR assumption does not imply that patients' survival returns to that observed in the general population after 2 years, nor that patients' quality of life returns to that of the general

	population. Therefore, the company's assumption is not the equivalent of a "structural cure" in the model. The EAG's clinical experts explained that R/R LBCL patients who have not progressed 2 years *after the end of their treatment* would be considered to be in LTR, with further disease progression events being unlikely to occur. The clinical experts added that they would discharge patients from follow-up at this point. However, the company's assumption of LTR in the model diverged from the clinical expert's opinion in two ways: 1. For comparator treatments – the company assumed that progression-free patients 2 years *after treatment initiation* (not treatment end) are in LTR. For axi-cel, treatment consists of a one-off treatment at the beginning of the model, thus the company's approach is reasonable for axi-cel; however, treatment duration in the company's base case with R-based CIT in the model is 7 months and 4 months with Pola + BR, therefore the model should account for LTR to begin at 2 years and 7 months for progression-free R-based CIT patients and 2 years and 4 months for progression-free Pola + BR patients. 2. For epcoritamab – the company applied the same assumption that progression-free patients are in LTR 2 years *after treatment initiation*. The EAG's clinical experts advised that patients on epcoritamab would not be considered to enter LTR while on treatment, nor would they be discharged. The company's approach, therefore, assumes that patients enter LTR and are discharged from any follow-up (although still incurring the costs of treatment) while still on treatment. Epcoritamab does not have a stopping rule and is indicated to be given until progression or unacceptable toxicity. In the company's base case patients stay on treatment for much longer than 2 years, with patients in the population B (for example) having a mean duration of treatment of [redacted] years, even though they enter LTR at 2 years in the model. The LTR assumption mainly effects follow-up costs in the model and survival, as patients in LTR are assumed to not be followed up anymore (as well as having an increase in their probability of survival). The company's approach, therefore, underestimates the costs of follow up associated with epcoritamab treatment in the NHS and overestimates survival. These issues are discussed in turn in Issue 13 and issue 18, respectively.
What alternative approach has the EAG suggested?	The company should include a scenario analysis allowing the model to have a flexible option, whereby the time at which patients enter the LTR assumption can be selected for different points in time for each comparator and for epcoritamab in each comparison. This scenario should also allow for the removal of the LTR assumption in the model for epcoritamab only.
What is the expected effect on the cost-effectiveness estimates?	Given the company's assumption that epcoritamab patients enter LTR at the same time as patients in the comparator arms, currently varying the point in time at which patients enter LTR has a modest impact on the estimated treatment costs, and thus on the ICER. The EAG notes that if epcoritamab and comparator patients entered LTR at different points in the model, the point at which this happens for each treatment would have a major impact on the final ICER.

	In the exploratory analysis conducted by the EAG where the LTR in the model was removed for epcoritamab (only affecting costs due to limitations in the flexibility of the company's model), this was found to be the key driver of the economic results (see Issue 18).
What additional evidence or analyses might help to resolve this key issue?	The company should provide the additional analysis requested above.

Abbreviations: LTR: long-term remission; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine

Table 13. Issue 12. Estimation of overall survival in the model

Report section	Section 4.2.4.1 and Section 4.2.4.2
Description of issue and why the EAG has identified it as important	As described in Issues 2, 3, 6, 7, 9, and 10, the EAG has serious concerns with the MAICs undertaken to estimate the relative treatment effect of epcoritamab on OS (and PFS) outcomes compared to other treatments. Furthermore, the EAG considers the company's approach of jointly fitting survival curves unfit for purpose, particularly for the comparison of epcoritamab with Pola + BR and axi-cel, where the underlying OS (and PFS) KM curves cross for both outcomes, between each comparator and epcoritamab. The EAG is concerned with the company's approach of applying 2 different HRs to the epcoritamab OS curve to estimate a Pola + BR OS curve, before and after [redacted] months in the model. The EAG has not seen any evidence to justify the existence of PHs before and after this timepoint in the model (even if a different HR would apply) and notes that the company's approach leads to the underestimation of survival in the fitted OS curve for Pola + BR. The EAG is particularly concerned with the company's use of a single HR to estimate the OS axi-cel curve as it is clearly methodologically flawed when the underlying KM curves cross. The company's approach is likely to underestimate the proportion of patients alive in the axi-cel arm of the model. Overall, the EAG considers that the relative effect of epcoritamab on OS is overestimated for every comparison in the model: 1. The OS curve for R-based CIT underpredicts OS in the long-term model for this treatment when compared to the long-term SCHOLAR-1 data (see Table 46 in the EAG report). This directly impacts the estimated PFS curve for R-based CIT, given the company's approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve. 3. The OS curve estimated for Pola + BR is likely to considerably underpredict OS in the long-term model for this treatment, when compared to the observed data in Sehn *et al.* (see Table 47) in the EAG report). 4. The OS curve estimated for axi-cel is likely to underpredict OS in the long-term model for this treatment when compared to the long-term ZUMA-1 data (see Table 48) in the EAG report).

	5. The OS curve for epcoritamab in all compassions is likely to be overestimated, particularly for the comparison with R-based CIT and axi-cel, where there is approximately an average of [redacted] of epcoritamab patients alive at the age of 90. The overestimation of OS in the model is intrinsically related to the overestimation of PFS in the model (given the convergence of the curves so early in the model), which is discussed in Issue 13.
What alternative approach has the EAG suggested?	See recommendations given in Issues 2, 3, 6, 7, 9, and 10. Furthermore, the EAG recommends that the company independently fits OS curves for each comparator and epcoritamab in the model (as requested by the EAG at the clarification stage). The EAG anticipates that the more mature OS data cut which will be available in August might help inform the curve fitting exercise.
What is the expected effect on the cost-effectiveness estimates?	If the fitted OS comparator curves become more representative of the underlying KM data available for each comparator, the relative effect of epcoritamab on OS will decrease (even if the epcoritamab fitted OS curves remain the same), therefore, increasing the ICER for epcoritamab vs all comparators.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that the company produces state occupancy traces for the company's base case corrects for the error identified in the model (described in Section 4.2.2.1.) for all comparators and all populations.

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; UK, United Kingdom.

Table 14. Issue 13. Estimation of progression-free survival in the model

Report section	Section 4.2.4.2 and Section 4.2.4.3
Description of issue and why the EAG has identified it as important	As described in Issues 2, 3, 6, 7, 9, and 10, the EAG has serious concerns with the MAICs undertaken to estimate the relative treatment effect of epcoritamab on PFS (and OS) outcomes. The EAG considers the company's approach of jointly fitting survival curves unfit for purpose, particularly for the comparison of epcoritamab with Pola + BR and axi-cel, where the underlying PFS KM curves cross for the treatments. The same issues discussed in Issue 12 are applicable to PFS outcomes, where the company applied 2 different HRs to the epcoritamab PFS curve to estimate a Pola + BR PFS curve, and a single HR to estimate the PFS axi-cel curve. Furthermore, the EAG is concerned with the company's approach of assuming that the HR derived for OS outcomes is the same as the HR for PFS outcomes between epcoritamab and R-based CIT as the company's assumption relies on the OS gain for epcoritamab being proportionately the same as the PFS gain associated with the treatment. The company has not provided any evidence to justify this assumption. The EAG is concerned with the company's estimated PFS survival curves for epcoritamab given these provide a considerably bad visual fit to the end of the KM PFS data. Crucially, the EAG is concerned that the KM PFS data from EPCORE™ NHL-1 drops to [redacted] at 21 months, whereas the company's

base case extrapolations assume that a considerably high proportion of patients are progression-free in the epcoritamab arm at the same time point. The company's base case model assumes that at 24 months, about [redacted] of patients are progression-free in population A, for R-based CIT and Pola + BR, respectively; [redacted] of patients in population B are progression-free in the epcoritamab arm. Given the lack of evidence presented to substantiate the company's assumptions, the EAG asked the company to provide any evidence available to justify the proportion of progression-free patients on the epcoritamab arms of the model during clarification. The company reported that data from a more recent data-cut of EPCORE™ NHL-1 exist ([redacted]), which further support that the [redacted] PFS seen at 21 months is not representative of the treatment effect of epcoritamab. The company also mentioned that clinical expert opinion provided to the company estimated a "*most likely value*" for PFS to be "*a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively*".

The EAG notes that, while it might agree with the company's view that it is unlikely that all epcoritamab patients have progressed at 21 months, this does not provide any further information on what the plausible proportion of PFS patients is in that point in time, when there are no observed PFS data. The EAG notes that the proportion of patients assumed to be progression-free at 24 months in the company's base case model is above the range considered most likely plausible by the company's own experts for epcoritamab vs R-based CIT (population A) and for epcoritamab vs axi-cel (population B).

Overall, the EAG is concerned that the company's base case PFS epcoritamab curves are not robust enough to be considered in the cost-effectiveness model. The lack of observed data to substantiate what proportion of epcoritamab patients could be progression-free at 2 years; combined with the company's assumption that the proportion of patients in the PFS epcoritamab curves dictate the proportion of patients who enter LTR; and crucially; the EAG's clinical experts' view that progression-free epcoritamab patients should not be considered to enter LTR at 2 years after initiation of treatment (as discussed in Issue 15), mean that the company's approach to estimating PFS for epcoritamab appears to be fundamentally flawed.

The EAG considers that the relative effect of epcoritamab on PFS is overestimated for every comparison in the model:

1. The proportion of patients on R-based CIT entering LTR at 2 years might be underestimated based on the underestimated OS curve when compared to the observed SCHOLAR-1 OS data; and the proportion of epcoritamab patients entering LTR in this comparison is overestimated (and above what was deemed plausible by the company's clinical experts).
2. The proportion of patients on Pola + BR entering LTR at 2 years is considerably underestimated when compared to the observed PFS data from Sehn *et al*; even though the proportion of epcoritamab patients entering LTR in this comparison is plausible according to the company's clinical experts.
3. The proportion of patients on axi-cel entering LTR at 2 years might

	be a reasonable prediction of PFS for this treatment when compared to the underlying observed ZUMA-1 PFS data; with the main problem in this comparison being the overestimation of the PFS epcoritamab curve, according to the proportion deemed plausible by the company's clinical experts.
What alternative approach has the EAG suggested?	See recommendations given in Issues 2, 3, 6, 7, 9, and 10. The EAG recommends that the company independently fits PFS curves for each comparator and epcoritamab in the model (as requested by the EAG at the clarification stage). The EAG also recommends that the company includes a scenario analysis where the HR between the OS and PFS KM curves for epcoritamab for the unadjusted, DLBCL population, no prior CAR-T from EPCORE™ NHL-1 is used to estimate a PFS curve for R-based CIT, as requested by the EAG at the clarification stage. Currently, the EAG only has the company's clinical experts' advice on the plausibility of the proportion of patients in the PFS epcoritamab curve at 2 years. Nonetheless, this is unlikely to be robust enough to validate such a crucial parameter in the model. The EAG anticipates that the more mature PFS data cut which will be available in August might help inform the plausible proportion of patients in the PFS curve past 20 months in the model, and potentially allow the company to re-fitting PFS (and OS) curves for epcoritamab. Additionally, the EAG recommends that the company includes a scenario analysis in the model allowing for the removal of the LTR assumption in the model for epcoritamab only (i.e., allowing for the PFS curves for epcoritamab to be dictated by the parametric curves fitted to the more mature epcoritamab data).
What is the expected effect on the cost-effectiveness estimates?	If the fitted PFS comparator curves become more representative of the underlying KM data available for each comparator, the relative effect of epcoritamab on PFS will decrease, therefore, increasing the ICER for epcoritamab vs all comparators. In order to help understand the impact of reducing the proportion of LTR patients in the epcoritamab curves, the EAG has also conducted some exploratory analysis. Nonetheless, the EAG notes that these analyses are uncertain as the company's model lacks transparency and ease of manipulation, which made it impossible to remove the LTR assumption from the epcoritamab curve alone. This means that the EAG still had to assume that the PFS curves plateau at 2 years for epcoritamab, which the EAG considers to be a highly uncertain assumption. The EAG also had to fix the comparator PFS curves, as it considers these to already be potentially underestimated in the model (or to provide a reasonable prediction). Therefore, the EAG's approach indirectly changed the HRs used by the company to generate PFS curves. Even though the EAG notes that the MAIC HRs are fundamentally flawed in the company base case analysis, the EAG reiterates that this approach lacks methodological robustness and is only intended as an exploratory analysis of uncertainty. The EAG's exploratory analysis increased all the ICERs for epcoritamab.

What additional evidence or analyses might help to resolve this key issue?	The company should provide the additional analysis requested above.

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; UK, United Kingdom.

Table 15. Issue 14. Estimation of time to treatment discontinuation in the model

Report section	Section 4.2.4.5 and Section 4.2.4.6
Description of issue and why the EAG has identified it as important	The EAG is concerned with the company's choice of models to fit the TTD KM data for epcoritamab, particularly with the discrepancy in the rationale for choosing the TTD distributions for population A and population B (i.e., the criterion to have the same distribution as that used for the epcoritamab PFS curves). The EAG notes that after 2 years in the model, the TTD and the PFS curves all take roughly the same shape (regardless of the underlying distribution used to model the curves) given that patients in the PFS and TTD curve enter LTR and not only are assumed to not progress but also start incurring the same probability of death (that of the general population mortality increased by the SMR). Furthermore, for population B, the company chose the Gompertz distribution to model TTD for epcoritamab and a generalised gamma to model PFS for epcoritamab. The EAG accepts that as a result of conducting 3 different MAICs and adjusting the epcoritamab outcomes to 3 different studies for each comparator, all epcoritamab TTD (and OS and PFS) curves will be different. Nonetheless, there is a lack of consistency in the company's approach in accepting that TTD and PFS curves for epcoritamab might (or might not) be the same; therefore, implicitly assuming different levels of toxicity for epcoritamab in each of the comparator analysis. Finally, the EAG notes that company's assumption for R-based CIT and Pola + BR of assuming that patients never discontinue due to toxicity is highly unlikely to be plausible, considering the toxicity of these treatments. The EAG notes that the company's assumption biases the cost-effectiveness results in favour of epcoritamab.
What alternative approach has the EAG suggested?	The EAG anticipates that the more mature TTD and PFS data might help to better inform the relationship between PFS and TTD fitted curves. Furthermore, the EAG recommends that the company conducts the fully adjusted MAICs (see recommendations given in Issues 2, 3, 6, 7, 9, and 10) which will add robustness to the adjusted PFS and TTD curves for epcoritamab. The EAG also recommends that the company reconsiders the assumption that TTD for R-based CIT and Pola + BR is the same as PFS.
What is the expected effect on the cost-effectiveness estimates?	It is not possible to predict the impact that more mature PFS and TTD data, and fully adjusted MAIC curves will have on the cost-effectiveness results. If the company varies the assumption that TTD for R-based CIT and Pola + BR is the same as PFS, then the costs associated with these treatments will decrease in the model, therefor, increasing the ICER for epcoritamab.
What additional evidence or	The company should provide the additional analysis requested above.

analyses might help to resolve this key issue?	

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; TTD: time to treatment discontinuation; OS, overall survival; PFS, progression-free survival; UK, United Kingdom.

Table 16. Issue 15. Utilities used in the model

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The population used to derive utilities for population A does not seem to have been limited in the same way as the subgroup of patients used in the effectiveness analysis, given that the company did not mention CAR-T eligibility for this population in the utility analysis. Therefore, the EAG assumes that the company included all patients who had DLBCL and had received no prior CAR-T treatment. As discussed in Issue 6, the EAG is unsure whether the data used in MAICs for population A were reflective of a group ineligible for intensive treatments; however, the EAG's preference is that the populations used to derive the utility and the effectiveness estimates are the same. For population B, the EAG is satisfied with the use of the LBCL population (instead of the DBCL population); however, would have preferred to have restricted the population further to no prior CAR-T, eligible to receive future CAR-T.
What alternative approach has the EAG suggested?	The EAG recommends that the company provides the analysis requested in Issue 6 for the MAIC and that the utility estimates used for population A in the model are derived from the respective population (i.e., patients not previously treated with CAR-T and ineligible to receive CAR-T subsequently). For population B, the EAG recommends that the company provides the estimates utilities in the DBCL, no prior CAR-T, eligible to receive future CAR-T population.
What is the expected effect on the cost-effectiveness estimates?	It is not possible to predict how the utility estimates will be impacted compared to those used in the company's base case.
What additional evidence or analyses might help to resolve this key issue?	The company should provide the additional analysis requested above.

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; TTD: time to treatment discontinuation; OS, overall survival; PFS, progression-free survival; UK, United Kingdom.

Table 17. Issue 16. Treatment and administration costs of comparators in the model

Report section	Section 4.2.6.1 and Section 4.2.6.2
Description of issue and why the EAG has identified it as important	The EAG considers the company's approach to costing the administration of chemotherapies in the R-based CIT and the Pola + BR treatment combinations to be inconsistent. For Pola + BR, the company used the SB143 and the SB15Z codes to reflect the delivery of first and subsequent

	chemotherapies (£502.74 and £358.62, respectively); however, the company applied an administration cost of £5,660 (£5,063 updated with inflation) for R-based CIT. In TA559, where the company states the administration cost for R-based CIT was taken from, the company costed the administration of a basket to BSC treatments (of which R-based CIT was part) at £5,063, based on the hospital admission of nonelective long-stay HRGs for malignant lymphoma. The EAG in TA559 criticised the company's approach and noted this cost should be replaced with the SB14Z and the SB15Z code to reflect the delivery of first and subsequent chemotherapies. Therefore, the EAG considers that the costs of administrating R-based CIT should be based on the SB14Z and the SB15Z cost codes. The EAG notes that the company assumed 8 cycles of treatment with R-based CIT in the model. Nonetheless, the EAG's clinical experts explained that several centres in the UK only allow a maximum of 6 cycles of treatment with R-based CIT. Therefore, the EAG has conducted a scenario analysis in the model where a maximum of 6 cycles of R-based CIT is given. Finally, the EAG disagrees with the company's addition of monitoring costs to the axi-cel administration cost. The final appraisal determination document and the committee slides in TA872 (where the company sourced the administration costs for axi-cel) stated that, "*NHSE have accepted this* [£41,101] *as a total cost for the first 100 days and recommend NICE consider this in all ongoing CAR-T appraisals*". Therefore, the EAG conducted a scenario analysis where a total cost of £40,638 for the administration of axi-cel was used in the model ([£41,101 excluding the costs of CRS).
What alternative approach has the EAG suggested?	The EAG recommends that the company includes a scenario analysis where the costs of administrating R-based CIT are based on the SB14Z and the SB15Z codes for every cycle of treatment.
What is the expected effect on the cost-effectiveness estimates?	Due to the difficulty in navigating the cost calculations in the company's model and time restraints, the EAG could not conduct a scenario analysis where the costs of administrating R-based CIT according to the SB14Z and the SB15Z were applied every cycle. Instead, the EAG conducted a simplified analysis, which increased the ICER for epcoritamab vs R-based CIT by approximately £1,000 per QALY gained. The EAG conducted a scenario analysis where treatment with R-based CIT was reduced to 6 cycles and the impact on the ICER was minimal. The EAG conducted a scenario analysis where the company's monitoring costs for axi-cel were removed from the model which reduced the total costs associated with axi-cel by approximately £1,500.
What additional evidence or analyses might help to resolve this key issue?	The EAG is unsure why all costs in the model were inflated to the 2021 cost year and recommends that the company inflates all relevant costs to the most recent cost year (as per the list of recommendations in Section 1.4 of the EAG report).

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; TTD: time to treatment discontinuation; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; UK, United Kingdom.

Table 18. Issue 17. Subsequent treatments in the model

Report section	Section 4.2.6.3 and Section 4.2.6.4
Description of issue and why the EAG has identified it as important	The EAG's clinical experts explained that 3rd line treatments influence patents' eligibility to receive subsequent treatments, therefore rendering the company's assumption of the same subsequent treatments being received in both populations A and B implausible. For example, patients previously treated with a rituximab-based combination should receive subsequent palliative chemotherapy (and not a subsequent rituximab combination as assumed by the company). Additionally, patients previously treated with epcoritamab would have differing future treatments depending on if they were eligible to receive CAR-T therapy (i.e., if patients were part of population A or B). The EAG finds the company's costing of administration for subsequent events in the model to be inconsistent with the administration costs applied for 3rd line treatments. Even though it is not clear in the model (or reported in the CS), the EAG investigated the model and concluded that an administration cost for all subsequent treatments was applied, and assumed to be £358.62, the cost of a subsequent administration of chemotherapy based on the SB15Z code.
What alternative approach has the EAG suggested?	The EAG recommends that the company includes a scenario analysis in the model where subsequent treatments are informed by the proportion of patients receiving subsequent treatments as suggested by the EAG's clinical experts (and outlined in Table 59 of the EAG report). The EAG requests that the company clarifies and justifies its approach to estimating administration costs for subsequent treatments.
What is the expected effect on the cost-effectiveness estimates?	The EAG conducted the scenario analysis where subsequent treatments were informed by the EAG's clinical experts; however, due to time constraints, for the R-based CIT and Pola + BR patients receiving subsequent palliative chemotherapy, the EAG undertook the simplifying assumption of removing the costs of rituximab from the R-based CIT combination used in the model as a subsequent treatment. It is likely that these patients would get different chemotherapies from GemOx, therefore, the EAG recommends that the company conducts the scenario analysis accordingly. The EAG's scenario analysis led to a large increase in the final ICER for epcoritamab vs R-based CIT and Pola + BR, and a large decrease in the total costs associated with axi-cel in the analysis (even though the ICER for this comparison remained dominant in favour of epcoritamab).
What additional evidence or analyses might help to resolve this key issue?	The company should provide the additional analysis requested above.

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; TTD: time to treatment discontinuation; OS, overall survival; PFS, progression-free survival; UK, United Kingdom.

Table 19. Issue 18. Disease follow-up costs in the model

Report section	Section 4.2.6.5 and Section 4.2.6.6

Description of issue and why the EAG has identified it as important	The EAG has several concerns with the company's implementation of follow-up costs in the model. Firstly, investigations of the company's model led the EAG to the conclusion that for R-based CIT; Pola + BR; and axi-cel; all patients incurred the "PFS on-treatment" for the initial 2 years of the model, after which progression-free patients started incurring no costs as these were considered to be in LTR. This is inconsistent with the company's approach to estimating follow-up costs for epcoritamab where patients incurred a "PFS off-treatment" follow-up cost after [redacted] months in the model. The company's approach is biased in favour of epcoritamab and is unjustified, as patients who finished their comparator treatments (before 2 years) and were in the PFS state should have incurred the "PFS off-treatment" lower costs. Furthermore, the EAG disagrees with the company's assumption that after [redacted] months in the PFS state epcoritamab patients would move to the off-treatment resource as assumed in the model. The company justified this approach based on it reflecting median PFS for patients who achieved partial response (PR) or complete response (CR) in the DLBCL population of EPCORE™ NHL-1. The EAG does not understand how median PFS would dictate resource use for patients on epcoritamab treatment – the EAG's clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued, meaning that the resource use estimated by the company for epcoritamab for the progression-free, on treatment period should be observed for as long as treatment is given in the model. However, in contrast to this, epcoritamab patients in the model are assumed to incur less resource uses after what seems a poorly-defined threshold of [redacted] months and crucially, patients stop incurring any follow-up costs when entering LTR even though they would continue to be on treatment. The EAG notes that the company's base case approach is biased in favour of epcoritamab and artificially underestimates the disease management costs associated with the treatment, without a plausible clinical explanation. The EAG is also concerned that some resources lack clarity around what was included in their costs leading to potentially double counting of some services. This is the case for residential care, day care, home care and hospice care. For example, the PSSRU22 source used by the company to cost day care, included 1 working hour of a band 7 nurse. However, the company also included time with a specialist nurse; district nurse; and nurse time separately. During clarification, the company stated that the district nurse resource use is considered to be community-based health care, while the specialist nurse and nurse resource use are hospital-based health care. However, the cost associated with the district nurse, specialist nurse and nurse time are all based on the National Schedule of Reference Costs 2019-20 (N02AF), in line with previous NICE TAs in R/R LBCL. The EAG is unclear how this avoids double counting of resources in the model. The company's justification for other queries about double counting of resources in the model was generally that, "*all cost categories and cost sources used in the model are aligned with previous NICE appraisals in R/R LBCL (such as TA649, TA306 and TA559).*" and, "*TA649 does not include a detailed explanation of what is included in these two resource use categories, but they are both part of professional and social services*.". The EAG is not satisfied that the cost sources used to cost resource use in the model are not double counting resources in the model.

What alternative approach has the EAG suggested?	The company should allow R-based CIT; Pola + BR and axi-cel patients in the model to switch from the "PFS on-treatment" to the "PFS off-treatment" resource use in the model after finishing their treatment. The EAG requests that the company includes a scenario analysis where patients on treatment with epcoritamab experience the same resource use (that of the "PFS on-treatment" state) from cycle 0 to end of treatment in the model.
What is the expected effect on the cost-effectiveness estimates?	The EAG has conducted an exploratory analysis where R-based CIT; Pola + BR; and axi-cel patients incurred lower resource use costs before 2 years. Ideally, the EAG would have changed the company's assumption to reflect the "PFS on-treatment" for the duration of treatment with each comparator. However, due to time restraints and the difficulty in making changes to the company's model separately for each comparator (to reflect different treatment durations), the EAG had to run a simplified approach where all patients in the comparator treatment were assumed to incur the "PFS off-treatment" from the beginning of the model. This assumption is reasonable for axi-cel (given this is a one-off treatment), although for R-based CIT and Pola + BR, ideally patients would have incurred "PFS on-treatment" costs for 8 (or 6) and 4 doses of treatment, respectively. The ICER increased substantially for epcoritamab vs R-based CIT and Pola + BR, and the total costs associated with axi-cel in the analysis decreased by more than £10,000 (even though the ICER for this comparison remained dominant in favour of epcoritamab). The EAG conducted an exploratory analysis where the follow-up costs ("PFS on-treatment") were incurred for epcoritamab while patients were on treatment. Due to lack of transparency in the company's model, the EAG cannot ensure that the implementation of this assumption in the model does not contain errors. This assumption is the key driver of the economic results, leading to an increase in the ICER of over £20,000 per QALY gained for the comparison with R-based CIT; over £50,000 per QALY gained for the comparison with Pola + BR; and changing the ICER for epcoritamab vs axi-cel from dominant to £15,432 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The company should provide the additional analysis requested above.

Abbreviations: R-based CIT, rituximab-based chemoimmunotherapy; axi-cel, axicabtagene ciloleucel; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; EAG, External Assessment Group; HR: hazard ratio; PH: proportional hazards; KM: Kaplan-Meier; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusting indirect comparison; NHL, Non-Hodgkin lymphoma; TTD: time to treatment discontinuation; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; UK, United Kingdom.

1.4 Summary of EAG's preferred assumptions and resulting ICER

As explained throughout the report, the EAG considers that the cost-effectiveness of epcoritamab is overestimated for every comparison in the model and that the company's base case model is fundamentally flawed. Due to this, the analyses conducted by the EAG are meant to help depict the potential impact of the EAG's changes to the model (with the main concern being around reducing

the proportion of LTR patients in the epcoritamab curves); however, they do not provide ICERs robust enough to become alternative base case results.

For the same reason, and due to there being three comparator treatments, which required the EAG to have three separate model versions (due to the already discussed lack of flexibility in the company's model to change assumption separately for each comparator), the EAG provided the impact of the changes made to the model cumulatively (i.e., the EAG did not implement each change to the model separately, but instead presents the impact of changing assumptions in a cumulative way). At the end of this section the EAG lists all the recommended changes to the company's model to be conducted at technical engagement (TE) that would help mitigate the uncertainty in the company's model results.

The exploratory analysis conducted by the EAG are explained throughout the report. These consisted of the following:

1. For population A, for the comparison of epcoritamab with R-based CIT the EAG used the company's lognormal model for progression-free survival (PFS), which was the second best-fitting model according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for epcoritamab. The lognormal curve provided a proportion of patients in remission at 2 years of approximately [redacted] (instead of approximately [redacted] as in the company's base case model).
2. For population B, the EAG chose the company's lognormal model, which the EAG acknowledges was the third best-fitting model for PFS for epcoritamab according to AIC and BIC statistics. Nonetheless, the lognormal curve provided a proportion of patients in remission at 2 years below [redacted] and is more aligned with the company's clinical experts view of this proportion being between 30–35%.
3. The EAG has conducted a scenario analysis where the best-fitting Gompertz curve was used to model time to treatment discontinuation (TTD) for epcoritamab vs R-based CIT.
4. The EAG conducted a scenario analysis using the Gompertz model, which was the fourth best-fitting model according to AIC and BIC statistics and provided a better visual fit to the Kaplan-Meier (KM) curve up to month 15 for epcoritamab vs Pola + BR.
5. A total administration cost of £41,101 for axi-cel was used in the model, excluding the costs of cytokine release syndrome (CRS), therefore totalling £40,638.
6. Assuming a maximum of 6 cycles of R-based CIT (instead of 8).

7. The EAG conducted a simplified analysis where the total administration cost of R-based CIT of £5,063 was replaced by £2,297 (1 first administration of chemotherapy followed by 5 rounds of subsequent administrations).
8. The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model (as per Table 59 in the report). For the R-based CIT patients receiving subsequent palliative chemotherapy, the EAG undertook the simplifying assumption of removing the costs of rituximab from the subsequent R-based CIT combination used in the model.
9. The EAG has conducted an exploratory analysis where R-based CIT; Pola + BR; and axi-cel patients incurred the "PFS off-treatment" costs before 2 years in the model, while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years.
10. The EAG conducted an exploratory analysis to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS and assumed that epcoritamab patients stay on the "PFS on-treatment" follow-up costs while on treatment.

For population A, for the comparison to R-based CIT, the EAG's exploratory ICER amounts to £47,454 per QALY gained, with a severity modifier of 1.2 applied (Table 20). Given the mean age of population A and the sex distribution at baseline ([redacted] respectively, in the company's base case), and the total QALY gain for R-based CIT in the EAG's final exploratory ICER of [redacted] QALYs, the severity modifier of 1.2 is applicable to the QALY gain generated in the analysis.

For population A, for the comparison to Pola + BR, the EAG's exploratory ICER amounts to £101,875 per QALY gained, with no severity modifier applied (Table 21). Given the mean age of population A and the sex distribution at baseline ([redacted] respectively, in the company's base case), and the total QALY gain for Pola + BR in the EAG's final exploratory ICER of [redacted] QALYs, no severity modifier is applicable to the QALY gain generated in the analysis.

For population B, the EAG's exploratory ICER amounts to £15,432 per QALY gained, with no severity modifier applied (Table 22). Given the mean age of population A and the sex distribution at baseline ([redacted] respectively, in the company's base case), and the total QALY gain for R-based CIT in the EAG's final exploratory ICER of [redacted] QALYs, no severity modifier is applicable to the QALY gain generated in the analysis. The EAG notes that axi-cel is subject to a confidential Patient Access Scheme (PAS), which is not included in the results presented in the EAG report.

The EAG notes that the age and sex distribution at baseline in the company's model was derived from the matching-adjusting indirect comparison (MAIC)-adjusted populations. Therefore, if the

MAICs are updated as suggested by the EAG in Section 1.3, it is likely that these parameters will change.

Table 20. Results of the EAG's exploratory analyses – R-based CIT

	Results per patient	Epcoritamab	R-based CIT	Incremental value	Incremental value with severity modifier
0	Company's corrected base case				
	Total costs (£)	[redacted]	£82,608	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£18,516	£15,430
1	Using company's lognormal model for PFS				
	Total costs (£)	[redacted]	£82,608	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£23,431	£19,526
3	Using the Gompertz curve to model TTD				
	Total costs (£)	[redacted]	£82,608	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£22,797	£18,998
6	Assuming a maximum of 6 cycles of R-based CIT (instead of 8)				
	Total costs (£)	[redacted]	£82,305	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£22,874	£19,062
7	The EAG conducted a simplified analysis where the total administration cost of R-based CIT of £5,063 was replaced by £2,297 (1 first administration of chemotherapy followed by 5 rounds of subsequent administrations).				
	Total costs (£)	[redacted]	£78,942	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£23,732	£19,777
8	The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.				
	Total costs (£)	[redacted]	£68,579	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£29,554	£24,629
9	R-based CIT patients incurred the "PFS off-treatment" costs before 2 years in the model while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years				
	Total costs (£)	[redacted]	£63,944	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£33,675	£28,063
10	The EAG conducted an exploratory analysis as a proxy to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS.				
	Total costs (£)	[redacted]	£63,944	[redacted]	[redacted]

	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£56,945	£47,454

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

Table 21. Results of the EAG's exploratory analyses – Pola + BR

	Results per patient	Epcoritamab	Pola + BR	Incremental value
0	Company's corrected base case			
	Total costs (£)	[redacted]	£146,295	[redacted]
	QALYs	[redacted]	2.05	[redacted]
	ICER (£/QALY)	-	-	£8,355
4	Using the Gompertz curve to model TTD			
	Total costs (£)	[redacted]	£137,552	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£7,580
8	The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.			
	Total costs (£)	[redacted]	£136,527	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£21,197
9	Pola + BR patients incurred the "PFS off-treatment" costs before 2 years in the model while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years			
	Total costs (£)	[redacted]	£123,383	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£43,102
10	The EAG conducted an exploratory analysis as a proxy to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS.			
	Total costs (£)	[redacted]	£123,383	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£101,875

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.

Table 22. Results of the EAG's exploratory analyses – axi-cel

	Results per patient	Epcoritamab	Axi-cel	Incremental value
0	Company's corrected base case			
	Total costs (£)	[redacted]	£369,767	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	8.536
2	Using company's lognormal model for PFS			

	Total costs (£)	[redacted]	£369,767	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	7.706
5	A total administration cost of £41,101 for axi-cel was used in the model, excluding the costs of CRS, therefore totalling £40,638.			
	Total costs (£)	[redacted]	£368,278	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	7.657
7	The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.			
	Total costs (£)	[redacted]	£363,470	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	5.290
9	Axi-cel patients incurred the "PFS off-treatment" costs before 2 years in the model while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years			
	Total costs (£)	[redacted]	£350,927	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	4.407
10	The EAG conducted an exploratory analysis as a proxy to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS.			
	Total costs (£)	[redacted]	£350,927	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	£15,432
	NHB	-	-	0.479

Abbreviations: axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year.

Modelling errors identified and corrected by the EAG are described in Section 6.1.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of epcoritamab ([redacted]; AbbVie) in the treatment of relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after 2 or more systemic treatments. The term LBCL in the company submission (CS) refers to diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B (FL Gr 3B). The company's anticipated marketing authorisation for this treatment, which is expected in [redacted], covers [redacted].

2.2 Background

Within Section B.1 of the CS, the company provides an overview of:

- epcoritamab, including its mechanism of action, indications, dose and method of administration (Section B.1.2 of the CS);
- LBCL and the various subtypes included in the CS (DLBCL, HGBCL, PMBCL, and Fl Gr 3B), including diagnosis and classification, clinical presentation, epidemiology, disease burden, and disease management (Section B.1.3 of the CS).

In this section, the External Assessment Group (EAG) focuses mostly on areas that were commented on by the EAG's clinical experts. The company's description of LBCL within the CS in terms of diagnosis, presentation, epidemiology, and disease burden is considered to be accurate by the EAG's clinical experts. The treatment pathway is also considered largely accurate but potential changes based on a new Cancer Drugs Fund (CDF) recommendation are noted, which is discussed in Section 2.2.1 below. For full details provided by the company, see Section B.1 of the CS.

The EAG's clinical experts note that R/R LBCL remains a very challenging cancer to treat and that at third line + (3L+), many are ineligible for chimeric antigen receptor T-cell (CAR-T) treatments or deteriorate and become ineligible while waiting for CAR-T cells to be manufactured. Epcoritamab being an "off-the-shelf" product, with no manufacturing wait time, is described by the EAG's clinical experts as being an advantage in comparison with CAR-T treatments. The potential for use in a homecare setting and reduction of hospital resource use is also noted, but epcoritamab is a non-finite treatment; that is, it is given until progression or intolerance unlike other treatments such as

CAR-T, polatuzumab vedotin (Pola) with bendamustine and rituximab (Pola + BR), and rituximab-based chemoimmunotherapy (R-based CIT). While the EAG's clinical experts highlight that the EPCORE™ NHL-1 trial appears to demonstrate efficacy in a prognostically poor population and that the results are promising, some concerns about the immaturity of data at this point in time were raised.

The EAG's clinical experts agree that treatment pathways for the various types of LBCL included in this submission are largely the same at 3L+; however, this could change for PMBCL as it is not covered by the CDF recommendation for axicabtagene ciloleucel (axi-cel) at second line in DLBCL (see Section 2.2.1 below).[1] In terms of prognosis, the clinical experts consider it to be largely similar across subtypes but note that historically transformed lymphomas (e.g. indolent lymphoma transformed to DLBCL/HGBCL) have been excluded from clinical trials due to potentially poorer prognosis. This is considered to be much improved within the rituximab era and outcomes are considered to be equivalent. In addition, at 3L+, historically PMBCL may have been associated with a slightly worse prognosis than others as they tend not to be salvaged by chemotherapy regimens and require novel agents.

2.2.1 Position of epcoritamab in the UK treatment pathway

A summary of the treatment pathway described by the company is presented in Figure 1 below. Of relevance to this appraisal is the 3L+ section, which outlines the appropriate comparators for epcoritamab at 3L+. Three comparators are subsequently included in the CS and the use of each is based on eligibility for intensive therapy and history of Pola use at earlier treatment lines. The EAG's clinical experts consider that this pathway largely captures the pathway at the time the CS was submitted but note that a recent CDF recommendation may change this, which is discussed later in this section.

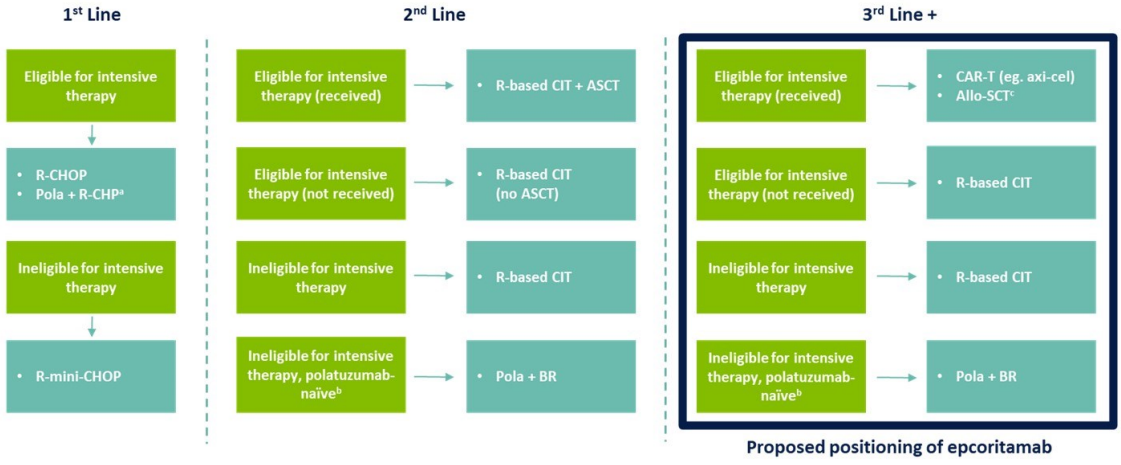
The company's primary focus is on comparisons vs axi-cel for those eligible for intensive treatments and R-based CIT for those that are not eligible. An additional comparison vs Pola + BR is presented in the CS for those that have not previously received Pola in an earlier treatment line; this was not considered to be a major comparison by the company given first-line use of Pola and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone (Pola + R-CHP) is becoming more frequent and use of Pola + BR at third line is subsequently expected to reduce. The EAG's clinical experts agreed with this statement but consider it is still a useful comparison to include given it will still be used in a proportion of patients at 3L+; for example, while this may also apply to patients with any type of LBCL, in particular, Pola + R-CHP is not used for those with PMBCL

as a first line option and so these patients would retain it as an option at 3L. In addition, DLBCL patients with an IPI score between 0 and 1 are not eligible for Pola + R-CHP first line, as an IPI score between 2 and 5 is required.[2]

The EAG's clinical experts note that palliation may also be used as opposed to R-based CIT in those ineligible for CAR-T, but that this would only apply for a small group of very frail patients who had either previously failed Pola + BR or are too unfit or unwilling to have any further chemotherapy at all. Therefore, the EAG considers the inclusion of R-based CIT only for this subgroup is reasonable.

The EAG's clinical experts agreed that the use of allogenic stem cell transplant (Allo-SCT) is rare at 3L+ and note that the current evidence base indicates that outcomes of this treatment are not promising, with high mortality/morbidity rates. In addition, the company states there is regional variation in access to CAR-T therapies, due to a limited number of CAR-T centres and apheresis slots, resulting in some patients being unable to access treatment with CAR-T therapies. While the EAG's clinical experts note that this is possible, they also note that this is becoming less of an issue as more centres are opening. The EAG's clinical experts agreed with the company in terms of the time required for CAR-T manufacture being a limitation of this treatment currently, given patients can deteriorate before the treatment is ready and become ineligible for the treatment.

Figure 1. Company's summary of the current clinical pathway of patients with LBCL in the UK, including the proposed positioning of epcoritamab (reproduced from Figure 2 of the CS)[3, 4]



[a]Feedback from clinical experts indicated that patients would receive Pola + R-CHP at the first line; [b]With the introduction of Pola-R-CHP as a first-line treatment for DLBCL, the proportion of newly diagnosed patients entering the treatment pathway who receive Pola + BR in the second or third line is expected to fall below 20% over the next 12 months and to as low as 5% in 24 months. Based on market share estimates included in the budget impact analysis alongside this submission, the market share of Pola + BR is anticipated to fall to [redacted] in five years; [c]Clinical experts stated that allo-SCT has minimal use at third line in UK clinical practice.
Abbreviations: Allo-SCT, allogenic stem cell transplantation; ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; Pola + BR, polatuzumab vedotin in combination with bendamustine plus rituximab; Pola + R-CHP, polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone; R, rituximab; R-CHOP, rituximab in combination with cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; UK, United Kingdom.

The EAG's clinical experts highlight that the recent recommendation of axi-cel within the CDF as a second-line option for a subset of DLBCL patients (GID-TA10580) is likely to change practice in terms of treatments used 3L+ and comparators relevant for this appraisal.[1]

National Institute for Health and Care Excellence (NICE) guidance for axi-cel, which is not specific to the CDF, currently positions it at 3L+ for those with DLBCL or PMBCL that are eligible for CAR-T treatments, and it is included as a comparator for epcoritamab at 3L+ in the CS.[5] The EAG's clinical experts estimate that this CDF recommendation (which applies to those where autologous stem cell transplant [ASCT] is suitable and where they have relapsed within 12 months after, or are refractory to, first-line chemoimmunotherapy [CIT]) means that 3L use of axi-cel would reduce by ~50% in those eligible for CAR-T. The EAG's clinical experts anticipate that this would leave a gap in terms of standard of care for this group at 3L and that options would primarily be a clinical trial or palliative care. While intensive R-based CIT with autologous stem cell transplant was also mentioned as an option for those fit enough, the EAG's clinical experts also noted that there is concern about how successful a stem cell harvest would be following CAR-T and also how effective intensive chemotherapy would be in this very high-risk group.

The EAG notes these comments and the potential impact on suitable comparators at 3L+ for the CAR-T eligible subgroup; however, as this recommendation is solely within the CDF and the NICE manual for health technology evaluations states in Section 2.2.15 that, "*technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators*", the EAG considers the treatment pathway described by the company in the CS (and summarised in Figure 1 above) to be appropriate, as is the inclusion of only axi-cel as a 3L+ comparator for those eligible for CAR-T treatments.[6]

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE,[7] together with the company's rationale for any deviation from this, is provided in Table 23 below. Key differences between the decision problem addressed in the CS and the NICE final scope are discussed in greater detail in the sections that follow this table, but the EAG notes that the main concerns are around the applicability of populations analysed in indirect comparisons to the full decision problem population, particularly as those with prior CAR-T treatments have been excluded from these analyses.

Table 23. Summary of decision problem

	Final scope issued by NICE[7]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with R/R LBCL who have had 2 or more systemic treatments	[redacted]	N/A	The EAG considers that the main trial in the CS (EPCORE™ NHL-1, aNHL cohort) matches the population described in the final scope. Clinical expert feedback suggests patient characteristics for the whole LBCL population in this study are a reasonable reflection of those in UK practice at 3L+ but that the trial population may have a slightly worse prognosis than would be expected in practice. Inclusion criteria for EPCORE™ NHL-1 limit inclusion only to those with prior ASCT failure (or ineligibility for it) and with ECOG scores 0-2; while not thought to be major issues, they may be important factors to consider in terms of the setting of any recommendations made. The EAG notes that for indirect comparisons performed via MAICs (see Sections 2.3.1.2 and 3.4), smaller subsets of the EPCORE™ NHL-1 population have been utilised and population characteristics have been adjusted according to the comparator trials. The EAG acknowledges this was required to perform comparisons but notes potential limitations of these

				population amendments in terms of applicability to the whole decision problem population. See Section 2.3.1 below for further discussion.
Intervention	Epcoritamab	Epcoritamab, administered via subcutaneous injection	N/A	The EAG considers that the intervention in the CS and EPCORE™ NHL-1 study matches that in the final scope. Concomitant medications used in EPCORE™ NHL-1 are considered standard by the EAG's clinical experts. See Section 2.3.1.1 below for further discussion.
Comparators	Established clinical management without epcoritamab including but not limited to: • Salvage chemotherapy with rituximab: ○ DHAP (dexamethasone, cytarabine, cisplatin) ○ ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ○ GDP (gemcitabine, dexamethasone, cisplatin)	The comparators considered in this submission include: • R-based CIT • CAR-T therapy (axicabtagene ciloleucel)	The comparators considered within this submission align with current UK clinical practice. Based on consultation with UK clinical experts, pixantrone monotherapy is not used in UK clinical practice due to a lack of efficacy and high toxicity. This is supported by the recent appraisal by NICE of tafasitamab with lenalidomide [ID3795],[8] in	The EAG considers comparisons vs R-based CIT, axicabtagene cilloleucel and Pola + BR to be important. The EAG's clinical experts agreed that pixantrone is not used in UK practice and the EAG agree with the exclusion of tafasitamab + lenalidomide given it is not currently recommended by NICE (now NICE TA883).[8] The EAG notes that in the CS, including the economic model, R-based CIT is considered to be R-GemOx, which the EAG's clinical experts considered to be a reasonable proxy. The type of R-based CIT

	○ GEMOX (gemcitabine and oxaliplatin) ○ ICE (ifosfamide, carboplatin, etoposide) ○ IVE (ifosfamide, etoposide, epirubicin) • Pixantrone • Pola + BR (only when stem cell transplantation is not suitable) • Axicabtagene ciloleucel for treating refractory or relapsed DLBCL after 2 or more systemic therapies (subject to NICE appraisal process) • Tafasitamab with lenalidomide (only when stem cell transplantation is unsuitable and subject to NICE appraisal process)		which clinical experts and NHSEI confirmed that pixantrone is not prescribed due to a lack of efficacy and high toxicity. As such, pixantrone is not considered a relevant comparator in this submission. Tafasitamab with lenalidomide is not recommended by NICE following its appraisal and therefore is not yet routinely used in UK clinical practice.[8] As such, it is not considered a relevant comparator in this submission. Pola + BR is recommended by NICE as a treatment option for R/R DLBCL. However, following the NICE recommendation of Pola + R-CHP for untreated DLBCL in February 2023, UK clinicians stated that Pola + BR will no longer be used for the majority of patients who have previously	used in the comparator trial for this comparison (SCHOLAR-1) is unclear. The EAG notes that suitable comparators at 3L+ for this appraisal are based on the treatment pathway prior to the CDF recommendation of axicabtagene ciloleucel at second-line in DLBCL (see Section 2.2.1).[1] See Section 2.3.3 below for further discussion.

			received polatuzumab as a component of frontline treatment.[2, 4] As such, Pola + BR is not considered a relevant comparator in this submission but has been considered in a scenario analysis for completeness.	
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rates • AEs of treatment • HRQoL • ToT	The outcome measures to be considered include: • OS • PFS • Response rates (including ORR, CR, PR and DOR) • AEs of treatment • HRQoL • TTD • TTNT	All outcomes requested in the final scope are presented, with additional outcomes that are important to demonstrate the benefits of epcoritamab.	The EAG considers that the outcomes described in the CS match those in the final scope. Outcomes informing the model are OS, PFS, TTD, AEs, and HRQoL utility data. The EAG's clinical experts consider that all of the important adverse events have been considered in the economic model. See Section 2.3.4 below for further discussion.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and PSS over a lifetime time horizon. Cost-effectiveness was expressed based on incremental cost per QALY, as per the NICE reference case.	N/A	N/A

	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	No subgroups of interest were listed in the NICE final scope.	N/A	N/A	While no subgroups of interest were listed in the NICE final scope, various subgrouping strategies are described by the company in the CS. Given analysis populations in MAICs excluded those with prior CAR-T treatments (see Sections 2.3.1.2 and 3.4), and results for OS and PFS in the CSR suggest [redacted] these subgroups as well as line of therapy subgroups, the EAG requested further outcome data be provided for these subgroups at clarification (CQs A1 and A2; see Sections 3.3.4.2 and 3.3.4.3).
Special considerations, including issues	No special considerations were listed in the NICE final scope.	N/A	N/A	N/A

related to equity or equality				

Abbreviations: 3L+, third line and beyond; AE, adverse event; AESI, adverse event of special interest; aNHL, aggressive non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; CIT, chemoimmunotherapy; CQ, clarification question; CR, complete response; CS, company submission; CSR, clinical study report; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EAG, External Assessment Group; FL Gr 3B, follicular lymphoma Grade 3B; HGBCL, high-grade B-cell lymphoma; HRQoL, health-related quality of life; LBCL, large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; N/A, not applicable; NHL, non-Hodgkin lymphoma; NHS, National Health Service; NHSEI, National Health Service England and National Health Service Improvement; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PR, partial response; PMBCL, primary mediastinal B-cell lymphoma; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; Pola + R-CHP, polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life year; R-based CIT, rituximab based chemoimmunotherapy; R-GemOx, rituximab with gemcitabine and oxaliplatin; R/R, relapsed or refractory; ToT, time on treatment; TTD, time to treatment discontinuation; TTNT, time to next treatment; UK, United Kingdom.

2.3.1 Population

2.3.1.1 Trial population

The EAG considers the aggressive non-Hodgkin lymphoma (aNHL) cohort in the EPCORE™ NHL-1 trial, which was used to provide epcoritamab data in the CS, to match the NICE final scope;[7] it included patients ≥18 years old with R/R LBCL (according to World Health Organization classification) that have had at least two lines of systemic antineoplastic therapy (including one anti-CD20 monoclonal antibody-containing treatment). The NICE final scope and population focused on in the NICE decision problem does not limit only to those that had failed (or were ineligible for) prior ASCT, whereas the EPCORE™ NHL-1 trial does. This criterion within EPCORE™ NHL-1 is not an issue in terms of applicability to UK practice, as the EAG's clinical experts note that in UK practice those eligible would usually have this as part of their second line treatment. Therefore, to reach 3L+ patients would usually have failed or been ineligible for ASCT at second line. However, the NICE decision problem does not specify a requirement for prior ASCT failure or ineligibility for ASCT, which may mean it is broader than the population covered by the trial. The EAG highlights that there is no evidence within EPCORE™ NHL-1 for those that had not previously failed ASCT but were eligible (if such a group exists in UK clinical practice at 3L+; see Key Issue 1 in Table 2).

The inclusion of patients with Eastern Cooperative Oncology Group (ECOG) performance scores between 0 and 2 is considered reasonable by the EAG's clinical experts; while they wouldn't want to rule out epcoritamab use in people with ECOG scores higher than this (and where the impairment is thought to be largely due to the lymphoma rather than other patient factors), they note that it would be less likely. The EAG notes that [redacted] provided by the company but that equally there is no evidence for its use in these groups within the EPCORE™ NHL-1 trial, which may be an important consideration in terms of wording if epcoritamab is recommended (see Key Issue 1 in Table 2).

Overall, the EAG's clinical experts consider the baseline characteristics for the whole LBCL population in EPCORE™ NHL-1 to be a reasonable reflection of UK clinical practice at 3L+; however, they note that they may be slightly worse in terms of prognostic factors than would be expected in clinical practice. For example, proportions with International Prognostic Index (IPI) ≥3 (52.2%), Ann Arbor disease stage IV ([redacted]), primary refractory disease (61.1%), and double or triple hit lymphomas ([redacted] based on central laboratory analysis, of [redacted] analysed) may be higher than expected.

Comments about it being a heavily pre-treated population and a high proportion with prior CAR-T treatments ([redacted]) were also noted, which again may indicate a slightly worse population in terms of prognosis. The EAG notes that the median number of prior lines of anti-lymphoma therapy was [redacted] (range 2 to 11), with 70.7% having epcoritamab as their fourth or later line treatment.

2.3.1.2 Populations used in indirect comparisons

In order to perform comparisons between epcoritamab and comparator treatments at 3L+, matching adjusted indirect comparisons (MAICs) vs various comparators were performed. Methods involved in these analyses, as well as results and limitations, are discussed further in Section 3.4. To ensure populations between EPCORE™ NHL-1 and comparator trials were more comparable, the populations analysed in EPCORE™ NHL-1 were first narrowed and then adjusted via propensity score methods to produce baseline characteristics that were a better reflection of the comparator trial. The results based on this adjusted population could then be used to inform epcoritamab efficacy in the relevant population. While in the company's original submission they did not use these adjusted results for all comparisons, after the clarification stage the model for each comparison used adjusted results as favoured by the EAG.

The EAG provides an outline below of the amendments made for four of the analyses presented in the CS, which includes comparisons vs R-based CIT (population A), axi-cel (population B) and Pola + BR (population A). Further details are provided in Section 3.4.

Epcoritamab vs R-based CIT in DLBCL patients ineligible for (or choose not to receive) intensive therapy – used as the updated base case in the company's model for population A

The company used the SCHOLAR-1 study as a source of outcome data for R-based CIT. After clarification (CQ A7), the company also adjusted the EPCORE™ NHL-1 population to this study in the MAIC.

Limitations of SCHOLAR-1 and adjusting to this study are described in Section 3.4.2.1; of particular importance to the population, the paper used to inform SCHOLAR-1 outcomes was a subset that had already been matched to ZUMA-1 (a CAR-T eligible group) and is, therefore, not reflective of a group ineligible for intensive treatments such as CAR-T.[9] This may, therefore, impact the applicability of this analysis to the target population for this comparator (those ineligible for or who choose not to receive intensive therapy). In addition, SCHOLAR-1 appears to only include those refractory to treatment; given the clinical experts highlight that refractoriness to treatments is generally

associated with worse prognosis, the omission of relapsed patients in SCHOLAR-1 may mean less favourable outcomes for R-based CIT are obtained from this population compared to a R/R population (see Section 3.4.2.1). Furthermore, while the company suggest that the population included in the paper they use for SCHOLAR-1 is limited to those with at least two prior treatments, the EAG could not confirm this and considers that it likely still includes a proportion with one prior treatment, which is out of line with the decision problem.[9] These factors are included as part of Key Issues 2 and 3 (Table 3 and Table 4) in terms of the suitability of the MAIC adjusted to SCHOLAR-1.

Other limitations include the exclusion of those with HGBCL, PMBCL or FL Gr 3B and those that had received prior CAR-T treatment from the EPCORE™ NHL-1 population analysed in the MAIC, which is further critiqued below and in Section 3.4.2.1. These points are covered as part of Key Issues 2 and 5 (Table 3 and Table 6) respectively.

In the company's model, therefore, the epcoritamab population included the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 adjusted to the SCHOLAR-1 population through an MAIC, while the R-based CIT population reflected the unadjusted SCHOLAR-1 trial data.

As noted above in Section 2.2.1, treatment pathways for DLBCL and other types of LBCL are generally considered to be the same currently. While some potential differences in terms of prognosis between DLBCL and other types of LBCL were mentioned by the EAG's clinical experts, these are not thought to be substantial. Results for epcoritamab discussed in Section 3.3.4.1 demonstrate that [redacted] based on type of LBCL, [redacted] given their rarity in the trial and in UK practice. For this reason, while it would be preferable to include the full LBCL population to capture the population of interest as accurately as possible, the EAG accepts that exclusion of non-DLBCL may be required to improve the comparability of trials used in MAICs. This is considered a limitation of the analyses rather than a major flaw. However, as noted in Section 3.4.2.1 and in Key Issue 2 (Table 3), it is unclear if limiting to DLBCL was necessary for this particular MAIC and the uncertainty introduced as a result of this is unclear.

In terms of excluding those with prior CAR-T treatment, the EAG and the experts it consulted consider that this brings the population in line with those receiving 3L treatment in the UK (as, outside of the CDF, axi-cel is currently an option at 3L and patients would not be expected to receive it earlier than this) or those who were not eligible for CAR-T at 3L. However, given that axi-cel is a 3L

option, the EAG considers that this exclusion may affect the applicability of these analyses to later therapy lines in UK practice (fourth line and beyond), as some patients may be expected to have received CAR-T if eligible at the time. One of the EAG's clinical experts considered that being refractory or relapsed to CAR-T treatment, which is an intensive and novel treatment option, may mean they are also less likely to do well with bispecific antibodies such as epcoritamab. Results provided in the CS, CSR and response to clarification questions (CQs) A1 and A2 (discussed in Section 3.3.4.2) suggest [redacted], which may limit the applicability of these analyses to those with prior CAR-T treatment. Given when those with prior CAR-T use are removed from the analyses, a proportion with fourth line treatments and beyond remain in the analysis, the EAG considers this limitation to be specific to those with prior CAR-T use rather than any patient at 4L and beyond (see Key Issue 5, Table 6).

On reviewing baseline characteristics for DLBCL patients with no prior CAR-T (n=[redacted]; Table 26 of the CS, see Section 3.4.2.1) in EPCORE™ NHL-1 before adjustments to the comparator trial, the EAG notes that baseline characteristics for key prognostic factors are very similar to the overall LBCL population (see Tables 7-9 of the CS). However, the proportion with only two prior lines of therapy has [redacted] from 29.3% to [redacted], potentially reflecting the exclusion of those with prior CAR-T treatments (as it may have been a common 3L option in those eligible meaning the exclusion of these patients reduces the proportion left in the trial receiving epcoritamab as a fourth or later line treatment). The EAG is unsure whether the [redacted] analysed for epcoritamab in this MAIC represents a group ineligible for intensive treatments, which is the population the company state that the comparison vs R-based CIT would be applicable to; further clarification on this and, if some eligible for intensive treatments are included, exploration of the impact on the results of the MAIC and the economic model if the analysis was limited to those not eligible would help to address this uncertainty. This is included as key issue 6 (Table 7).

The population in SCHOLAR-1 appears to be better in terms of some prognostic factors (such as lower age and lower proportions with disease stage III-IV, IPI score ≥3 and primary refractory disease) compared to EPCORE™ NHL-1; while this may be appropriate given the EAG's clinical experts considered the EPCORE™ NHL-1 population to be worse prognostically vs UK clinical practice, the EAG is unsure if the extent of the differences are reasonable and whether the population is better than would be expected in clinical practice as a result of the paper used for SCHOLAR-1 already being adjusted to the CAR-T eligible population in ZUMA-1 (see Key Issue 2, Table 3). Factors

adjusted for in the MAIC vs SCHOLAR-1 are described in Section 3.4.2.1; while most factors with the largest differences have been adjusted for, there are some potentially important omissions, most of which the EAG anticipate would bias against epcoritamab. This is included as part of Key Issue 7 (Table 8).

Overall, the EAG notes that the exclusion criteria used to align EPCORE™ NHL-1 with the comparator trial for R-based CIT introduces limitations in terms of the applicability of the evidence from MAICs. The impact of excluding forms of LBCL other than DLBCL for this analysis is unclear, given that the EAG considers some of these patients may have been included in the SCHOLAR-1 population but proportions were not reported, meaning it could not be adjusted for. The exclusion of those with prior CAR-T treatments may be important, particularly [redacted] for this subgroup. The EAG also highlights uncertainty about whether the EPCORE™ NHL-1 population analysed for this comparison reflected a group ineligible for intensive treatments (Key Issue 6, Table 7). The EAG also has concerns about the lack of adjustment for some characteristics and the suitability of the paper used to inform SCHOLAR-1 data, given it is likely to represent a CAR-T eligible group, likely includes some with only one prior treatment and only includes those with refractory disease.[9]

Epcoritamab vs Pola + BR in DLBCL patients ineligible for (or choose not to receive) intensive therapy – used as scenario analysis A.1 in the company's model for population A

The company used a study by Sehn *et al.* as the source for 3L+ Pola + BR data.[10-12] An MAIC analysis involving adjustment of the EPCORE™ NHL-1 population to Sehn *et al*. was performed, including limiting inclusion to those with DLBCL and no prior CAR-T treatment and subsequently adjusting for various baseline characteristics. Limitations of the Sehn *et al.* study and adjusting to this study are described in Section 3.4.2.2.

In the company's model the epcoritamab population included the MAIC-adjusted DLBCL, no prior CAR-T population from EPCORE™ NHL-1, while the Pola + BR population reflected the unadjusted Sehn *et al.* 3L+ population trial population.

The company did further scenarios (scenarios A.2 and A.3) where they used an alternative source for Pola + BR (Liebers *et al.* 2021) within the DLBCL and LBCL populations, but the EAG considers this to be more limited than Sehn and did not use this further (see Section 3.4.2.2).[13]

As above for the comparison vs R-based CIT, baseline characteristics for the population analysed are very similar to the overall LBCL population, with the exception that the proportion with only two prior lines of therapy has [redacted] from 29.3% to [redacted], potentially reflecting the exclusion of those with prior CAR-T treatments. In addition, the EAG notes that the adjustment of EPCORE™ NHL-1 to Sehn *et al*. means the adjusted EPCORE™ NHL-1 population is even worse in terms of some prognostic factors (such as disease stage III-IV, ECOG score 2 and IPI score ≥3), which may increase the difference from UK clinical practice as the EAG's clinical experts highlighted that the overall EPCORE™ NHL-1 trial population was already slightly worse prognostically. The EAG is unclear of the impact this would have in terms of relative treatment effectiveness given they have been brought in line with the comparator trial. The EAG notes that not all factors have been adjusted for in the MAIC and one in particular (refractory to last anti-lymphoma treatment) was substantially higher in the Sehn *et al.* population compared to EPCORE™ NHL-1, which may be important and introduce bias against Pola + BR given the EAG's clinical experts highlight it as an important indicator of prognosis (see Section 3.4.2.2). This is included as part of Key Issue 7 (Table 8).

The EAG notes that this analysis population leads to the same limitations described above for the comparison vs R-based CIT in terms of excluding those with prior CAR-T use and limiting to the DLBCL population. Only one patient in Sehn *et al.* for the group with at least two prior treatments had non-DLBCL (follicular lymphoma) and it is unclear if this was FL Gr 3B as in the decision problem for the CS. The company assume for this analysis that this study only included DLBCL. The EAG could not find a clear statement that prior CAR-T use was excluded. However, the EAG notes that it is not listed in the table providing a breakdown of prior treatments received. There is not a huge concern about limiting to DLBCL but limiting to those with no prior CAR-T treatment may impact the applicability of analysis results to those with previous CAR-T use. These factors are covered as part of Key Issues 4 and 5 (Table 5 and Table 6).

As above for R-based CIT, the EAG is unsure whether the [redacted] analysed for epcoritamab in this MAIC represents a group ineligible for intensive treatments, which is the population the company state that the comparison vs Pola + BR would be applicable to; further clarification on this and, if some eligible for intensive treatments are included, exploration of the impact on the results of the MAIC and the economic model if the analysis was limited to those not eligible would help to address this uncertainty. This is included as Key Issue 6 (Table 7).

An additional factor to consider is how well the population included for this analysis reflects one that is naïve to Pola (as set out in Table 95 of the CS appendices as the relevant population for this comparison). In response to CQ A11, the company confirmed that [redacted] patients in the DLBCL, no prior CAR-T analysis population had received prior treatment with Pola. While this introduces some diversion from the population that would be eligible for Pola + BR, given this is a small proportion and there is no mention of those with prior Pola use being excluded from the Sehn *et al.* trial, the EAG does not consider it would have a large impact on results.

Overall, the EAG notes that the exclusion criteria used to align EPCORE™ NHL-1 with the comparator trial for Pola + BR introduces limitations in terms of the applicability of the evidence from MAICs. While the EAG is less concerned about the effect of excluding forms of LBCL other than DLBCL, the exclusion of those with prior CAR-T treatments may be important, particularly [redacted] for this subgroup (see Key issues 4 and 5, Table 5 and Table 6). The inclusion of some with prior Pola use in the analysis population for EPCORE™ NHL-1 is highlighted by the EAG but this is not considered to be a major issue. The EAG also highlights uncertainty about whether the EPCORE™ NHL-1 population analysed for this comparison reflected a group ineligible for intensive treatments (Key Issue 6, Table 7). Adjustments made to baseline characteristics means the baseline characteristics of the analysis population may be even worse prognostically compared to the original trial, and slightly less reflective of UK practice, but the EAG highlights that not all important factors have been adjusted for, which may favour epcoritamab (see Key Issue 7, Table 8).

Epcoritamab vs axi-cel in LBCL patients eligible for intensive therapy – used as the updated base case in the company's model for population B following clarification (scenario B.1 in the original CS)

The EAG notes that the company provided a version for DLBCL only and a version with LBCL overall, as the ZUMA-1 trial was not limited solely to DLBCL. The EAG prefers the analysis with LBCL overall included (scenario B.1 in the original CS) to increase the applicability of the analysis to the decision problem. In the LBCL population, n=[redacted] were included from EPCORE™ NHL-1. While the company's original base case for population B included the DLBCL population only (n=[redacted]), this was updated at the clarification stage to focus on the LBCL population in line with the EAG's preference (CQ A9).

For the comparison vs axi-cel, the company used the ZUMA-1 trial as a source of comparator data.[14] For the MAIC, the company matched and adjusted the EPCORE™ NHL-1 population to this trial in the

original submission but an updated MAIC with adjustment for all reported baseline characteristics (within the LBCL population) and use of 5-year data from the ZUMA-1 trial was requested by the EAG at clarification (CQ A9). These two requests were not implemented and this is described further in Section 3.4.2.3.

To better align the EPCORE™ NHL-1 population with ZUMA-1, those with prior CAR-T use were excluded. In addition, the analysis was limited to those who were eligible for CAR-T treatment in the EPCORE™ NHL-1 trial. Although highlighted as a limitation above for comparisons vs R-based CIT and Pola + BR, the EAG does not consider the exclusion of those with prior CAR-T use to be an issue for this particular comparison; as feedback from the EAG's clinical experts indicated that CAR-T would only be used once in each patient, this comparison vs axi-cel would, therefore, only be relevant for patients who are eligible for CAR-T and have not previously used it.

The EAG notes that while an adjusted version was performed, the company's preference in the original CS was to use the unadjusted population from EPCORE™ NHL-1 as it deemed the baseline characteristics to be similar enough between the two populations. For reasons described in Section 3.4.2.3, the EAG did not agree with this and prefers the use of EPCORE™ NHL-1 results adjusted to ZUMA-1. As a result, the company amended their base case at clarification to use results that had been adjusted to ZUMA-1.

In the company's model (updated base case for population B), therefore, the epcoritamab population included the LBCL, no prior CAR-T and CAR-T eligible population from EPCORE™ NHL-1 adjusted to ZUMA-1, while the axi-cel population reflected the unadjusted ZUMA-1 trial data.

Before adjustment, baseline characteristics for the population analysed (n=[redacted]) are similar to the overall LBCL population. Proportions with certain disease severity factors are lower in the analysis population compared to the original trial population (including disease stage III-IV, IPI ≥3 and primary refractory disease). The EAG considers this to be expected given these are factors that affect prognosis and are likely to impact eligibility for CAR-T. As above for comparisons vs R-based CIT and Pola + BR, the proportion with only two prior lines of therapy has [redacted] in the analysis population (29.3% to [redacted]), potentially reflecting the exclusion of those with prior CAR-T treatments. The EAG's clinical experts consider the ZUMA-1 population (and adjusted EPCORE™ NHL-1 population) to be a reasonable reflection of UK clinical practice in this subgroup that are eligible for CAR-T. However, the EAG notes that not all factors imbalanced between the studies are

adjusted for in the MAIC, with some of those remaining in imbalance potentially favouring epcoritamab (see Section 3.4.2.3). This is included as part of Key Issue 7 (Table 8).

Overall, the EAG has no concerns about the exclusion criteria used to align EPCORE™ NHL-1 with the comparator trial for axi-cel in CAR-T eligible LBCL patients. Baseline characteristics for the adjusted EPCORE™ NHL-1 population are considered to be reasonable but the EAG notes that adjustments for all potential prognostic factors in imbalance were not performed in the original analysis, which may favour epcoritamab to some extent (Key Issue 7, Table 8).

2.3.2 *Intervention*

The intervention in the CS is epcoritamab (brand name [redacted]), matching the NICE final scope,[7] to be delivered subcutaneously by a healthcare professional preferably in the lower part of the abdomen or the thigh. It is a non-finite treatment and should be administered until disease progression or unacceptable toxicity. The dosing schedule is presented below in Table 24, with doses varying across different 28-day cycles.[15] Subjects were hospitalised for at least 24 h after the first full dose of epcoritamab (third dose below in Table 24); as a planned hospitalisation, this would not be reported as a serious adverse event.

Table 24. Dosing schedule for epcoritamab (reproduced from Table 3 of the CS)

Cycle	1				2 and 3				4-9		10+
Day of cycle	1	8	15	22	1	8	15	22	1	15	1
Dose (mg)[a]	0.16	0.80	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00

[a] 0.16 mg is a priming dose, 0.80 mg is an intermediate dose and 48.00 mg is a full dose.
Abbreviations: CS, company submission.

Marketing authorisation is expected to be granted [redacted].

The EAG notes that no concomitant medications were specifically mentioned in the NICE final scope,[7] but the EAG's clinical experts agreed that those permitted in the EPCORE™ NHL-1 trial (Table 6 of the CS) would be standard practice.

As anti-lymphoma treatments subsequent to epcoritamab were mentioned in the CSR, the EAG asked at clarification whether patients were included in analyses after starting these treatments or whether they were censored from analyses (CQ A3). The company explained that for the primary

definition of progression-free survival (PFS), censoring was performed at the point of subsequent anti-lymphoma treatment (where this had been started without progressed disease, as detailed in Table 3 of the statistical analysis plan) but this was not the case for overall survival (OS).[16] The EAG considers this to be reasonable.

2.3.3 Comparators

While comparisons vs R-based CIT and axi-cel are the focus of the CS, the company also provided a comparison vs Pola + BR as a scenario (scenario A.1). The company argue that Pola + BR is not a relevant comparator for this appraisal given feedback from clinical experts they consulted that suggests that Pola + BR will be used less often at 3L+ following the recent recommendation for Pola + R-CHP as a first line treatment in DLBCL.[2] While the EAG's clinical experts agreed that use of Pola + BR will reduce for this reason, they note that it will still be an option for a small proportion of the population and is a relevant comparator. Based on this, and the fact that the first-line Pola + R-CHP recommendation does not apply to PMBCL and IPI score between 2 and 5 is required for DLBCL patients,[2] the EAG considers it important to include Pola + BR as a comparator.

Other comparators listed in the NICE final scope but not included in the CS are pixantrone and tafasitamab with lenalidomide.[7] The EAG agrees with the company's rationale for not including either of these comparators; tafasitamab with lenalidomide is not currently recommended as part of NICE TA883 for R/R DLBCL and the EAG's clinical experts confirmed the company's conclusions about pixantrone, which is that it is not used in UK clinical practice due to a lack of efficacy and high toxicity.[8]

In terms of the comparison vs R-based CIT, the EAG notes that the company uses rituximab with gemcitabine and oxaliplatin (R-GemOx) as a proxy for all R-based CIT at this stage in the treatment pathway, including in the economic model. The EAG's clinical experts highlighted R-GemOx as likely to be the most commonly used R-based CIT at this stage in the pathway, particularly in those <80 years old (those >80 years may be more likely to receive best supportive care or other R-based CIT that are palliative, such as R-PMitCEBO (rituximab with prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin and vincristine), R-CE (rituximab with cyclophosphamide/etoposide) or PEP-C (prednisone, etoposide, procarbazine, and cyclophosphamide). They note that the choice of R-based CIT is patient dependent and that there is no agreed standard choice. They are all considered to be similar in terms of efficacy at this stage in the treatment pathway but the EAG's clinical experts noted that R-GemOx may be less well tolerated

than some of the less intensive, palliative regimens mentioned for the group >80 years old. Palliative lenalidomide with or without rituximab was also mentioned as a potential option for older and frailer patients if unfit for chemotherapy. In terms of the comparator trial used to inform outcomes for R-based CIT (SCHOLAR-1), the EAG notes that the types of R-based CIT patients were on and the proportions using each type does not appear to be reported (see Section 3.4.2.1) this is included as part of Key Issue 3 (Table 4).[9, 17]

While the EAG's clinical experts highlight that the recent CDF recommendation for axi-cel after one treatment failure may change the treatment pathway particularly for those eligible for CAR-T,[1] decisions made by the EAG about suitable comparators for the appraisal have been made based on the treatment pathway before this recommendation given it only applies within the CDF (see Section 2.2.1 above).

Similarly, the EAG's clinical experts also noted that another CAR-T treatment, tisagenlecleucel, is also used in UK clinical practice as an alternative to axi-cel. While this treatment is recommended for those with R/R LBCL with at least two prior systemic therapies, this recommendation is solely within the CDF and it cannot therefore be included in NICE appraisals. This is based on the NICE manual for health technology evaluations, which states in Section 2.2.15 that, "*technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators*".[6] The EAG's clinical experts consider it likely that axi-cel is used more often than tisagenlecleucel.

2.3.4 Outcomes

The EAG considers that the CS includes all outcomes listed in the NICE final scope in some form.[7] Time to treatment discontinuation (TTD) was not a prespecified trial outcome and thus was not presented in the CSR or clinical section in terms of results for the overall EPCORE™ NHL-1 population; however, it has been used in the economic model. In addition, while not reported in the CSR tables provided, time to next treatment is summarised in Section B.2.6.1 of the CS for EPCORE™ NHL-1. See Section 3.3 for results from the overall EPCORE™ NHL-1 trial and Section 3.5 for results of indirect comparisons.

The EAG notes that outcomes used in the economic model are OS, PFS, TTD and adverse events (AEs), as well as health-related quality of life (HRQoL) utility data. Multiple variations of PFS were presented in the CSR (based on Lugano or LYRIC criteria, assessed by investigator or independent

review committee [IRC], and primary or secondary definition, where patients are censored upon receiving subsequent anti-lymphoma treatments in the primary definitions). The EAG considers the outcomes based on Lugano criteria, assessed by IRC and using the primary definition to be most appropriate. The company confirmed at the clarification stage that this definition had been the focus of the CS and data used in the model (CQ B3).

The EAG's clinical experts reviewed the AEs included in the economic model and considered that all of the important ones, including AEs of special interest (AESI), had been included. A discussion of the rates and costs used for AEs is provided in Sections 3.3.3 and Section 4.2.6.7.

The EAG notes that the data provided at CS and in response to CQs is based on the [redacted] data-cut for EPCORE™ NHL-1. However, the response to CQs also indicated that a later data-cut, from [redacted], is also available. The EAG considers that the most recent data-cut should be used to inform all clinical data and economic modelling in this appraisal for review by the committee. This is included as Key Issue 8 (Table 9).

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence from randomised controlled trials (RCTs) of epcoritamab or any other pharmacological intervention for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL), after two or more lines of systemic therapy. The External Assessment Group (EAG) notes that the company reported that the SLR was conducted in line with the guidelines set out by Cochrane and the Centre for Reviews and Dissemination (CRD)[18] and the 27-item PRISMA Statement checklist.[19] Methods and search results for the company's SLR are provided in Sections B.2.1, B.2.2 and Appendix D of the company submission (CS) and the EAG critique of the methods is provided in Table 25 below.

The clinical SLR searches were initially conducted on 11 October 2022 and updated on 8 December 2022. A total of 310 publications were eligible for inclusion based on the pre-specified criteria and this was narrowed down by applying further inclusion criteria to limit the studies for data extraction to those in the third line of treatment or beyond (3L+) LBCL or diffuse large B-cell lymphoma (DLBCL) population with ≥20 patients and providing evidence from a European, Northern American or global perspective. The additional criteria resulted in the final inclusion of 138 publications. The EAG notes

that the number of included publications reported in the CS document B do not correspond with those in the PRISMA diagram from Appendix D; the EAG critique focuses on the numbers from Appendix D and the PRSMA diagram.

Of the 138 included publications, 56 related to 31 clinical trials, with eight publications only presenting 3L+ data from subgroup or multivariate analyses (Table 15, CS Appendix D). The remaining 82 publications reported on observational studies that describe R/R patients with a diagnosis of either LBCL or DLBCL. Amongst the observational studies, nine studies only reported data for the 3L+ patient population from subgroup analyses. The company reported that a list of the included observational studies was provided in the reference pack but the EAG notes that the reference cited by the company comprises a list of 227 included references which corresponds to the number of publications included from database sources in the company SLR.[20]

The clinical SLR identified only one clinical trial for epcoritamab in patients with LBCL: EPCORE™ NHL-1 (NCT03625037), which provides clinical evidence for the efficacy of epcoritamab as a treatment for adult patients with R/R LBCL after two or more lines of systemic therapy.[21] The EAG critique and the study conduct of EPCORE™ NHL-1 are discussed further in Section 3.2. The company also highlighted the presence of the EPCORE™ DLBCL-1 (NCT04628494) phase 3 clinical trial, which is an ongoing study of epcoritamab versus investigators' choice of bendamustine and rituximab (BR) or rituximab with gemcitabine and oxaliplatin (R-GemOx) in patients with LBCL who are ineligible for or have failed high-dose therapy followed by autologous stem cell transplant (ASCT).[22] The company reported that results from EPCORE™ DLBCL-1 are not yet available and therefore it is not discussed further.

In summary, the EAG considers the company SLR searches to be appropriate. However, the EAG has some concerns regarding the *post hoc* application of criteria to limit the final inclusion of studies (3L+ LBCL or DLBCL population with ≥20 patients and providing evidence from a European, Northern American or global perspective), although with the exception of the study size restriction, the criteria appear to be reasonable in terms of identifying studies meeting the appropriate population for addressing The National Institute for Health and Care Excellence (NICE) final scope[7] and UK population. Additionally, the EAG notes that only one study of epcoritamab[21] was identified and included from the SLR despite the inclusion of 138 publications in the company SLR: the EAG considers that the CS lacks detail on how the remaining included publications from the company SLR were utilised or subsequently excluded but notes that some studies were used in the indirect

treatment comparisons presented in the CS (CS Section B.2.8 and discussed further in Sections 2.3.1.2 and 3.4).

Table 25. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**The EAG considers the sources and dates searched to be comprehensive and appropriate.** Databases searched: • Embase; MEDLINE; CDSR and CENTRAL. Registries: • ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) and EU Clinical Trials Register Conference proceedings: • Manual hand-searching of key conference proceedings from the last 3 years (2020-2022; European Hematology Association (EHA), International Conference on Malignant Lymphoma (ICML), American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO)). The original database searches were conducted in October 2022 and updated in December 2022. The EAG notes that reference list searches of relevant studies and SLRs were not reported to have been conducted but considers the database and conference proceeding searches conducted by the company to be comprehensive.
Search strategies	Appendix D.1.1	**The EAG considers the search strategies used likely to be appropriate but notes that search filters were used to limit by study design for the searches in MEDLINE and Embase** The search strategies for the literature review used free-text keywords, MeSH and EMTREE terms for the population and interventions of interest. In addition, the EAG notes that the company has used search terms to limit results from MEDLINE and EMBASE to trials and observational studies based on search filters by the Scottish Intercollegiate Guidelines Network (SIGN).[23]
Inclusion criteria	Appendix D.1 (Table 1) and D.1.3	**The EAG considers the inclusion criteria for the SLR to be reasonable although there were restrictions applied prior to data extraction based on study sample size and geographic location** The eligibility criteria for the SLR were generally consistent with the NICE final scope[7] but the EAG notes that additional inclusion criteria were applied following full text screening to further restrict the included studies that were data extracted. Publications were only deemed relevant for data extraction if they reported on clinical evidence of studies including sample sizes of ≥20 patients in ≥3rd line R/R (D)LBCL. In addition, studies that were conducted in a single country outside of Europe and the Northern Americas were excluded from the CS. The EAG considers these additional criteria likely to be reasonable given the UK

		focus of NICE, the population specified in the NICE final scope and the identification of studies with larger sample sizes than 20 patients but is concerned that they appear to have been utilised *post hoc*.
Screening	Appendix D.1.2	**The EAG considers the methods for screening to be robust.** Abstract and title reviews of all references identified from the database searches were reported to be performed independently by two reviewers with any discrepancies resolved by a third reviewer. The same process was applied to articles that were selected for full-text review. Searches of conference proceedings and clinical trial registries were performed by a single reviewer and checked by a second reviewer. Results of the literature screening processes were summarised in a PRISMA diagram.
Data extraction	Appendix D.1.2	**The EAG considers the methods for data extraction to be reasonable.** One researcher extracted the data and a second researcher independently reviewed all data extracted for each endpoint.
Tool for quality assessment of included study or studies	Appendix D.1.2, D.1.9, D.3 and Section B.2.5 of the CS	**The EAG considers the company's choice of quality assessment tool for RCTs to be reasonable but the EAG was unable to locate the checklist for non-randomised studies in the reference cited by the company** The company used the Appraisal of RCT checklist by the Centre for Reviews and Dissemination (CRD) for quality assessing included RCTs.[18] For non-randomised clinical trials, the company reported that they used the checklist for non-randomised clinical trials from the CRD Guidance for Undertaking Reviews in Health Care (2009).[18] The EAG was unable to locate this checklist and could, therefore, not validate its use. The EAG critique of the key features of EPCORE™ NHL-1 is presented in Section 3.2.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; (D)LBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; EMTREE, Embase subject headings; EU, European ; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; R/R, relapsed or refractory; SLR, systematic literature review; WHO, World Health Organisation.

3.2 Critique of trials of the technology of interest

The evidence for epcoritamab included in the CS is from one single arm, phase 1/2 open-label clinical trial (EPCORE™ NHL-1; NCT03625037).[21] Data from the aggressive non-Hodgkin lymphoma (aNHL) cohort of this trial were the focus of the CS, which represented the LBCL group relevant to the appraisal. The EAG's clinical experts agreed it is appropriate to focus on this group (and not indolent B-cell non-Hodgkin lymphoma or mantle cell lymphoma cohorts). Applicability of this trial to the decision problem is discussed throughout Section 2.3.

Methodology used in this trial is described in Section B.2.3 of the CS, with statistical analysis and critical appraisal described in Sections B.2.4 and B.2.5, respectively. The EAG notes that the

company's quality assessment of EPCORE™ NHL-1 is provided in Table 26 below. The company suggests in Table 21 of the CS appendices that this is from the CRD Undertaking Reviews in Health Care 2009 checklist;[18] however, the EAG were not able to identify this checklist within the resources cited and could not validate its use.

The EAG is not aware of any widely used and accepted risk of bias checklists for single arm studies and comments on the quality of the EPCORE™ NHL-1 trial are therefore made in line with the table provided by the company, with some adaptations to consider guidance for non-randomised studies provided in the Cochrane Handbook, using the ROBINS-I tool. [24]

The EAG highlights that being a single-arm trial is a limitation as it does not provide direct comparative evidence and requires the use of indirect techniques in the form of matching-adjusted indirect comparisons (MAICs), which introduce additional uncertainty. In addition, the open-label nature of the trial means bias may have been introduced, for example in terms of outcome assessment, particularly for outcomes with subjective elements such as confirming progression or health-related quality of life (HRQoL) outcomes.

While the recruitment and statistical analysis appears to be reasonable overall, the EAG notes that the rationale for some decisions is unclear (for example, why DLBCL only were included in stage 1 of recruitment with capped inclusion of other LBCL in stage 2 after the futility analysis). In addition, methods for dealing with missing data for some outcomes are unclear; however, information about how patients are included in analyses after last follow-up is provided for outcomes key to the economic model (overall survival [OS], progression-free survival [PFS], EQ-5D-3L utility and adverse events [AEs]), which the EAG considers to be appropriate.

Bias introduced as a result of the comparisons performed between EPCORE™ NHL-1 and comparator trials used in MAICs is discussed in Section 3.4.2.

The EAG notes that there is an ongoing phase 3 open-label randomised controlled trial (EPCORE™ DLBCL-1; NCT04628494) of EPCORE™ vs investigator's choice of chemotherapy in patients with R/R DLBCL. Data for this is not yet available ([redacted]) and is, therefore, not included in the CS (Section B.2.10 of the CS).

Table 26. Quality assessment of EPCORE™ NHL-1 (adapted from Table 13 of the CS)

Question	Company response	Location where information reported	EAG comment
What is the study design?	Single-arm trial	Section B.2.3.1 in CS	The trial being single-arm is a limitation given it does not provide direct comparative evidence and indirect comparisons via MAICs have instead had to be performed, which introduce more uncertainty (see Section 3.4)
Was the study prospective or retrospective?	Prospective	Table 13 in CS	N/A
Was recruitment of patients appropriate? – *EAG addition*	NR	Section 9.1.1 of CSR; Tables 6 and 12 of the CS	The EAG notes that enrolment was performed in stages based on interim analyses and the rationale for decisions is not always clear. In particular, only DLBCL patients were included up to the 12-week futility stage; after this, up to 30 patients with other types of LBCL could be included in stage 2. A rationale for why their inclusion was only after stage 2 and why it was limited to up to 30 patients does not appear to be provided. The EAG's clinical experts are not concerned about any inclusion/exclusion criteria and consider them to be reflective of clinical trials. In response to CQ A5, the company noted that LBCL diagnosis confirmation was made at a local/site level and details of whether this was based on a single individual or MDT review was not collected as part of the trial.
Was the intervention used appropriately?	Yes	Draft SmPC; Table 6 of the CS; Section 10.3 of CSR	The intervention appears to have been used as indicated in the draft SmPC.[15] Concomitant medications permitted in the trial are considered standard practice by the EAG's clinical experts. The EAG notes that as of [redacted], there were [redacted] protocol deviations related to dosing in the LBCL group – these were [redacted]. The EAG could not identify equivalent data for the [redacted] data cut.
Were the outcome measures in the study reliable?	Yes	Section 11.2 and 11.2.2.5.3 of CSR; Table 6 of the CS	Valid tools appear to have been used for outcomes, including Lugano criteria for defining response/progression. The EAG notes that individual investigators assessed progression to decide whether treatment should continue but progression was confirmed by IRC; the EAG is unclear whether this means patients could have been removed from treatment unnecessarily before IRC confirmation. However, given that concordance between investigator and IRC assessments was [redacted] for PFS (primary definition) in the
Were the outcome measures in the study valid?	Yes		

			[redacted] (the EAG could not find equivalent data for [redacted]), the EAG is not concerned that the risk of this is high. Primary definitions of response/progression outcomes are appropriate and based on IRC. The EAG considers the company's approach addressing subsequent anti-lymphoma treatments in analyses to be reasonable. Patients starting subsequent anti-lymphoma treatment were censored for PFS (if this was started without progressed disease, see Table 3 of the statistical analysis plan) but not for OS.[16] Bias in terms of outcome assessment may be introduced due to its open-label nature; while outcomes such as OS are objective and should not be impacted by the participant knowing the intervention being received, investigators, patients and outcome assessors being aware of the intervention assigned may have introduced bias in terms of outcome assessment for some outcomes with subjective elements (e.g. defining progression, adverse events, patient HRQoL assessments).
Was the statistical analysis conducted appropriately in the study?	Yes	Section 9.1.1 of CSR; Tables 11 and 12 of CS	Rationale for the numbers assessed for futility criteria in stage 1 is unclear. The EAG notes futility assessment was based solely on DLBCL patients. The number of DLBCL patients enrolled was [redacted] than that required to provide 90% power to detect an alternative hypothesis of at least 50% ORR. The analysis was performed in the FAS population (any patient enrolled and receiving at least one dose of epcoritamab), which the EAG considers to be appropriate.
Is there missing data and how is this addressed? – *EAG addition*	NR	Section 9.7.4 of the CSR; Section 5.7.1.5.1 of SAP; Section O.1 of the CS appendices	Methods for handling missing data are not described for most outcomes, but the EAG notes that for key outcomes used in the economic model (e.g. OS and PFS), censoring was performed at time of last follow-up and has, therefore, been accounted for. While not used to inform HRQoL in the model, patients with <50% responses missing for a particular subscore on the FACT-Lym questionnaire, the subscale score was prorated as the sum of item responses for that subscale (i.e. replacing missing values with the mean of the completed items for that subscale); if ≥50% responses are missing, the subscale was classed as missing (as would overall scores based on that subscale). Missing data for EQ-5D-3L utility is reported not to be imputed in Section O.1 of the CS, and analyses in the clinical section of the CS are based on the number with available data at each time-point.
Was the quality of reporting appropriate in the study?	Yes	CSR including tables for [redacted]	Results for all prespecified outcomes appear to have been provided in the CSR to a good level of detail, including for subgroups.

Can the study results be generalised to routine practice?	Yes	Section B.2.3.2 of the CS	The EAG's clinical experts note that it is a reasonable reflection of a UK population but that it may be slightly worse prognostically (see Section 2.3.1.1)
Additional comments – *EAG addition*	N/A	N/A	N/A

Abbreviations: CQ, clarification question; CS, company submission; CSR, clinical study report; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; FAS, full analysis set; HRQoL, health-related quality of life; IRC, independent review committee; LBCL, large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; MDT, multidisciplinary team; N/A, not applicable; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SmPC, Summary of Product Characteristics; UK, United Kingdom.

3.3 Critique of the clinical effectiveness analysis

3.3.1 Survival and response outcomes

The primary outcome of the trial was overall response rate (ORR), defined as the proportion of patients achieving a best overall response of complete response (CR) or partial response (PR). The primary definition was based on independent review committee (IRC) assessment as per the Lugano criteria, which the EAG prefers as opposed to individual investigator assessment. The results for the LBCL population in Table 75 of the CS appendices indicate that the ORR was [redacted]% (95% confidence intervals [CI] [redacted]% to [redacted]%), with the rate for CR being [redacted]% (95% CI [redacted]% to [redacted]%). Duration of response in those with CR or PR was a median of [redacted] months, ranging between [redacted] months (Table 76 of the CS appendices). The EAG notes that these response outcomes do not inform the economic model.

OS and PFS are both used to inform the economic model, though the results used in the model are for specific adjusted populations obtained via MAICs and not from the overall LBCL population (see Sections 3.4 and 3.5). Kaplan-Meier (KM) curves for the overall LBCL population (and subgroups based on type of LBCL) for these outcomes are presented below in Figure 2 and Figure 3. Median OS for the LBCL population was [redacted] months and median PFS for this group was [redacted] months. At 6, 9, 12, 15 and 18 months, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% remained alive, respectively (Table 78 of the CS appendices). The equivalent values for PFS at 6, 9 and 12 months were [redacted]%, [redacted]% and [redacted]%, respectively (Table 77 of the CS appendices).

Results for various subgroups including LBCL compared with DLBCL and other subtypes can be found in Section 3.3.4.

The EAG also notes that time to treatment discontinuation (TTD) was used in the economic model but was not a prespecified outcome and was not reported in the clinical section of the CS (see Section 4.2.4.5.

Figure 2. KM plot of OS[a] in LBCL overall, DLBCL and other LBCL types (FAS; [redacted] data cut-off) – reproduced from Figure 8 of the CS

[redacted]

[a]OS is defined as time from C1D1 to death from any cause. Subjects that were not known to have died were censored at the latest date they were known to be alive.
Abbreviations: C1D1, day 1 of cycle 1; CI, confidence interval; CS, company submission; DLBCL, diffuse large B-cell lymphoma; FAS, full analysis set; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NR, not reported; OS, overall survival.

Figure 3. KM plot of PFS[a] in LBCL overall, DLBCL and other LBCL types (FAS; [redacted] data cut-off) – reproduced from Figure 7 of the CS

[redacted]

[a]PFS is defined as the time from C1D1 of epcoritamab treatment until date of disease progression (documented radiographical progression) or death due to any cause. The primary definition, which was also used in the economic model, was as assessed by IRC using the Lugano criteria to assess radiographical progression, with censoring at the time of subsequent anti-lymphoma

treatment. Patients were also censored at the date of their last evaluable tumour assessment if they did not experience events. The EAG prefers this definition to others reported in the CSR.
Abbreviations: C1D1, day 1 of cycle 1; CI, confidence interval; CS, company submission; CSR, clinical study report; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; FAS, full analysis set; IRC, independent review committee; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NR, not reported; PFS, progression-free survival.

3.3.2 Health-related quality of life

The EAG notes that HRQoL as used in the economic model is discussed later in Section 4.2.5. A brief overview of the results from the trial are given here for the LBCL population, which includes utility scores for EQ-5D-3L and Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym). The latter is a disease-specific instrument that is validated for patients with lymphoma. It consists of a 27-item general quality of life instrument and a 15-item condition-specific module. All statements are ranked on a 5-point scale (0 to 4) and the FACT-Lym covers 5 subscale domains, including the lymphoma subscale (LymS). Total FACT-Lym scores (range 0 to 168; higher better) and the scores for the LymS subscale (range 0 to 60; higher better) are reported in the CS.

The results in Table 27 below indicate that, of those analysed at each follow-up time-point, epcoritamab treatment improved FACT-Lym total scores as well as FACT-LymS subscores. Changes from baseline appear to improve slightly as treatment continues. While the CS states that this was maintained up to cycle 13, the EAG only identified results up to cycle 9. This represents follow-up up to 9 months, which the EAG notes is [redacted] in the trial ([redacted] months, range [redacted] months), even though an end of treatment measurement was said to have been planned.

Results in Table 28 below demonstrate that a similar trend was observed for EQ-5D-3L utility scores across follow-up points; results had improved at the second assessment (day 1 of cycle 3). At subsequent time-points [redacted] remained higher than the mean value reported at baseline. The EAG notes that values for those with missing data were not imputed (Section O.1.1 of the CS appendices). As above for FACT-Lym, while an end of treatment measurement was said to have been planned, results for this do not appear to have been reported, with results available up to day 1 of cycle 9. Based on the description in Section O.1.1 of the CS appendices, the EAG understands that data up to end of treatment was, however, used in the economic model (see Section 4.2.5 for further discussion).

Results in the LBCL population compared with DLBCL only and other LBCL subtypes are mentioned in Section 3.3.4.1 below.

As the MAICs performed for survival outcomes focused on smaller populations of the original EPCORE™ NHL-1 trial, in clarification question (CQ) A4 the EAG requested that EQ-5D-3L results for the populations analysed in MAICs also be provided to allow any differences in populations to be assessed. These are presented in Table 28 for each analysis, alongside rates observed in the whole LBCL population. Given FACT-Lym was not used in the economic model this request was limited to EQ-5D-3L.

The EAG notes that the DLBCL no prior chimeric antigen receptor T-cell (CAR-T) population appears to be used to inform EQ-5D used in the economic model for comparisons vs rituximab-based chemoimmunotherapy (R-based CIT) and polatuzumab vedotin with rituximab and bendamustine (Pola + BR; Section B.3.4.1 – although the text states LBCL no prior CAR-T, the EAG believes this to be a typo given Table 56 does not present LBCL no prior CAR-T data). This is in line with the population analysed in the MAICs. For the comparison vs axicabtagene ciloleucel (axi-cel), Section B.3.4.1 states that for the analysis in the LBCL population (originally scenario B.1 and subsequently used in the updated base case analysis for population B post-clarification) EQ-5D data from the overall LBCL population (N=157) was used. This suggests the EQ-5D data used for the comparison vs axi-cel was not specific to LBCL patients with no prior CAR-T that were eligible for CAR-T ([redacted]). While results for this subgroup vs the overall LBCL population are similar in Table 28 below, there is some variation and it is unclear how this would impact the economic model. The EAG is unsure why the EQ-5D data used would be aligned with the population used in the MAIC analysis for comparisons vs R-based CIT and Pola + BR but not for axi-cel.

Table 27. Mean FACT-Lym total score and FACT-LymS while on treatment (FAS – LBCL population, N=157; [redacted] data cut-off) – adapted from Table 80 of the CS appendices

Time-point (sample size)	FACT-Lym total score, mean (SD)	FACT-LymS, mean (SD)
C1D1 [redacted]	[redacted]	[redacted]
C3D1 [redacted]	[redacted]	[redacted]
Change from baseline [redacted]	[redacted]	[redacted]
C5D1 [redacted]	[redacted]	[redacted]
Change from baseline [redacted]	[redacted]	[redacted]
C7D1 [redacted]	[redacted]	[redacted]
Change from baseline [redacted]	[redacted]	[redacted]

C9D1 [redacted]	[redacted]	[redacted]
Change from baseline [redacted]	[redacted]	[redacted]

Abbreviations: CS, company submission; CXDX, cycle X day X; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; FACT-LymS, Functional Assessment of Cancer Therapy – Lymphoma Subscale; FAS, full analysis set; LBCL, large B-cell lymphoma; SD, standard deviation.

Table 28. Mean scores for EQ-5D-3L health utility while on treatment (various analysis populations) [redacted] data cut-off) – adapted from Table 82 of the CS appendices and the company's response to CQ A4

	Health utility score, mean (SD)		
Time-point (sample size)	**Overall LBCL (N=157)[a]**	**DLBCL, no prior CAR-T (n=[redacted])[a]**	**LBCL, no prior CAR-T, CAR-T eligible (n=[redacted])[b]**
C1D1	[redacted]	[redacted]	[redacted]
C3D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C5D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]

[a]Population analysed in the MAICs vs R-based CIT and Pola + BR; [b]Population used in the MAIC vs axi-cel.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CS, company submission; CXDX, cycle X day X; CQ, clarification question; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; SD, standard deviation.

3.3.3 *Adverse events*

A breakdown of AEs occurring within the EPCORE™ NHL-1 up to [redacted] was provided within the CS (Section B.2.9). Analyses were performed in the safety analysis set, which included those that received at least one dose of epcoritamab (N=157). Mean duration of exposure was [redacted] (standard deviation, [redacted]; range, [redacted]).

The EAG summarises these below in Table 29, with focus on AEs that were classed as serious, were related to the study drug and/or led to a downstream event (e.g. death or discontinuation), AEs of

special interest (AESI) or others that were included in the economic model. The EAG also focuses on the overall LBCL population (see Section 3.3.4.1 for comment on the DLBCL population). AESI are defined in the CS as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANs) and clinical tumour lysis syndrome. The EAG also notes that [redacted] are mentioned in the draft Summary of Product Characteristics (SmPC) provided by the company,[15] which combines events including [redacted], some of which were observed as serious events in ≥2% of patients and are included in Table 29 below.

The EAG notes that [redacted] of patients experienced a treatment-emergent AE (TEAE), with [redacted] also reporting serious or grade 3+ events. While [redacted] proportions experienced serious or grade 3+ events related to treatment, rates were [redacted]%. [redacted] fatal events was judged to be related to epcoritamab, which was associated with [redacted] event. Of all AEs reported, the main concern with epcoritamab appears to be the risk of CRS; this was [redacted] in terms of serious events ([redacted]%) and was the AESI with the [redacted] for events of any severity ([redacted]%).

AE rates included in the economic model were restricted to grade ≥3 that occurred in ≥5% of patients in any of the relevant trials (Table 55 of the CS). The rates used in the economic model for epcoritamab are those from the whole LBCL population of EPCORE™ NHL-1, rather than from adjusted populations formed as a result of MAIC analyses described in Sections 3.4 and 3.5. This means that the same AE rates are used for epcoritamab for population A and population B. Rates used in the economic model for epcoritamab and comparator treatments are included in Table 30 below.

In CQ A4 the EAG requested that a breakdown of AEs for the populations analysed in MAICs also be provided to allow any differences in populations to be assessed. These are presented in Table 29 for each analysis, alongside rates observed in the whole LBCL population; overall, the EAG does not consider there to be a pattern in terms of increased or decreased events vs the overall LBCL population, with event rates for definitions used in the model [redacted]; of AEs used in the model, those with any serious CRS event appears to be [redacted] in the two MAIC populations). The EAG is not concerned that these slight differences would impact the outcome of the cost-effectiveness analyses and, therefore, did not explore this further in the economic model. The EAG also asked that AE rates

for prior CAR-T and number of prior treatment subgroups be provided at clarification (CQ A2), which are discussed in Section 3.3.4.2 and 3.3.4.3).

The EAG notes that while epcoritamab AE rates were reported by the company to be taken from the EPCORE™ NHL-1 trial for LBCL, some values in the model (including those for hypokalaemia, leukopenia, lymphopenia, neutropenia and pneumonia) did not match values identified by the EAG in the clinical study report (CSR; according to the definition described by the company in Section B.3.3.5; CSR table 14.3.1.5.1). This was corrected by the company to reflect values from the [redacted] data-cut at clarification (CQ B22), as those originally used were from an earlier data-cut. In addition, some values lacked overall face validity due to lack of consistency across similar events (lymphopenia, leukopenia, neutropenia and neutrophil count decrease, based on feedback from the EAG's clinical experts). The EAG asked the company to clarify the incidence rates used for these AEs as part of CQ. The company confirmed that those reported in the CS (for R-based CIT, axi-cel and Pola + BR) and updated in response to CQ B24 (for epcoritamab) were the correct values used.

The incidence of grades 1 and 2 events was also included by the company for B-cell aplasia for patients receiving axi-cel, which the company notes is in line with NICE TA559 (now NICE TA872; company response to CQ B21).[5] The company also used differing inclusion criteria for the incidence of CRS in the economic model, with the incidence in the epcoritamab arm being sourced from the proportion of patients experiencing any serious adverse events (and not just grade ≥3) across the EPCORE™ NHL-1 trial. At the clarification stage (CQ B23) the company was asked to explain why, in the economic model, CRS incidence for epcoritamab was based on any serious event but for axi-cel was those experiencing grade ≥3 CRS events; the company explained that epcoritamab was based on any serious event in order to reflect the cost impact of CRS for epcoritamab and that the tariff associated with axi-cel includes hospitalisation in the first 100 days. The company also noted that the ZUMA-1 trial used the most recent version of CRS criteria at the time of conduct but that this was different to those used for EPCORE™ NHL-1 as a more recent version was available. The EAG considers the explanation for the difference in inclusion criteria to be reasonable given that hospitalisation constitutes part of the cost for axi-cel and so grade serious events of lower grades would already be adequately covered.

The EAG's clinical experts also considered that the incidence of many of the AEs included for axi-cel did not reflect the findings of the ZUMA-1, the pivotal trial used to inform NICE TA559 (now NICE TA872) and used to inform the relative treatment effect for axi-cel in the model.[5] At clarification (CQ

B20), the EAG requested that the company explain the discrepancy in incidence rates between ZUMA-1 and those used in the model, and that the company conduct a scenario analysis using the incidence of grade ≥3 AEs as identified in the ZUMA-1 trial. The company explained that neutropenia, anaemia and thrombocytopenia were not costed individually for axi-cel as axi-cel administration already includes hospitalisation (and costing an additional bed day for these AEs would lead to double counting, assuming these events occurred within the period covered by axi-cel administration cost). The company also performed the scenario analysis requested by the EAG. The EAG acknowledges that given the cost of axi-cel includes hospitalisation the addition of events which included a cost for hospitalisation would be inappropriate. As such the EAG considers the approach taken by the company in the base case appropriate.

Additional details around the disutilities and costs associated with AEs and their application in the model are outlined in Sections 4.2.5.3 and 4.2.6.

Table 29. Summary of AEs in EPCORE™ NHL-1 – full LBCL population (adapted from Tables 32, 34 and 35 of the CS, Table 14.3.1.5.1 of the CSR tables provided for [redacted] and the company's response to CQs A2 and A4)

Adverse event	EPCORE™ NHL-1 LBCL (N=157)[a]	EPCORE™ NHL-1 DLBCL, no prior CAR-T treatment ([redacted])	EPCORE™ NHL-1 LBCL, no prior CAR-T treatment, CAR-T eligible ([redacted])
TEAEs[b]			
Any TEAE	[redacted]	[redacted]	[redacted]
TEAE ≥ grade 3[c]	[redacted]	[redacted]	[redacted]
TEAE related to treatment	[redacted]	[redacted]	[redacted]
TEAE ≥ grade 3[c]	[redacted]	[redacted]	[redacted]
Serious TEAEs[d] or those leading to events			
Serious TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE related to treatment	[redacted]	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
TEAE leading to dose delay/interruption	[redacted]	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]	[redacted]
Fatal TEAE related to treatment	[redacted]	[redacted]	[redacted]
Specific serious TEAEs in at least 2% of patients			
Immune system			
CRS	[redacted]	[redacted]	[redacted]
Infections			
Sepsis	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Nervous system disorders			

ICANS	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders			
Pleural effusion	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders			
Febrile neutropenia	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions			
Pyrexia	[redacted]	[redacted]	[redacted]
AESI (of any severity)			
CRS	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]
CTLS	[redacted]	[redacted]	[redacted]
Definitions as used in the economic model, as reported in the CSR and clinical section of the CS			
TEAEs of grade 3 or above[c,e]			
Anaemia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]

Any serious TEAE			
CRS	[redacted]	[redacted]	[redacted]
TEAEs of grade 1 or 2			
B-cell aplasia[g]	[redacted]	[redacted]	[redacted]

[a]AEs in this population was used to inform the company's base case for populations A and B; TEAE is defined as an event judged by the investigator to be related to treatment with epcoritamab; [c]AEs were graded by the investigator according to National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0, except for CRS, CTLS and ICANS, which were graded according to American Society for Transplantation and Cellular Therapy criteria or according to Cairo-Bishop;[25, 26] [d]Serious events were defined as an AE that meets one of the following criteria; is fatal or life threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant (i.e. defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the aforementioned outcomes), or requires inpatient hospitalisation or prolongation of existing hospitalisation;[27] [e]Those occurring in ≥5% of patients in either the EPCORE™ NHL-1 trial or comparator trials for R-based CIT or axi-cel were included in the cost-effectiveness; [f]The EAG notes that [redacted] was reported and used by the company but that [redacted] was reported in the CSR; the EAG considers this would have a negligible impact on model results; [g]Only includes grade 1 and 2 AEs.

Abbreviations: AE, adverse event; axi-cel axicabtagene ciloleucel; CRS, cytokine release syndrome; CS, company submission; CSR, clinical study report; CTLS, clinical tumour lysis syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; R-based CIT, rituximab-based chemoimmunotherapy; TEAE, treatment emergent adverse event.

Table 30. AE rates for epcoritamab and comparators used in the cost-effectiveness model – adapted from Table 55 of the CS, Table 157 of the CS appendices and Table 34 of the company's response to CQ B22

Adverse event	Incidence per treatment arm			
	Epcoritamab[a]	R-based CIT	Pola + BR	Axi-cel
Anaemia	[redacted]	17.90%	28.20%	0.00%
B-cell aplasia[b]	[redacted]	0.00%	0.00%	11.00%
CRS	[redacted]	0.00%	0.00%	13.00%[c]
Febrile neutropenia	[redacted]	12.80%	10.30%	0.00%
Hypokalaemia	[redacted]	2.60%	7.70%	0.00%
ICANS	[redacted]	0.00%	0.00%	28.00%
Leukopenia	[redacted]	7.70%	7.70%	0.00%
Lymphopenia	[redacted]	0.00%	12.80%	0.00%

Neutropenia	[redacted]	33.30%	46.20%	0.00%
Neutrophil count decreased	[redacted]	0.00%	0.00%	0.00%
Pneumonia	[redacted]	2.60%	7.70%	0.00%
Rash	[redacted]	7.70%	0.00%	0.00%
Thrombocytopenia	[redacted]	23.10%	41.00%	0.00%
Source	Epcoritamab CSR, [redacted][28]; Table 34 of the company's response to CQ B22	NICE TA649[29]; Table 55 of the CS	NICE TA649[29]; Table 157 of the CS appendices	NICE TA559 (now NICE TA872)[5]; Table 55 of the CS

[a]Based on proportion with grade ≥3 AEs, other than CRS which is based on any serious event; [b]B-cell aplasia includes only grade 1 and 2 AEs; [c]The incidence of CRS in the axi-cel arm is based on the proportion of patients experiencing grade 3 or higher CRS events in line with TA559; this approach was taken to reflect the impact of CRS associated with axi-cel on quality of life.

Abbreviations: AE, adverse event; axi-cel, axicabtagene ciloleucel; CQ, clarification question; CRS, cytokine release syndrome; CS, company submission; CSR, clinical study report; ICANS, immune effector cell-associated neurotoxicity syndrome; NICE, The National Institute for Health and Care Excellence; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy; TA, technology appraisal;

3.3.4 Subgroups

3.3.4.1 Type of LBCL

Survival and response outcomes

For ORR, CR and duration of response (DOR) outcomes discussed in Section 3.3.1 above, results in the DLBCL subgroup are consistent with those reported for LBCL (Table 14 in the CS). While the ORR proportion is [redacted]%, 95% CI [redacted]% to [redacted]%) and median DOR is [redacted] months) for the other LBCL subtypes group (Table 14 of the CS), the EAG notes that this is a much smaller subgroup and [redacted] for ORR.

Similar was observed for OS and PFS outcomes; as demonstrated in Figure 2 and Figure 3 above, KM curves are very similar between LBCL and DLBCL groups, meaning the inclusion of patients with other types of LBCL has very little impact. Similar was observed in terms of proportions remaining event-free at particular time points (Tables 17 and 18 in the CS compared to Tables 77 and 78 in the CS appendices). Median PFS in the other LBCL types subgroup was fairly similar to LBCL overall ([redacted] months vs [redacted] months), as were proportions event-free at 6 and 9 months (Table 77 of the CS appendices). The [redacted] for OS, as median OS was [redacted] in the other LBCL types subgroup ([redacted] months vs [redacted] months), with proportions event-free at 6, 9, 12 and 15 months also [redacted] compared to the LBCL population and [redacted] ([redacted]% vs [redacted]%). However, as noted earlier, the EAG highlights that this is a much smaller subgroup and [redacted] for this subgroup.

Given the rarity of these other LBCL subtypes in the trial and in UK practice, focus on the DLBCL population in some MAIC analyses is unlikely to have a large impact on the results (see Section 3.4).

Health-related quality of life

The EAG notes that HRQoL results for FACT-Lym are very similar for DLBCL (n=139) when compared with the overall LBCL results presented in Section 3.3.2 (Table 20 of the CS). Results for the other subtypes (n=18) are [redacted] compared to the overall LBCL population and DLBCL subgroup at some time-points (Table 81 of the CS appendices) [redacted] vs baseline across the time-points. As noted earlier, the EAG highlights that this is a much smaller subgroup and [redacted] patients are analysed at each follow-up time-point for this subgroup.

Similar was observed for EQ-5D-3L results. Results for LBCL (Section 3.3.2 above) and DLBCL populations (Table 21 of the CS) were similar, with [redacted] improvements observed in the DLBCL population, with this most noticeable at day 1 of cycle 3 (change from baseline [redacted] in LBCL vs [redacted] in DLBCL). Differences at other time-points were much smaller. When looking at the other subtypes (n=18), EQ-5D-3L results were [redacted] vs baseline for all time-points apart from day one of cycle 3 (Table 83 of the CS appendices) [redacted] than observed in DLBCL or overall LBCL populations. The EAG highlights that [redacted] patients were analysed for each time-point post-baseline for this subgroup.

Given the rarity of these other LBCL subtypes in the trial and in UK practice, and the fact that results for DLBCL and LBCL populations are largely similar, the EAG does not consider the exclusion of other LBCL types from the economic models for comparisons vs R-based CIT and Pola + BR (focus is on DLBCL with no prior CAR-T [Section B.4.3.1 of the CS], in line with the population analysed in MAICs) with regards to EQ-5D-3L utilities used to be a major issue. The EAG notes that for analyses where MAICs were performed using the LBCL population from EPCORE™ NHL-1 (for example, the updated company base case for population B for the comparison vs axi-cel), results from the overall LBCL population were used to inform EQ-5D-3L utility inputs. It is unclear, however, if this directly matches the population used in the MAIC as it does not specify the CAR-T eligible LBCL population with no prior CAR-T. A comparison of results for EQ-5D-3L utilities between the overall LBCL population and populations analysed in MAICs is provided above in Section 3.3.2.

Adverse events

The EAG notes that the conclusions made in Section 3.3.3 in terms of AE profile can also be made when looking solely at the DLBCL population (n=139), with other LBCL types (n=18) removed (see Tables 32 to 36 of the CS, and Table 14.3.1.5.1 of the CSR tables provided for [redacted]).

3.3.4.2 Prior vs no prior CAR-T treatment

Given that subgroup results provided in Figure 10 of the CS indicate that prior CAR-T use may have an impact on ORR in DLBCL patients, and that those with prior CAR-T use are not included in the populations analysed in MAICs (see Sections 2.3.1.2 and 3.4), the EAG requested at clarification (CQs A1 and A2) that KM curves be provided for subgroups based on prior CAR-T use and that a breakdown of AEs also be provided for these groups.

Survival and response outcomes

KM curves provided for OS and PFS in response to CQ A1 (Figure 4 and Figure 5 below) show that while separation of curves [redacted] for OS, there is [redacted] for PFS, with those in the group with no prior CAR-T treatment [redacted]. Within the LBCL population, median OS and PFS [redacted] in the group with prior CAR-T experience (OS, [redacted] months vs [redacted] months; PFS, [redacted] months vs [redacted] months; Figures 14.2.1.5.2 and 14.2.1.3.2 of the CSR data tables provided for [redacted]).

Results for ORR and CR in the LBCL population broken down according to prior CAR-T use (Figures 14.2.1.1.2 and 14.2.1.2.2 of the CSR data tables provided for [redacted]) indicate that the response [redacted] in those with prior CAR-T use, although not [redacted]. Results for DOR were not reported for the two subgroups.

The fact that results for OS and PFS used in the economic model indicate that [redacted] for those with and without prior CAR-T use means that the EAG considers the exclusion of these patients from MAIC populations to be a limitation of the analyses for population A in terms of applicability to patients that have previously used CAR-T treatments (see Sections 2.3.1.2 and 3.4.2). This may mean that the applicability of these analyses to fourth line treatment or beyond is limited, given CAR-T would usually be an option at third line for those eligible at that point in time. Given when those with prior CAR-T use are removed from the analyses, a proportion with fourth line treatments and beyond remain in the analysis, the EAG considers this limitation to be specific to those with prior CAR-T use rather than any patient at 4L and beyond (see Key Issue 5, Table 6). For the comparison vs axi-cel, the EAG does not consider this to be an issue given to be eligible for axi-cel, patients would not have been treated with CAR-T previously.

Figure 4. KM plot of OS in EPCORE™ NHL-1 LBCL patients by prior CAR-T use (FAS; [redacted] data cut-off) – reproduced from Figure 2 of the company's response to CQ A1

[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CQ, clarification question; FAS, full analysis set; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; NR, not reported; OS, overall survival.

Figure 5. KM plot of PFS in EPCORE™ NHL-1 LBCL patients by prior CAR-T use (FAS; [redacted] data cut-off) – reproduced from Figure 4 of the company's response to CQ A1

[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CQ, clarification question; FAS, full analysis set; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; NR, not reported; PFS, progression-free survival.

Adverse events

On review of the results provided in response to CQ A2 for prior and no prior CAR-T groups (Tables 1 to 5 of the company's CQ response), the EAG considers that AE rates for certain outcomes may vary for these groups. For example, serious TEAEs (all and those related to treatment), TEAEs leading to treatment discontinuation or interruption of treatment and CRS of any severity are [redacted] in the group with no prior CAR-T. Given the company also provided results for the specific

groups analysed as part of MAICs (discussed in Section 3.3.3), the EAG focused on the results presented there to assess the comparability vs the overall LBCL population.

3.3.4.3 Prior anti-lymphoma treatments – 2, 3 and 4+

The subgroup results provided in the CSR for PFS and OS (Figures 14.2.1.3.2 and 14.2.1.5.2 of the CSR data tables provided for [redacted]) indicate that number of prior anti-lymphoma treatments may have an impact on results, and that exclusion of those with prior CAR-T use from populations analysed in MAICs impacts the proportion with different numbers of prior treatments (see Section 2.3.1.2), the EAG requested at clarification (CQs A1 and A2) that KM curves be provided for subgroups with different numbers of prior anti-lymphoma treatments, as well as a breakdown of AEs for these groups.

Survival and response outcomes

KM curves provided for OS and PFS in response to CQ A1 (Figure 6 and Figure 7 below) show that OS curves are [redacted], with [redacted] of those with two or three prior treatments from those with four prior treatments at [redacted]. For PFS, [redacted] occurs earlier [redacted]), with the group with only two prior treatments having [redacted] compared to the [redacted]. Within the LBCL population, median OS and PFS [redacted] for those with 3 or 4+ prior anti-lymphoma treatments compared to the group with only 2 (OS, [redacted] months and [redacted] months for 2 and 4+ groups, respectively [median value for the 3 prior treatments group was [redacted] for OS]; PFS, [redacted] months, [redacted] months and [redacted] months in 2, 3 and 4+ groups, respectively; Figures 14.2.1.5.2 and 14.2.1.3.2 of the CSR data tables provided for [redacted]).

Results for ORR and CR in the LBCL population broken down according to number of prior anti-lymphoma treatments (Figures 14.2.1.1.2 and 14.2.1.2.2 of the CSR data tables provided for [redacted]) indicate that the responses were [redacted] of number of prior treatments for ORR. While differences across groups for CR were [redacted], these were [redacted] and results were [redacted]. Results for DOR were not reported for all of these subgroups but where reported, there [redacted].

The fact that results for OS and PFS (outcomes used in the economic model) indicate that [redacted] for those with 2 and 3+ prior anti-lymphoma treatments is noted by the EAG. As the populations used in MAIC analyses do not completely exclude those receiving epcoritamab as a fourth line treatment or beyond (see Section 2.3.1.2), the EAG does not consider the results of these

analyses to be completely irrelevant to those at fourth line treatment or beyond; however, when considered in combination with the results for prior CAR-T use above in Section 3.3.4.2 for population A, these results may add to the uncertainty about the applicability of MAIC analyses to those with prior CAR-T use (given CAR-T becomes an option at third-line in UK clinical practice for those eligible at that point in time, and there may be some overlap in the EPCORE™ NHL-1 trial between those with 3+ prior anti-lymphoma treatments and prior CAR-T use as proportions with different numbers of prior anti-lymphoma treatments change when prior CAR-T use is excluded in MAICs; see Sections 2.3.1.2 and 3.4.2).

Figure 6. KM plot of OS in EPCORE™ NHL-1 LBCL patients by number of prior lines of therapy (FAS; [redacted] data cut-off) – reproduced from Figure 6 of the company's response to CQ A1

Abbreviations: 2L, two prior treatments; 3L, three prior treatments; 4L+, at least four prior treatments; CI, confidence interval; CQ, clarification question; FAS, full analysis set; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; NR, not reported; OS, overall survival.

Figure 7. KM plot of PFS in EPCORE™ NHL-1 LBCL patients by number of prior lines of therapy (FAS; [redacted] data cut-off) – reproduced from Figure 8 of the company's response to CQ A1

Abbreviations: 2L, two prior treatments; 3L, three prior treatments; 4L+, at least four prior treatments; CI, confidence interval;

CQ, clarification question; FAS, full analysis set; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; NR, not reported; PFS, progression-free survival.

Adverse events

On review of the results provided in response to CQ A2 for number of prior treatment lines (Tables 6 to 10 of the company's CQ response), despite some variation for some AEs, the EAG does not consider there to be a pattern between different lines of treatment and AE rates.

3.4 Critique of trials identified and methods used in the indirect comparisons (MAICs)

3.4.1 Identification of trials and critique of general methods

Included studies

The SLR performed by the company and critiqued by the EAG in Section 3.1 was used as the source of comparator studies for inclusion in the MAICs. In response to CQ A15, studies were said to be selected for inclusion in the MAICs if they:

- included patients that had received at least two prior lines of therapy;
- reported key baseline patient characteristics;
- included KM curve for OS and PFS that clearly displays the survival and progression events or enough information to extract or estimate curves for the population of interest;
- and reported outcomes that were defined in a similar way to the EPCORE™ NHL-1 trial.

The company provides an outline of reasons for exclusion of trials from MAICs in Table 21 of the company's response to CQ A15. Of studies reporting on the correct comparators, two studies were said to be excluded (CORAL and ZUMA-9) due to a lack of details about baseline characteristics and another (DLC-001) was excluded as it included a proportion with only one prior line of treatment,[30-32] which is not in line with the decision problem. Having reviewed these studies the EAG agrees with the company's reasoning. While the SCHOLAR-1 population used in the MAIC vs R-based CIT likely includes some patients with only one prior treatment, the DLC-001 trial is further limited in that it clearly does not represent an R-based CIT group as it involved single agent treatment with one of four drugs.

The EAG notes that Table 21 of the company's response to CQ A15 appears to refer to trials that were included in the SLR. Section D.1.4 of the CS appendices also describes observational studies that were identified through the SLR, with n=227 included in the Excel® sheet provided at submission. A breakdown of reasons why those not eventually included in MAICs was not provided and it is therefore unclear whether any of these may be more appropriate sources of comparator data, particularly for R-based CIT. While the EAG reviewed this list for any that looked relevant for R-based CIT, time constraints meant that this review was limited.

General methods

As EPCORE™ NHL-1 is a single arm study, the company performed unanchored MAICs to obtain comparative evidence. These analyses made use of individual patient data (IPD) available from the ECPORE™ NHL-1 trial and aggregate data from the comparator trials. These analyses require populations between any two trials to be as comparable as possible, which is achieved by excluding particular groups if they are not represented in the comparator trial as well as matching on baseline characteristics by applying propensity score methods to the IPD from EPCORE™ NHL-1.

The EAG agrees with this approach in general but notes that in an ideal situation the company would have access to the IPD comparator trials, which the EAG acknowledges is unlikely for those currently used in the MAICs. This would have been particularly useful for R-based CIT as it may have helped to resolve some limitations described in Key Issue 2 (Table 3) and allowed a comparison through propensity score methods using IPD from the comparator study as well as EPCORE™ NHL-1.[33] The EAG notes that while IPD for SCHOLAR-1 appears to have been available to the authors of the Neelapu *et al.* study used by the company to inform the MAIC vs SCHOLAR-1,[9] this is likely because Kite (a Gilead company) were involved in SCHOLAR-1 and ZUMA-1. IPD for SCHOLAR-1 is, therefore, not likely be available to the company and the same may be true for CORAL.[30]

Methods are described in Section B.2.8 of the CS and Appendix N of the CS appendices. Issues identified by the EAG specific to each MAIC are discussed in the sections that follow.

The EAG notes that across all MAICs, the company's focus on maintaining sample size rather than adjusting for all reported baseline characteristics is inappropriate. The EAG acknowledges that for anchored MAICs, a balance between adjusting for baseline characteristics and effective sample size (ESS) may be important, but that for unanchored MAICs it is crucial that all factors are adjusted for, even if this leads to reduced precision.[34] While the EAG acknowledges that ESS may reduce further

with adjustment of more baseline characteristics, it notes that this in itself indicates a lack of comparability between EPCORE™ NHL-1 and the comparator trial used for each MAIC. Therefore, it is inappropriate to conclude that results without adjustments for further characteristics are more suitable than those with further adjustments; while the precision would likely reduce, the EAG considers less precise and potentially more accurate estimates to be preferable to more precise estimates that are likely to be less accurate.

Age and sex included in the economic modelling

The EAG notes that baseline mean age and sex distribution for the epcoritamab population in the economic model differs for each population and comparator, as summarised in Table 31 below. The EAG considers this to be reasonable given the source matches the population analysed in the MAICs to obtain relative treatment effectiveness results. The mean age for the epcoritamab population when compared to R-based CIT (population A) and axi-cel (population B) is ~[redacted] than that of the overall EPCORE™ NHL-1 population ([redacted] for R-based CIT in population A and [redacted] for axi-cel in population B). The EAG's clinical experts noted that the median ages (which are similar to mean ages below) for EPCORE™ NHL-1 and comparator studies were all lower than might be expected for the 3L+ R/R LBCL population in UK clinical practice; therefore, mean ages for R-based CIT and axi-cel comparators may be particularly [redacted] when considering applicability to the target population in the decision problem. The EAG considers it unlikely that these differences in mean age would impact relative treatment effectiveness given age has been adjusted for in all MAICs. Some differences in the proportion female are also noted by the EAG; all are [redacted] than the EPCORE™ NHL-1 overall population but still consistent with feedback from clinical experts that it is a male dominant disease. The EAG's clinical experts did not highlight differences between males and females with regards to treatment effect. Overall, while the EAG highlights these differences between MAIC populations and the overall LBCL population in EPCORE™ NHL-1, it notes that adjusting the age and sex of each epcoritamab population to its comparator trial is essential to reduce bias associated with relative treatment effects obtained from MAICs and that it is appropriate to use the same adjusted populations to inform these baseline characteristics in the economic model (see Section 7). The EAG expects these values to change if MAICs are updated as requested in Section 1.3.

Table 31. Summary of baseline mean age and proportion female used for the epcoritamab population in the economic model for each comparison and comparison with overall EPCORE™ NHL-1 population

Population	Mean age (years)	Proportion female
A – R-based CIT	[redacted]	[redacted]
A – Pola + BR	[redacted]	[redacted]
B – axi-cel	[redacted]	[redacted]
Overall EPCORE™ NHL-1 LBCL population	[redacted]	[redacted]

Population A represents those who are ineligible for (or choose not to receive) intensive treatments, while population B represents those eligible for intensive treatments such as CAR-T.

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy

3.4.2 *Critique of methods specific to each comparison*

3.4.2.1 *Epcoritamab vs R-based CIT*

Paper used to inform data for SCHOLAR-1

This comparison was relevant to population A, which was those patients ineligible for intensive treatments. Aggregate data for a subset of the SCHOLAR-1 dataset reported in a secondary publication was used for R-based CIT data in the MAIC for epcoritamab vs R-based CIT.[9] This is despite aggregate data from the whole SCHOLAR-1 dataset being available.[9] While the company performed the MAIC adjusted to SCHOLAR-1 as requested in CQ A7 (rather than adjusting to Sehn *et al.* and naively comparing with SCHOLAR-1 results as in the original CS),[10-12] they used the Neelapu *et al.* paper rather than the Crump *et al.* paper recommended by the EAG. The company state that this is because the latter includes 28% of patients with only one prior treatment, which is out of line with the decision problem.

While the EAG acknowledges this, it notes the following:

- the Neelapu *et al.* paper involves an indirect comparison between ZUMA-1 (single arm study where patients received axi-cel) and SCHOLAR-1 through propensity score matching. This means the SCHOLAR-1 population reported in this paper has been adjusted to be more in line with that observed for the ZUMA-1 study. Given the MAIC for population A in the CS is

intended to be applicable to a group that is ineligible for intensive treatments (such as CAR-T), the EAG considers that this adjustment to ZUMA-1 is inappropriate and reduces the applicability of the SCHOLAR-1 population used to this ineligible group. For example, in the Neelapu *et al.* paper 100% of those in SCHOLAR-1 have Eastern Cooperative Oncology Group (ECOG) score 0-1, which is required to be eligible for CAR-T treatments.[9] This differs to Crump *et al.* where the proportion was 73%, with 14% having ECOG scores 2-4.[17] While the EPCORE™ NHL-1 study only includes patients with ECOG score 0-2, the EAG considers that this adjustment to ZUMA-1 removes a group from SCHOLAR-1 that would be considered ineligible for CAR-T treatments. This is subsequently carried through to the MAIC when results for EPCORE™ NHL-1 are adjusted to this paper, as [redacted]% of the adjusted EPCORE™ NHL-1 population has ECOG 0-1;

- the EAG could not confirm the company's assertion that the Neelapu *et al.* paper only includes those with at least two prior treatments; detailed description of the covariates considered for the analyses (page 4 of the supplementary material) suggests some may only have had one prior treatment (as prior treatment lines broken down by 1, 2, 3 or 4+ are described).[9] Therefore, the use of this paper may not resolve the company's concern about including those with only one prior treatment and its applicability to the decision problem.

Therefore, the EAG considers the use of the Neelapu *et al.* paper in the MAIC to be inappropriate. As detailed as part of Key Issue 2 (Table 3), the EAG considers that amendments to the way in which the indirect comparison between epcoritamab and R-based CIT is performed are required, which may include (in order of preference) identification of another source of data for R-based CIT that resolves issues in Table 3 and Table 4, or using the Crump *et al.* paper for SCHOLAR-1 and acknowledging the limitation of a proportion with only one prior treatment being included.[17] The EAG notes that if an alternative R-based CIT study resolving existing issues cannot be identified, use of IPD from SCHOLAR-1 (or any of the four trials that make up SCHOLAR-1, particularly CORAL; see *"other concerns"* below) would be the preferred second option (ahead of using Crump *et al.*) but considers this is unlikely to be available.

Matching of EPCORE™ NHL-1 to SCHOLAR-1

Amendments made to the EPCORE™ NHL-1 population in this MAIC include excluding those with HGBCL, PMBCL or FL Gr 3B and those that had received prior CAR-T treatment from the EPCORE™ NHL-1 population analysed. The EAG could not find a clear statement that prior CAR-T use was

excluded from SCHOLAR-1 in the paper used by the company but notes that it is plausible given the paper involved an indirect comparison between a study using CAR-T treatment (where prior CAR-T use was excluded) and chemoimmunotherapy (CIT), with adjustments performed to make the populations more comparable.[9] As discussed in Sections 2.3.1.2 and 3.3.4.2, as results for those with prior CAR-T use in the EPCORE™ NHL-1 [redacted], the EAG considers the results of this MAIC (and subsequently the economic model) may not be applicable to a group with prior CAR-T use (see Key Issue 5, Table 6).

In terms of the types of LBCL included, the EAG's understanding is that the paper included LBCL overall rather than DLBCL, although a breakdown of this in the paper could not be identified. Therefore, limiting the EPCORE™ NHL-1 population used in the analysis to DLBCL may not have been required and may add unnecessary additional uncertainty to the analysis; if these patients were included in the SCHOLAR-1 population but excluded from the EPCORE™ NHL-1 population analysed, this may introduce bias in favour of epcoritamab given feedback from the EAG's clinical experts (Section 2.3.1.2) that prognosis may differ slightly for certain LBCL types and results for epcoritamab in Section 3.3.4.1 that [redacted]. While other types may be rare and the impact may be small, the EAG considers this to be an uncertainty that would ideally be aligned in the two arms of the MAIC. This is covered as part of Key Issue 2 (Table 3).

The EAG is unsure whether the [redacted] analysed for epcoritamab in this MAIC represents a group ineligible for intensive treatments, which is the population the company state that the comparison vs R-based CIT would be applicable to; further clarification on this and, if some eligible for intensive treatments are included, exploration of the impact on the results of the MAIC and the economic model if the analysis was limited to those not eligible would help to address this uncertainty. This is included as Key Issue 6 (Table 7).

As part of the MAIC, adjustment of the EPCORE™ NHL-1 population to SCHOLAR-1 for baseline characteristics via propensity scores was performed. For reasons described in Section 3.4.1, the EAG requested that MAICs adjust for all reported baseline characteristics (CQ A7). While adjustment of baseline characteristics was performed by the company, this did not include all baseline characteristics reported for the SCHOLAR-1 population due to concerns about further reducing the ESS (see Section 3.4.1). A comparison of baseline characteristics for EPCORE™ NHL-1 (before and after adjustment) and SCHOLAR-1 is presented in Table 32 below.

The EAG notes that while most factors listed in this table have been adjusted for, others have not. Of particular concern to the EAG are the proportion with *"≥3 lines of chemo and ASCT"* and *"SCT any time after refractory disease"* as these clearly remain imbalanced. The EAG is unsure in which direction the latter may bias estimates but considers that the higher proportion with *"≥3 lines of chemo and ASCT"* in the EPCORE™ NHL-1 population would likely bias against epcoritamab. In addition, despite adjustment, the proportion with disease stage III-IV still appears to be fairly imbalanced, with the higher rate in the epcoritamab arm likely to bias against epcoritamab. Even if these remaining imbalances are conservative in terms of epcoritamab, the EAG's preference would be for these to be adjusted for or resolved, for reasons described in Section 3.4.1 (see Key Issues 2 and 7, Table 3 and Table 8). The EAG considers that if the Neelapu *et al.* paper was not used to inform SCHOLAR-1 data (and, for example, an alternative source of R-based CIT data is identified to resolve points highlighted in Key Issues 2 and 3 (Table 3 and Table 4), or if the Crump *et al.* paper is used), a better match for certain factors may be possible (for example, the Crump *et al.* paper reports a proportion with disease stage III-IV that is more comparable [72.0%] to that of the unadjusted EPCORE™ NHL-1 population in Table 32 below and if a SCHOLAR-1 population not adjusted to ZUMA-1 is used, imbalances may be reduced).

In addition, the EAG highlights that all patients in SCHOLAR-1 were refractory to treatment, whereas EPCORE™ NHL-1 includes refractory or relapsed patients. The EAG's clinical experts noted that whether someone relapsed or was refractory to their last treatment is an important prognostic factor, with refractory patients likely to experience worse outcomes. While some adjustments have been made for refractoriness, such as the number of consecutive treatments refractory to or primary refractoriness, differences between the two trials mean this could not be adjusted for and relapsed patients remain included in the EPCORE™ NHL-1 population (proportion unclear for the MAIC analysis), which may favour epcoritamab. The EAG considers this to be a limitation of this MAIC which is unavoidable when SCHOLAR-1 is used and represents a potentially important difference that is not accounted for. This is included as part of Key Issue 3 (Table 4).

Table 32. Baseline characteristics for updated base case analysis A (ECPORE™ NHL-1 DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) – reproduced from Table 18 of the company's response to CQ A7

	Unadjusted epcoritamab DLBCL, no CAR-T ([redacted])	Adjusted epcoritamab DLBCL, no CAR-T ([redacted])	SCHOLAR-1 CIT (n=340)
Age	-	-	
Median (years)	[redacted]	[redacted]	**55**

≥ 65 years	[redacted]	[redacted]	16.5%
Male	[redacted]	[redacted]	**67.9%**
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]	**100.0%**
Disease stage III-IV	[redacted]	[redacted]	**64.5%**
IPI score ≥3	[redacted]	[redacted]	27.7%
Number of prior lines	-	-	
≥3 lines of chemo and ASCT	[redacted]	[redacted]	28.8%
Primary refractory	[redacted]	[redacted]	**37.1%**
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]	**50.0%**
Relapse within 12 months of ASCT	[redacted]	[redacted]	**21.8%**
SCT any time after refractory disease	[redacted]	[redacted]	37.1%

Bold highlighted values indicate those adjusted for: age (≥65 years), male, ECOG performance status, disease stage, primary refractory, refractory to ≥2 consecutive lines of therapy, and relapse within 12 months of ASCT. Weights truncated at 1% and 99%.

Abbreviations: ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; CQ, clarification question; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance score; IPI, International Prognostic Index; n^{eff}, effective sample size; NHL, Non-Hodgkin lymphoma; SCT, stem cell transplant.

Other concerns about SCHOLAR-1 applicability

The EAG notes that there is not a breakdown of types of CIT used in the SCHOLAR-1 dataset and that not all patients included may necessarily have used R-based CIT. However, the Crump *et al.* paper describes SCHOLAR-1 as representing a large number of patients treated in the "modern rituximab era".[17] How representative SCHOLAR-1 is of R-based CIT is therefore, considered an uncertainty (Key Issue 3, Table 4), but the EAG's clinical experts considered it to be a reasonable source of data for CIT, and the largest they were aware of.

The EAG explored other studies that might be used to inform R-based CIT in this MAIC, including a paper by Mounier *et al.*, PIX301 and PIX306.[35-37]. However, these were considered to have their own limitations as well as being smaller studies and were not thought to be suitable alternatives. For PIX301, it appears that the comparator arm did not include rituximab even for a proportion of patients (options were vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone or gemcitabine), meaning this study is not a good representation of R-based CIT and may underestimate survival

outcomes.[36] For PIX306 (comparator of gemcitabine + rituximab), the EAG acknowledges the company's response to CQ B13, which indicates that 67.5% had either no or only one prior treatment. This is a higher proportion than that observed in the Crump *et al.* paper for SCHOLAR-1 (28%) making it less applicable to the decision problem population.[17, 37] The Mounier *et al.* (R-GemOx comparator) paper has a number of limitations, including the fact that only 63% of patients included had received prior rituximab treatment (which is not reflective of UK practice; SCHOLAR-1 included a requirement for patients to have had prior anti-CD20 treatment, which is the class that rituximab belongs to)[17] and it appears that the majority may have had only one prior treatment, although the latter is unclear.[35]

The EAG also explored the four trials that make up SCHOLAR-1 and noted that a paper identified for CORAL in those with at least two prior treatments may have been an option to avoid the issue of including patients with only one prior treatment, but the company notes in Table 21 of their response to CQ A15 that few baseline characteristics were reported. The EAG agrees that this would make an MAIC difficult, unless IPD were available.[30] Whether third-line treatments included rituximab was also unclear as for the SCHOLAR-1 paper currently used. Limitations of SCHOLAR-1 and potential ways of resolving this are covered as part of Key Issues 2 and 3 (Table 3 and Table 4).

Outcome data in SCHOLAR-1

The EAG notes that the SCHOLAR-1 KM curve used for OS was digitised from the study by Neelapu *et al.* (company response to CQ B6). As censoring was not presented in the version in the paper, the company created pseudo-IPD using assumptions based on censoring as reported in the Crump *et al.* study. While not ideal given the populations included in the Neelapu *et al.* and Crump *et al*. papers are different, the EAG is unclear as to how this would impact the distribution of censoring events for OS. Given the EAG has concerns about the use of the Neelapu *et al.* paper, this is considered to be an additional factor to consider with regards to using this paper, as included under Key Issue 2 (Table 3).

In terms of outcomes, the company concludes that outcome definitions were comparable between SCHOLAR-1 and EPCORE™ NHL-1. The EAG notes that response outcomes differed in terms of criteria used as well as who assessed them (International Working Group [IWG] by investigator for SCHOLAR-1 and IRC using Lugano criteria for EPCORE™ NHL-1), but these were not used in the

economic model. For OS, the EAG considers that definitions are likely to be comparable given the nature of this outcome. PFS was not reported for the SCHOLAR-1 trial.

Furthermore, while baseline characteristics for the SCHOLAR-1 population are provided for a sample size of n=340, the EAG notes that the curve obtained for OS is based on n=331. The baseline characteristics, therefore, do not quite match the population the curve is based on. However, the EAG notes that the difference is small (n=9) and this has very little impact on the baseline characteristics, with most being identical. This is, therefore, not considered to be a major issue.

3.4.2.2 Epcoritamab vs Pola + BR

Aggregate data for patients in the subset with at least two prior treatments from a study by Sehn *et al.* was used for Pola + BR data in the MAIC for epcoritamab vs Pola + BR.[10-12] Baseline characteristics for this population within this study were obtained from the EUnetHTA submission for Pola + BR, while data from Sehn *et al.* 2019 and 2022 papers were used to estimate survival curves and inform best response outcomes. This comparison was relevant to population A, which was those patients ineligible for intensive treatments.

Applicability of Sehn* et al*. and other sources of data

The EAG's clinical experts considered this study to be a reasonable source of data for Pola + BR. Data were obtained specifically for the subgroup with at least two prior treatments. The trial was limited to those with DLBCL, as described in the previous section. All patients included had received prior rituximab.

The company explored an alternative source for Pola + BR data as they noted limitations of Sehn *et al.* based on clinical expert feedback.[10-12] Feedback from their clinical experts, and based on comparisons with UK-based real world evidence (RWE),[38] suggested that data from Sehn *et al.* may be overly optimistic in terms of outcomes of Pola + BR; at second-line and beyond for R/R DLBCL, median OS and PFS were 12.4 months and 9.5 months, respectively, in Sehn *et al.* 2019,[10] while this was lower in the RWE study (median OS 8.2 months and median PFS 4.8 months).[38] The RWE study was not used by the company in the MAIC as it was not possible to obtain data solely for the group with one prior treatment.

A second RWE study is instead used as a scenario in the MAIC, with adjustments performed to this study (Sections N.2.2 and N.2.3 of the CS appendices).[13] This study was specific to LBCL patients with at least two prior treatment failures including rituximab. The salvage cohort, rather than bridging cohort, was used. The median OS in this paper was even lower than that mentioned above by the company. While the comparison in this MAIC is vs Pola + BR, the EAG notes that this paper refers to polatuzumab vedotin (Pola) in general; only 60% in the salvage cohort had Pola + BR. The applicability of this paper to Pola + BR is, therefore, limited. Given this limitation, the EAG did not consider this scenario further in the report. In the absence of any other identified papers, the EAG notes the potential overestimation of Pola + BR as a potential limitation of the MAIC, included as part of Key issue 9 (Table 10).

***Matching of EPCORE™ NHL-1 to Sehn* et al.**

To better align the EPCORE™ NHL-1 population with Sehn *et al.*, those with high-grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) or FL Gr 3B) were excluded given Sehn *et al.* was limited to DLBCL. Similarly, as there were said to be no patients with prior CAR-T use in the Sehn *et al.* population, these patients were also excluded from the revised EPCORE™ NHL-1 population. Only one patient in Sehn *et al.* for the group with at least two prior treatments had non-DLBCL (follicular lymphoma) and it is unclear if this was FL Gr 3B as in the decision problem for the CS. The company assumed for this analysis that this study only included DLBCL. The EAG could not find a clear statement that prior CAR-T use was excluded in Sehn *et al.* but notes that it is not listed in the table providing a breakdown of prior treatments received.

As discussed in Sections 2.3.1.2 and 3.3.4.2, as results for those with prior CAR-T use in the EPCORE™ NHL-1 [redacted], the EAG considers the results of this MAIC (and subsequently the economic model) may not be applicable to a group with prior CAR-T use (see Key Issue 5, Table 6). In terms of limiting to DLBCL, while some potential differences in terms of prognosis between DLBCL and other types of LBCL were mentioned by the EAG's clinical experts, these are not thought to be substantial. Results for epcoritamab discussed in Section 3.3.4.1 demonstrate that [redacted] based on type of LBCL, [redacted] given their rarity in the trial and in UK practice. The EAG acknowledges that while it would be preferable (see Key Issue 4,

Table 5) to include the full LBCL population where possible, the exclusion of non-DLBCL may be required for this comparison to improve the comparability of trials used in MAIC.

The EAG is unsure whether the [redacted] analysed for epcoritamab in this MAIC represents a group ineligible for intensive treatments, which is the population the company state that the comparison vs Pola + BR would be applicable to; further clarification on this and, if some eligible for intensive treatments are included, exploration of the impact on the results of the MAIC and the economic model if the analysis was limited to those not eligible would help to address this uncertainty. This is included as Key Issue 6 (Table 7).

At the clarification stage, for reasons described in Section 3.4.1, the EAG requested that the MAIC was updated to adjust for all reported baseline characteristics, including some mentioned by the EAG's clinical experts as potentially prognostic that were not already adjusted for (CQ A8). The company did not update the MAICs in response to this, as they maintain that all clinically important variables have been adjusted for and further adjustment would reduce the ESS unnecessarily. The EAG does not consider this to be appropriate, as discussed in Section 3.4.1 with regards to adjustment in unanchored MAICs.

A comparison of baseline characteristics for EPCORE™ NHL-1 (before and after adjustment) and Sehn *et al.* is presented in Table 33 below. The EAG notes that while six factors in this table have been adjusted for, there are others that have not and that remain imbalanced. Of particular concern to the EAG is the proportion refractory to last anti-lymphoma therapy. The EAG's clinical experts noted that whether someone relapsed or was refractory to their last treatment is an important prognostic factor, with refractory patients likely to experience worse outcomes. Given the proportion is higher in the Pola + BR study (93.1% vs [redacted]%), this may introduce bias in favour of epcoritamab. It would, therefore, be preferable for this factor to be adjusted for (see Key Issue 7, Table 8). While the company note that other measures of refractoriness have been adjusted for (refractory to last anti-CD20 treatment in this analysis), the EAG notes that this does not remove concerns about this remaining imbalance.

Other factors not adjusted for but that are reported in both studies include International Prognostic Index (IPI) score ≥3 and number of prior treatment lines. The company state (response to CQ A6) that IPI score was not adjusted for based on clinical expert feedback that if disease stage III-IV is adjusted for, this is not necessary. They also note that ECOG score and age, which are other

components of the IPI score, are also adjusted for and that even without adjustment for this factor they are very similar in the two arms (higher for EPCORE™ NHL-1, potentially biasing against epcoritamab). While they are similar and it may not be deemed a priority, inclusion of this factor would improve the comparability of the two studies, particularly as IPI score includes other factors such as extranodal sites and serum lactate dehydrogenase levels (see Key Issue 7, Table 8).

Number of prior lines of therapy was not included in the adjustment due to variability in the number of prior lines of therapy in each trial, exact regimens administered and sequences of administration. In addition, the company explain that as prior lines of therapy is deemed to be influenced by other factors adjusted for (such as ECOG score and age), it was not adjusted for to avoid issues with multicollinearity and over-adjustment of the data. For reasons described in Section 3.4.1 and as proportions with at least three prior treatments is imbalanced in the table below, the EAG consider that inclusion of this factor in the adjustment would be useful (see Key Issue 7, Table 8). Feedback from the EAG's clinical experts was that those with more treatment failures could represent a more difficult to treat population with worse prognosis.

Furthermore, due to not being reported in the Sehn *et al.* study, it is unclear how comparable the two studies included in the MAIC are in terms of other characteristics in the table below, in particular, primary refractoriness was highlighted by the EAG's clinical experts as an important prognostic factor. This is included as a limitation of the MAIC in Key Issue 9 (Table 10).

Table 33. Baseline characteristics for scenario analysis A.1 (ECPORE™ NHL-1 DLBCL, no prior CAR-T population adjusted to Sehn *et al.*) – adapted from Table 26 of the CS

	Unadjusted epcoritamab DLBCL, no CAR-T ([redacted])	Adjusted epcoritamab DLBCL, no CAR-T ([redacted])	Pola + BR 3L+ subgroup, EUnetHTA publication (n=29)[a, 12]
Age	-	-	-
Median (years)	[redacted]	[redacted]	65
≥ 65 years	[redacted]	[redacted]	**51.7%**
Male	[redacted]	[redacted]	**72.4%**
DLBCL (including TFL)	[redacted]	[redacted]	Assumed 100%
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]	**89.3%**
Disease stage III-IV	[redacted]	[redacted]	**86.2%**
IPI score ≥3	[redacted]	[redacted]	55.2%
Number of prior lines	-	-	-
2 lines of prior therapy	[redacted]	[redacted]	37.9%

≥3 lines of chemo and ASCT	[redacted]	[redacted]	62.1%
Primary refractory	[redacted]	[redacted]	-
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]	-
Refractory to second line or subsequent therapy	[redacted]	[redacted]	-
Refractory to last prior anti-CD20 agents[b]	[redacted]	[redacted]	**51.7%**
Refractory to last prior anti-lymphoma therapy[c]	[redacted]	[redacted]	93.1%
Prior ASCT	[redacted]	[redacted]	**34.5%**
Relapse within 12 months of ASCT	[redacted]	[redacted]	-
SCT any time after refractory disease	[redacted]	[redacted]	-

[a]Data from the EUnetHTA submission for Pola + BR were used to inform baseline characteristics of the 3L+ population. Data from Sehn *et al.* (2019) and Sehn *et al.* (2022) were used to estimate 3L+ survival curves and inform best response outcomes; [b]Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date in patients whose last prior regimen contained anti-CD20; [c]Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date.

Bold highlighted values indicate those adjusted for: age (≥65 years), male, ECOG performance status, disease stage, refractory to last prior anti-CD20 agents, and prior ASCT. Weights truncated at 1% and 99%.

Abbreviations: 3L+, third line or beyond; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; CS, company submission; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance score; IPI, International Prognostic Index; n^{eff}, effective sample size; NHL, Non-Hodgkin lymphoma; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; SCT, stem cell transplant; TFL, transformed follicular lymphoma.

Obtaining survival curves for Pola + BR

In Appendix N.1 and response to CQ A13, the company explain that OS and PFS KM curves for the subgroup with at least two prior treatments were not available in any of the papers. Instead, the company used data provided in the publications cited to derive synthetic OS and PFS KM curves by number of prior treatment lines using the Guyot algorithm to simulate patient-level data from curves published for the overall population. As highlighted in Tables 93 and 94 of the CS appendices, the EAG agrees that derived synthetic survival summary statistics appear to be a good match for those reported in the publications regarding prior treatment lines. While there are some differences for certain groups, values for the group used in the CS (two or more prior lines) are very similar and the EAG does not consider the use of this methodology to be a major concern.

***Outcome data in Sehn* et al.**

In terms of outcomes, the company concludes that outcome definitions were comparable between Sehn *et al.* and EPCORE™ NHL-1. The EAG notes that response and PFS outcomes differed slightly in terms of criteria used (Lugano vs modified Lugano) but that both were based on an independent review committee. The EAG is unsure how the modified Lugano criteria described in the Sehn *et al.* study and those used in the EPCORE™ NHL-1 study differ. Given they are both versions of the same criteria, the EAG does not consider this to be a major concern. For OS, the EAG considers that definitions are likely to be comparable given the nature of this outcome.

3.4.2.3 Epcoritamab vs axi-cel

Aggregate data for patients from ZUMA-1, a single-arm study including people with LBCL that was refractory or relapsed, was used for axi-cel data in the MAIC for epcoritamab vs axi-cel.[14] This comparison was relevant to population B, which included those eligible for intensive treatments.

Applicability of ZUMA-1 and other sources of data

The EAG's clinical experts considered this study to be a reasonable source of data for axi-cel. While the company state that this study was specific to those with at least two prior treatments, the EAG notes a small proportion with one prior treatment on review of the paper (three patients [3% of n=101 analysed]; Table 1 of the Locke *et al.* paper).[14] Given this small proportion, the EAG do not consider this to be a major issue. The trial was not limited to DLBCL, meaning the MAIC could include LBCL. While the company's preference in the original CS in terms of the base case for population B was to use an analysis limited to DLBCL, at clarification this was amended based on the EAG's preference for the LBCL analysis (CQ A9).

No other sources of data for axi-cel were explored as part of the CS but the EAG has no major concerns about the use of this study.

Matching of EPCORE™ NHL-1 to ZUMA-1

To better align the EPCORE™ NHL-1 population with ZUMA-1, those with prior CAR-T use were excluded from the revised EPCORE™ NHL-1 population. In addition, the analysis was limited to those who were eligible for CAR-T treatment in the EPCORE™ NHL-1 trial. The EAG does not consider the

exclusion of those with prior CAR-T use to be an issue for this particular comparison given feedback from the EAG's clinical experts was that CAR-T would only be used once in each patient. Therefore, this comparison vs axi-cel would only be relevant for patients who are eligible for CAR-T and have not previously used it.

At the clarification stage, for reasons described in Section 3.4.1, the EAG requested that the MAIC was updated to adjust for all baseline characteristics, including some mentioned by the EAG's clinical experts as potentially prognostic that were not already adjusted for (CQ A9). The company did not update the MAICs in response to this, as they maintain that all clinically important variables have been adjusted for and further adjustment would reduce the ESS unnecessarily. The company considers that any remaining imbalances would likely bias against epcoritamab. The EAG does not consider this to be appropriate, as discussed in Section 3.4.1 with regards to adjustment in unanchored MAICs. The company did, however, update their base case in the model for population B to use the adjusted results from the MAIC rather than unadjusted results (CQ A9).

A comparison of baseline characteristics for EPCORE™ NHL-1 (before and after adjustment) and ZUMA-1 is presented in Table 34 below. The EAG notes that while various factors in this table have been adjusted for, there are others that have not and that remain imbalanced. Of particular concern to the EAG are proportions with IPI score ≥3 and ≥3 prior lines of treatment. The rationale provided by the company for not including these two factors in the adjustment is the same as that described above for the MAIC vs Pola + BR (see response to CQ A6). Given these factors are imbalanced and may bias in favour of epcoritamab (as higher proportions are seen in the ZUMA-1 arm and these are factors that may be associated with worse outcome), and for reasons described above for the comparison vs Pola + BR, the EAG considers that the MAIC would be improved by inclusion of these factors. The EAG also notes that the proportion refractory to second line or subsequent therapy is imbalanced, with a higher proportion in the epcoritamab arm; ideally all factors in imbalance would be included in MAIC adjustments but the EAG notes that other measures of refractoriness have already been included and based on feedback from the EAG's clinical experts the EAG considers primary refractoriness and refractoriness to last treatment to be most important in terms of history of refractoriness. This is included as part of Key Issue 7 (Table 8).

Furthermore, due to not being reported in ZUMA-1, it is unclear how comparable the two studies included in the MAIC are in terms of other characteristics, including refractory to last anti-lymphoma treatment, which was raised by the EAG's clinical experts as being important in terms of prognosis.

In addition, some factors adjusted for in MAICs for the other comparisons were not reported (such as prior ASCT) and could not be adjusted for. This is included as a limitation of the MAIC Key Issue 10 (Table 11).

Table 34. Baseline characteristics for updated base case analysis B (ECPORE™ NHL-1 LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – reproduced from Table 28 of the CS

	Unadjusted epcoritamab LBCL, no CAR-T, CAR-T eligible ([redacted])	Adjusted epcoritamab LBCL, no CAR-T, CAR-T eligible ([redacted])	Axi-cel, ZUMA-1 (n=101)
Age	-	-	-
Median (years)	[redacted]	[redacted]	58
≥ 65 years	[redacted]	[redacted]	**23.8%**
Male	[redacted]	[redacted]	**67.3%**
DLBCL (including TFL)	[redacted]	[redacted]	**92.1%**
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]	**100.0%**
Disease stage III-IV	[redacted]	[redacted]	**85.1%**
IPI score ≥3	[redacted]	[redacted]	47.5%
Number of prior lines	-	-	-
≥3 lines of treatment	[redacted]	[redacted]	69.3%
History of primary refractory disease	[redacted]	[redacted]	**25.7%**
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]	**53.5%**
Refractory to second line or subsequent therapy	[redacted]	[redacted]	77.2%
Relapse within 12 months of ASCT	[redacted]	[redacted]	**20.8%**

Bold age (≥65 years), male, DLBCL, ECOG PS (0 or 1), disease stage III–IV, history of primary refractory disease, history of resistance to two consecutive lines of therapy and relapse after autoSCT within 12 months. Weights truncated at 1% and 99%.

Abbreviations: ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CS, company submission; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance score; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; n^{eff}, effective sample size; NHL, Non-Hodgkin lymphoma; TFL, transformed follicular lymphoma.

Outcome data in ZUMA-1

In terms of outcomes, the company concludes that outcome definitions were comparable between ZUMA-1 and EPCORE™ NHL-1. The EAG notes that response and PFS outcomes differ in terms of

criteria used (Lugano vs IWG criteria) but that both were based on an IRC. Various differences between these criteria are apparent, which includes factors such as how responses are defined and how progression is defined.[39] The EAG is unsure how these differences would impact the results of the MAIC, but notes that the criteria used to define progression using Lugano may be more sensitive, and any differences might bias against epcoritamab. The EAG consider this, however, to be an uncertainty and it may be possible for the company to explore how the IWG criteria would impact the MAIC if applied to IPD from the analysed EPCORE™ NHL-1 population (Key Issue 10, Table 11). For OS, the EAG considers that definitions are likely to be comparable given the nature of this outcome.

The EAG notes that CQ A9 also requested that 5-year data for ZUMA-1 was incorporated. The company have not implemented this given they note that a similar follow-up was not available for EPCORE™ NHL-1 currently but would consider this when further data becomes available. While the EAG does not consider this would affect results generated from the MAICs, 5-year data from ZUMA-1 would be important had the company implemented the EAG's request (CQ A10) for independent fitting of survival curves for each arm (rather than using hazard ratios [HRs] obtained from MAICs) to model survival in the economic model (see Section 4.2.4).

As noted by the company in response to CQ B15, the EAG's clinical experts note that there is a risk of bias in favour of axi-cel in studies that use only those infused with the treatment. This is because in clinical practice there is a delay between deciding to give the treatment and receiving the treatment, as the CAR-T treatment needs to be manufactured specific to the patient. In the time between these steps, patients can progress and become ineligible for CAR-T. Studies focusing on those infused would, therefore, not capture this group. The EAG notes that ZUMA-1 was limited to those receiving infusion. The EAG considers this to be a limitation of the MAIC that can't be resolved when using ZUMA-1 (see Key Issue 10, Table 11).

3.5 Results of the indirect comparisons (MAICs)

3.5.1 Epcoritamab vs R-based CIT

The results from the MAIC for epcoritamab vs R-based CIT are summarised in Table 35 and Figure 8 below. These are taken from the company's response to CQ A7. The EAG notes that of these outcomes, only OS is used in the economic model (see Section 4.2.4). PFS was not reported in the

SCHOLAR-1 study so a MAIC for this outcome could not be performed. Results for naïve comparisons (unadjusted epcoritamab) and results following adjustment in the MAIC (adjusted epcoritamab) are presented.

The results indicate better OS with epcoritamab, which is [redacted] and improved further when adjustments are made via the MAIC. Similar conclusions can be made based on response rates reported, with higher rates of CR and ORR for epcoritamab and [redacted]. The EAG has concerns about using HRs to generate curves for R-based CIT in the economic model, for reasons described in Section 4.2.4.2.1 and Section 4.2.4.4.2.

The EAG notes that important sources of uncertainty regarding this MAIC remain and should be considered (see Section 3.4.2.1). These include the SCHOLAR-1 study only including refractory patients and it being unclear if all or most patients used R-based CIT, use of the Neelapu *et al.* paper, whether it was necessary to limit the EPCORE™ NHL-1 population to DLBCL for this analysis, some factors in imbalance not being adjusted for and the need to assume that censoring in the Neelapu *et al.* population for SCHOLAR-1 is proportional to that observed in Crump *et al.*. While some may introduce bias against epcoritamab, others have the potential to bias in favour of epcoritamab (or the likely direction of impact is uncertain) and they do not necessarily balance out. In addition, the EAG considers the same results may not be applicable to a population that has previously had CAR-T treatment.

Table 35. Unadjusted and adjusted outcomes for epcoritamab vs R-based CIT (updated base case analysis A – epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) – adapted from Table 19 of the company's response to CQ A7

Outcome (epcoritamab vs R-based CIT)	Unadjusted epcoritamab ([redacted])	Adjusted epcoritamab ([redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
Response rates		
CR	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CQ, clarification question; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; n^{eff}, effective sample size; ORR, overall response rate; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy.

Figure 8. Unadjusted and adjusted OS for epcoritamab vs R-based CIT (updated base case analysis A – DLBCL, no prior CAR-T population adjusted to SCHOLAR-1[a]) – reproduced from Figure 10 of the company's response to CQ A7

[a]Number at risk for SCHOLAR-1 was derived from the synthetic IPD because the number at risk was not reported in the published article.
Abbreviations: CAR-T, chimeric antigen receptor T-cell; CQ, clarification question; DLBCL, diffuse large B-cell lymphoma; EPCO, epcoritamab; NHL, Non-Hodgkin lymphoma; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy.

3.5.2 Epcoritamab vs Pola + BR

The results from the MAIC for epcoritamab vs Pola + BR are summarised in Table 36, Figure 9 and Figure 10 below. These are taken from Section N.2.1 of the CS appendices. Of these outcomes, only OS and PFS are used in the economic model (see Section 4.2.4). Results for naïve comparisons (unadjusted epcoritamab) and results following adjustment in the MAIC (adjusted epcoritamab) are presented for response outcomes but only adjusted results are presented for survival outcomes.

The EAG notes that due to concerns about proportional hazards being violated, separate HRs for up to and after [redacted] were calculated. The EAG agrees that proportional hazards appear to be

violated for this comparison and that KM curves for OS and PFS cross at a time-point of ~[redacted], but notes that for PFS this is not the only place where curves cross meaning the HRs generated for this outcome may not be as reflective of the survival data. The EAG has concerns about using HRs to generate curves for Pola + BR in the economic model, for reasons described in Section 4.2.4.2.2 and Section 4.2.4.4.3. Results for survival outcomes (OS and PFS) indicate a [redacted] with Pola + BR up to [redacted]. P-values are not reported but based on confidence intervals [redacted], the difference for OS appears [redacted] but not for PFS. After [redacted], results for both outcomes [redacted] though differences [redacted]. The company explained that these observations are clinically plausible based on the fact that Pola + BR is given for a fixed duration and progression may increase once treatment is stopped, while epcoritamab is a non-finite treatment, and that the mechanism of action of epcoritamab means that efficacy builds over the first month during the dosage increase. The EAG agrees with the company's point about Pola + BR treatment duration potentially contributing to this, as patients in Sehn *et al.* received up to six 21-day cycles of treatment. While the EAG notes that epcoritamab dosing builds in the first cycle (see Table 24), the EAG is unsure how much this contributes to the differences observed between time-points given the maximum dose is being received by the second month in EPCORE™ NHL-1.

Results for response rates are not broken down by time-point and suggest that overall, a [redacted] proportion of patients with epcoritamab experience CR ([redacted]) while a [redacted] proportion reached the criteria for inclusion under ORR ([redacted]). The company explained in the CS (footnote of Table 24) that information on best overall response was not available for the group with at least two prior treatments in the EUnetHTA submission (n=40) and that they instead assumed the rate was the same as this subgroup within the long-term extension of the Sehn *et al.* study (n=102) for response rate outcomes in Table 36 below.[11, 12] The EAG highlights this as an area of uncertainty but notes that these response outcomes were not used to inform the economic model.

The EAG notes that important sources of uncertainty regarding this MAIC remain and should be considered (see Section 3.4.2.2). These include the fact that the outcomes for Pola + BR in the Sehn *et al.* study are considerably better than RWE identified by the company and that not all factors imbalanced, including those that are thought to be prognostic, have been adjusted for as part of the MAIC. While some may introduce bias against epcoritamab, others have the potential to bias in favour of epcoritamab and they do not necessarily balance out. In addition, the EAG considers the same results may not be applicable to a population that has previously had CAR-T treatment.

Table 36. Unadjusted and adjusted outcomes for epcoritamab vs Pola + BR (scenario A.1 – epcoritamab DLBCL, no prior CAR-T population adjusted to Sehn *et al.*) – adapted from Table 96 of the CS appendices

Outcome (epcoritamab vs Pola + BR)	Unadjusted epcoritamab ([redacted])[a]		Adjusted epcoritamab ([redacted])	
	Up to [redacted]	After [redacted]	Up to [redacted]	After [redacted]
Survival, HR (95% CI)				
OS	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]
Response rates[b]				
CR	[redacted]		[redacted]	
Difference, % (95% CI)	[redacted]		[redacted]	
ORR	[redacted]		[redacted]	
Difference, % (95% CI)	[redacted]		[redacted]	

[a]Unadjusted piecewise HRs for OS and PFS were not generated; [b]information on best overall response was not available for the group with at least two prior treatments in the EUnetHTA submission (n=40) and the rate was instead assumed to be the same as this subgroup within the long-term extension of the Sehn *et al.* study (n=102) for response rate outcomes.[11, 12]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CR, complete response; CS, company submission; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; n^{eff}, effective sample size; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine.

Figure 9. Unadjusted and adjusted OS for epcoritamab vs Pola + BR (scenario A.1 – DLBCL, no prior CAR-T population adjusted to Sehn *et al.*[a]) – reproduced from Figure 14 of the CS appendices

[redacted]

[a]The KM curve for Pola + BR is a synthetic curve specific for the group with at least two prior treatments, derived using the Guyot algorithm to simulate patient-level data using information provided in Sehn *et al.* 2019 and the EUnetHTA submission.[10, 12]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CS, company submission; DLBCL, diffuse large B-cell lymphoma; EPCO, epcoritamab; KM, Kaplan-Meier; NHL, Non-Hodgkin lymphoma; OS, overall survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine.

Figure 10. Unadjusted and adjusted PFS for epcoritamab vs Pola + BR (scenario A.1 – DLBCL, no prior CAR-T population adjusted to Sehn *et al.*[a]) – reproduced from Figure 15 of the CS appendices

[redacted]

[a]The KM curve for Pola + BR is a synthetic curve specific for the group with at least two prior treatments, derived using the Guyot algorithm to simulate patient-level data using information provided in Sehn *et al*. 2019 and the EUnetHTA submission.[10, 12]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CS, company submission; DLBCL, diffuse large B-cell lymphoma; EPCO, epcoritamab; IRC, Independent Review Committee; KM, Kaplan-Meier; NHL, Non-Hodgkin lymphoma; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine.

3.5.3 Epcoritamab vs axi-cel

The results from the MAIC for epcoritamab vs axi-cel are summarised in Table 37, Figure 11 and Figure 12 below. These are taken from Section B.2.8.2 of the CS and the company's response to CQ A14. Of these outcomes, only OS and PFS are used in the economic model (see Section 4.2.4). Results for naïve comparisons (unadjusted epcoritamab) and results following adjustment in the MAIC (adjusted epcoritamab) are presented.

HRs obtained for survival outcomes (OS and PFS) indicate a [redacted] with epcoritamab overall, although differences are [redacted]. The EAG notes that looking at the KM curve for OS, axi-cel appears to result in [redacted] outcomes for an initial period (up to ~[redacted]), after which the curves suggest [redacted] with epcoritamab. For PFS, the curves are [redacted] up until ~[redacted], after which curves for epcoritamab indicate [redacted] PFS compared to

axi-cel. As noted above for Pola + BR, the EAG considers that these differences could be partly due to the fact that epcoritamab is a continuous treatment, whereas axi-cel is not.

Similar results for response rates were observed; there were [redacted] for CR and ORR ([redacted] proportion with CR and [redacted] proportion with ORR in the epcoritamab arm) but these were [redacted] and [redacted].

The EAG notes that due to concerns about proportional hazards being violated, separate HRs for OS and PFS up to and after [redacted] were explored by the company at the clarification stage (see company's response to CQ A10); however, these were not taken forward by the company as they deemed the OS after [redacted] to be implausibly low. The EAG agrees that proportional hazards appear to be violated for this comparison. While the EAG agrees that the KM curves for OS cross at a time-point of ~[redacted], this is not the case for PFS. After clarification, the company retained the use of a single HR to model survival for axi-cel in the economic model; the EAG has concerns about using HRs to generate curves for axi-cel in the economic model, for reasons described in Section 4.2.4.2.3 and Section 4.2.4.4.4. The EAG notes that important sources of uncertainty regarding this MAIC remain and should be considered (see Section 3.4.2.3). These include the fact that some characteristics that are imbalanced between arms have not been adjusted for as part of the MAIC, including some that are thought to be prognostic, the fact that outcome definitions used in the two studies differ for PFS and that ZUMA-1 represents a population infused with axi-cel, not accounting for those that may deteriorate while CAR-T cells are manufactured. While some may introduce bias against epcoritamab, others have the potential to bias in favour of epcoritamab and they do not necessarily balance out.

Table 37. Unadjusted and adjusted outcomes for epcoritamab vs axi-cel (updated base case analysis B – epcoritamab LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – adapted from Table 31 of the CS

Outcome (epcoritamab vs axi-cel)	Unadjusted epcoritamab ([redacted])	Adjusted epcoritamab ([redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates		
CR	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

	[redacted]	[redacted]
ORR	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CR, complete response; CS, company submission; HR, hazard ratio; LBCL, large B-cell lymphoma; n^{eff}, effective sample size; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Figure 11. Unadjusted and adjusted OS for epcoritamab vs axi-cel (updated base case analysis B – LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – reproduced from Figure 16 of the company's response to CQ A14

[redacted]

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CQ, clarification question; EPCO, epcoritamab; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; OS, overall survival.

Figure 12. Unadjusted and adjusted PFS for epcoritamab vs axi-cel (updated base case analysis B – LBCL, no prior CAR-T, CAR-T eligible population adjusted to ZUMA-1) – reproduced from Figure 15 of the CS

[redacted]

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CS, company submission; EPCO, epcoritamab; LBCL, large B-cell lymphoma; NHL, Non-Hodgkin lymphoma; PFS, progression-free survival.

3.6 Conclusions of the clinical effectiveness section

Evidence submitted by the company to support the clinical safety and efficacy of epcoritamab for LBCL patients with at least two prior treatments is from a single-armed study (EPCORE™ NHL-1). This has inherent limitations given its open label nature and the lack of a randomised comparator, but the EAG considers it to otherwise be a well conduced study (Section 3.2). It aligns well with the NICE final scope in terms of population, intervention and outcomes but is limited to those with ECOG score 0-2 and those with previous failure (or ineligibility for) ASCT (Section 2.3.1). The data provided in the CS was based on a [redacted] data-cut. However, in response to CQ the company refers to a later data-cut ([redacted]).

The EAG's clinical experts consider it to be a reasonable representation of the population with at least two prior treatments but noted that it may be slightly worse than expected in terms of prognosis based on characteristics such as disease severity (Section 2.3.1).

Results from the trial indicate that median OS in the overall LBCL population was [redacted] months and median PFS was [redacted] months. Between [redacted] and [redacted] of patients achieved a response with epcoritamab, depending on whether CR or ORR was considered, respectively. Improvements from baseline in HRQoL with epcoritamab were also observed. Serious or grade 3+ events were not rare and the main concern appears to be for CRS ([redacted] had a serious event; Section 3.3). The EAG notes only a small number of patients with types of LBCL other than DLBCL were included and outcomes

with and without these patients included [redacted] outcomes (Section 3.3.4). Subgroup results for those with and without prior CAR-T use [redacted] outcomes, particularly PFS, with PFS [redacted] in those with prior CAR-T use (Section 3.3.4).

Given EPCORE™ NHL-1 was a single arm study, indirect comparisons were required. As a result, unanchored MAICs were performed for three different comparisons (R-based CIT and Pola + BR in those ineligible for or who choose not to receive intensive treatments, and axi-cel in those eligible for intensive treatments). The EAG highlights limitations of these analyses in terms of the data that has been used to inform them, particularly in relation to the comparator trials, as well as the level of adjustment for baseline characteristics. The EAG considers that amendments could still be made to improve the applicability and accuracy of the results of the MAICs (Section 3.4).

The results of the MAICs for survival outcomes (PFS and/or OS) currently indicate a [redacted] of epcoritamab compared to R-based CIT. Similar was observed for Pola + BR but only after ~[redacted] and results were also [redacted]. For axi-cel, results were also [redacted] and, similar to Pola + BR, there appeared to be [redacted] where axi-cel led to [redacted]. The differences compared to Pola + BR and axi-cel were less clear. The EAG highlights the uncertainty associated with these conclusions given the uncertainty associated with unanchored MAICs in general, in addition to potential methodological issues that the company could address (Section 3.5).

4 Cost effectiveness

As a result of the clarification stage, the company updated their cost-effectiveness model. Section 4 of the External Assessment Group (EAG) report describes the company's updated approach after clarification, while providing a critique of the company's updated approach.

The company undertook the following comparisons in their updated base case:

1. Comparison of epcoritamab vs rituximab-based chemoimmunotherapy (R-based CIT).
2. Comparison of epcoritamab vs polatuzumab vedotin with bendamustine and rituximab (Pola + BR).
3. Comparison of epcoritamab vs axicabtagene ciloleucel (axi-cel).

The company also applied a severity modifier of 1.2 to the incremental quality-adjusted life years (QALYs) in their updated base case for the comparison of epcoritamab with R-based CIT and Pola + BR. Table 38 and Table 39 report the probabilistic and deterministic incremental cost-effectiveness ratios (ICERs) for the comparison of epcoritamab and R-based CIT, respectively, whereas Table 40 and Table 41 report the equivalent results for the comparison of epcoritamab and Pola + BR. Finally, Table 42 and Table 43 report the probabilistic and deterministic ICERs for the comparison of epcoritamab and axi-cel, respectively, where no severity modifier was used.

The probabilistic ICERs reported by the EAG slightly differ from those reported by the company in Tables 39, 37, and 43 of the company's response to clarification questions. This is because the EAG had to re-run the probabilistic ICERs for all comparisons given that the company originally included discounted life-years gained in their probabilistic ICERs (instead of undiscounted life-years). Furthermore, there was a reporting mistake in the probabilistic ICER for epcoritamab vs Pola + BR, which the EAG corrected.

Table 38. Company's base case probabilistic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
R-based CIT	£85,009	[redacted]	1.005	[redacted]	[redacted]	[redacted]	[redacted]	£19,260	£16,050

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy.

Table 39. Company's base case deterministic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
R-based CIT	£82,610	[redacted]	0.900	[redacted]	[redacted]	[redacted]	[redacted]	£18,598	£15,498

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy.

Table 40. Company's probabilistic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	£141,171	[redacted]	1.803	[redacted]	[redacted]	[redacted]	[redacted]	£7,584	£6,320

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year.

Table 41. Company's deterministic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	£138,794	[redacted]	1.488	[redacted]	[redacted]	[redacted]	[redacted]	£4,892	£4,077

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year.

Table 42. Company's base case probabilistic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£375,814	[redacted]	3.799	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 43. Company's base case deterministic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£370,344	[redacted]	3.842	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

4.1 EAG comment on the company's review of cost effectiveness evidence

An economic systematic literature review (SLR) was conducted on 10 October 2022, with a subsequent search being conducted in November, to identify published cost-effectiveness studies in large B-cell lymphoma (LBCL) patients, including diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapies. The searches identified 26 relevant economic evaluations, 16 of which were relevant to LBCL and the other 10 to DLBCL populations. The patient population inclusion criterion was adult patients with relapsed/refractory (R/R) LBCL (including DLBCL; high-grade B-cell lymphoma [HGBCL]; follicular lymphoma grade 3B [FL Gr 3B]; and primary mediastinal B-cell lymphoma [PMBCL]), previously treated with at least 2 lines of systemic antineoplastic therapy

including anti-CD20 monoclonal antibody containing combination chemotherapy. The EAG's assessment of the steps taken by the company in conducting the SLR are described in Table 44.

Table 44. Assessment of company conducted systematic literature review.

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix G	Appendix G	**Appropriate.** The following electronic databases were searched: EMBASE, Medline, EconLit, using the ProQuest engine. Conference proceedings were "hand searched" using the terms LBCL, DLBCL, large B-cell lymphoma, cost, resource, and quality. HTA websites were also searched for relevant economic evidence in health technology appraisals in ≥3rd line R/R LBCL.
Inclusion / exclusion criteria	Appendix G	Appendix G	Appendix G	**Appropriate.** The SLR for cost-effectiveness evidence was conducted to be broad, with no restrictions applied to healthcare resource use costs or health related quality of life utilities. The only inclusion criteria applied to cost-effectiveness studies of interventions/comparators was the inclusion of systemic antineoplastic therapy in LBCL patients.
Screening	Appendix G	Appendix G	Appendix G	**Appropriate.** References were exported into the reference screening software, DistillerSR©. During both title/abstract and full-text screening phases, articles that were excluded were documented with reasons for their exclusion according to the pre-defined criteria.
Data extraction	Appendix G	Appendix G	Appendix G	**Appropriate.** After all relevant articles had been identified, one researcher extracted the data, while a second reviewer checked the data extraction files for extraction and completeness.

Quality assessment of included studies	Appendix G	Appendix G	Appendix G	**Appropriate.** Quality assessment was performed for all cost-effectiveness publications except for conference proceedings. The Drummond checklist was used to assess quality of cost-effectiveness publications.

Abbreviations: CS, company submission; DLCBL, diffuse large B-cell lymphoma; EAG, evidence review group; HRQoL, health related quality of life; LBCL, large B-cell lymphoma.

From a total of 1,705 cost-effectiveness studies identified from the electronic databases, 1,154 were taken through to the screening stage, after 551 duplicates were removed. A further 1,076 publications were excluded at the title and abstract screening stage, leaving 78 eligible for full-text screening. Thirty-three studies were excluded after this stage, with the predominant reason for exclusion being the ineligibility of the population, leaving 45 publications. At this stage 51 conference abstracts and 32 HTA sources were full text screened. Eighteen of these were not excluded and added to the 45 publications, resulting in 63 total relevant studies at this stage. Of these, 28 presented economic evidence in LBCL populations and 35 for DLBCL populations.

Further refining the search to economic evaluations in the ≥3rd line LBCL/DLBCL population, reduced the total publications to 26. Ten of these were specific to DLBCL patients with 16 focusing on LBCL patients. The publications consisted of 11 partitioned survival models, four decision tree models, and one budget impact model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 45 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the National Institute for Health and Care Excellence (NICE) reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 45. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.

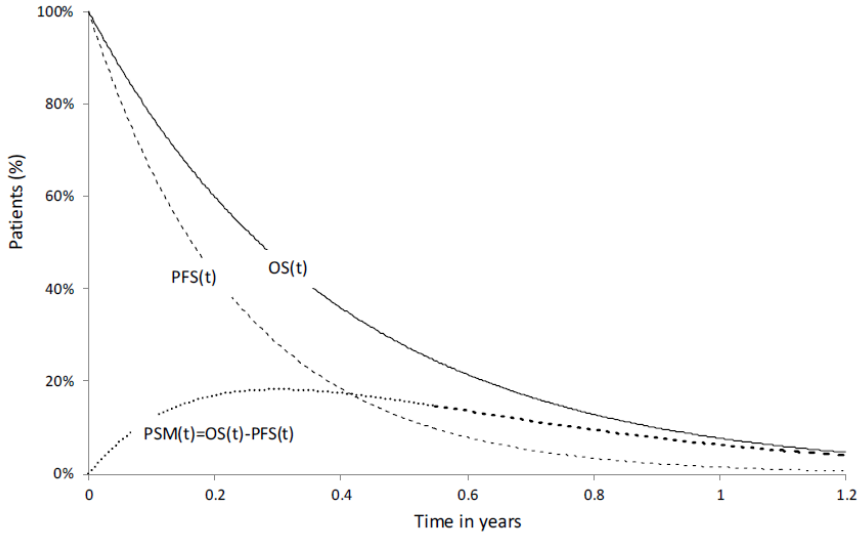
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes.
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: EAG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 *Modelling approach and model structure*

The company developed a *de novo* model in Microsoft Excel®. The model adopts a partitioned survival approach comprising of three health states: progression-free survival (PFS); disease progression (PD); and death (Figure 13). Patients in population A enter the model in the PFS state at a mean age of [redacted] years for the comparison with R-based CIT and a mean age of [redacted] for the comparison with Pola + BR, while patients in population B enter the model at [redacted] years. The probability of being alive and free from disease progression was calculated using the cumulative PFS curve in the model, while the probability of being alive was calculated from the cumulative overall survival (OS) curve.

Figure 13. Company's model (reproduced from Figure 16 CS)



The company also incorporated a long-term remission (LTR) assumption in their modelling approach. Based on clinical expert advice, the company chose 2 years as the point in the model when patients who were progression-free would be considered to enter LTR and thus, experience no further progression events.

Patients in LTR experienced an adjusted background mortality rate from 2 years onwards, where a standardised mortality ratio (SMR) of 1.41 was applied to the general population mortality matched for age and sex. Patients in LTR were also assumed to not use any healthcare resources, an assumption discussed in detail in Section 4.2.6. Patients in LTR continued to experience the utility value associated with being in the PFS state while alive. The EAG notes that the company's LTR assumption does not imply that patients' survival returns to that observed in the general population after 2 years, nor that patients' quality of life returns to that of the general population. Therefore, the company's assumption is not the equivalent of a "structural cure" in the model.

4.2.2.1 EAG critique

The EAG notes that the LTR assumption mainly effects disease monitoring costs in the model and survival, as patients in LTR are assumed to not be followed up anymore (as well as having an increase in their probability of survival). The EAG is generally satisfied with the SMR of 1.41 (95% CI: 1.35 to 1.48) used by the company to model survival for LTR as it reflects the increase in mortality associated with DLBCL survivors having a higher risk of non-cancer death than the general population, which was previously suggested by the EAG in TA649.[29] However, the EAG has concerns

with the company's application of the LTR assumption in the model, which are discussed in detail below but can be summarised as:

1. For R-based CIT and Pola + BR, the EAG considers that the company's approach is oversimplistic in that it assumes that all patients enter LTR 2 years after the beginning of the model.
2. For epcoritamab, the EAG disagrees with the company's approach to when the LTR assumption starts in the model in its entirety.
3. The EAG found an implementation error in the company's model.

The EAG's clinical experts agreed that R/R LBCL patients who have not progressed 2 years *after the end of their treatment* would be considered to be in LTR, with further disease progression events being unlikely to occur. However, this differs from the company's assumption in the model, which is that progression-free patients 2 years after treatment initiation (not treatment end) are in LTR. During clarification, the EAG asked that the company justified this assumption in light of the EAG's clinical expert view – the company replied that for:

1) for axi-cel treatment consists of a one-off treatment at the beginning of the model, thus this issue doesn't apply. The EAG agrees with the company;
2) for R-based CIT, the company reported to conduct a scenario analysis where patients would enter LTR at 2 years and 4 months after the beginning of the model, to account for 4 months of treatment with R-based CIT.

The EAG notes that the company's model assumes a treatment duration with R-based CIT of 7 months, therefore the EAG is unsure how 4 months would reflect treatment duration in the model. Crucially, the company scenario analysis varies the point in the model when the LTR assumption starts incurring for all treatments simultaneously, which defeats the EAG's point that patients will enter LTR at different points in time for all treatments. Therefore, the EAG does not consider the company's scenario analysis to be helpful. Finally, the EAG notes that the company did not acknowledge this issue for Pola + BR; however, the EAG notes that treatment duration with Pola + BR in the model lasted for 4 months.

Given the company's assumption that epcoritamab patients enter LTR at the same time as patients in the comparator arms, varying the point in time at which patients enter LTR by a few months has a modest impact on the estimated treatment costs, and thus on the ICER. However, the EAG does not

consider that this assumption should be applied to the epcoritamab arm. The EAG's clinical experts stated that they would not consider patients to enter LTR if treatment for LBCL was still ongoing. Therefore, the clinical experts advised that they would not consider progression-free patients on epcoritamab to enter LTR at 2 years after initiation of treatment (as these patients would remain on treatment until progression; or discontinuation due to toxicity). This is in direct contradiction with the company's assumption that at 2 years after treatment initiation, progression-free epcoritamab patients enter LTR, thus stop incurring any follow-up costs.

The EAG notes that if epcoritamab and comparator patients entered LTR at different points in the model, the point at which this happens for each treatment would likely have a major impact on the final ICER. During clarification, the EAG requested that the company conducted a scenario analysis where epcoritamab patients remained to be follow-up while on treatment. The company did not conduct the analysis requested by the EAG and this is further discussed in Section 4.2.6.

Furthermore, the EAG has several concerns with the company's assumptions around the proportion of epcoritamab patients who were considered to be progression-free at 2 years in the model (and thus considered to be in LTR). This issue is discussed in detail in Section 4.2.4.

Finally, the EAG notes that the final mortality rates used in OS curves in the model were based on the maximum between the hazard of the extrapolated OS and the hazard of the general population to ensure that mortality hazards for the modelled population could not be lower than the mortality hazard observed in the general population at any point in time. In addition, for LTR patients in the PFS curve, the increased background mortality was applied to the general population mortality after 2 years in the model. The company then took the maximum between the OS curve and the PFS curve, therefore when the OS and PFS curves converged in the model, the OS curve became the same as the PFS curve.

As an example, for population A, Figure 14 shows that from about month 96 onwards, the OS and the PFS curves become the same, implying that all progressed patients have died at this point, and that all patients alive in the model are all in the PFS state. However, at month 384 (approximately 32 years in the model), the PFS curve drops below the OS curve because the mortality in the OS curve at that point reflects the general population mortality while the PFS curve reflects the general population mortality increased by the SMR of 1.41. The modelled difference in the curves implies that a proportion of patients starts progressing at 32 years in the model, which is in direct

contradiction with the company's intended assumption of no further progression after 2 years in the model for PFS patients. Therefore, the EAG corrected this in the model, by taking the minimum between the PFS and the OS curve when the PFS curve dropped below the OS curve for all populations. This was a simplistic correction due to time constraints, and one that relies on manually doing this for each comparator treatment, which needs to be run separately (but not allowed to run simultaneously) in the company's base case model. Ideally, this would be automated via embedded formulae, to avoid mistakes and to allow for this error to be automatically corrected for each comparator. The EAG, therefore, recommends that the company implements this at technical engagement (TE). The impact on the final ICERs was minimal and is presented in Section 6.1.

Figure 14. Implementation error in OS and PFS curves used in the company's base case for epcoritamab (population A, for the comparison with R-based CIT).

[redacted]

4.2.3 Perspective, time horizon and discounting

A lifetime horizon of 45 years was adopted in the model and time was discretised into 28-day cycles, with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

4.2.4 Treatment effectiveness

In order to estimate survival outcomes (PFS; OS; and time to treatment discontinuation [TTD]) for epcoritamab, the company used the KM data for each outcome from the EPCORE™ NHL-1 trial. Population A is described in the CS as patients ineligible for (or who choose not to receive) intensive treatments, while population B is described as those eligible for intensive treatments (such as chimeric antigen receptor T-cell [CAR-T] therapy). For population A, the company used the DLBCL, no prior CAR-T population from EPCORE™ NHL-1; whereas for population B, the company used the LBCL, no prior CAR-T, eligible to receive CAR-T therapy population from EPCORE™ NHL-1. The EAG is unsure whether the data used in MAICs for population A was reflective of a group ineligible for intensive treatments (see Sections 2.3.1.2, 3.4.2.1 and 3.4.2.2, and Key Issue 6, Table 7).

In order to generate measures of relative treatment effectiveness, the company undertook the following approach for each population and comparator, respectively, for their updated base case:

- Population A, for the comparison of epcoritamab vs R-based CIT: The company conducted an MAIC to adjust the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 to a subgroup of patients from the SCHOLAR-1 trial who had themselves already been matched to patients in the ZUMA-1 trial (and who were described in a publication by Neelapu *et al.*). The details of this MAIC are described in detail Sections 2.3.1.2, 3.4.2.1 and 3.5.1;[11, 12]
- Population A, for the comparison of epcoritamab vs Pola + BR: The company conducted an MAIC to compare the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 to the Sehn *et al.* 3L+ population. The details of this MAIC are described in detail in Sections 2.3.1.2, 3.4.2.2 and 3.5.2;
- Population B, for the comparison of epcoritamab vs axi-cel: The company conducted an MAIC to compare the LBCL, no prior CAR-T population from EPCORE™ NHL-1 (eligible to receive CAR-T) to the ZUMA-1 trial population. The details of this MAIC are described in detail in 2.3.1.2, 3.4.2.3 and 3.5.3.[14]

The company fitted different parametric survival models to the MAIC-adjusted KM data from EPCORE™ NHL-1 in population A and population B. In order to assess the relative goodness-of-fit of the different models for each population, the company: (1) generated Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics for the epcoritamab arm; (2) visually assessed the parametric curves against the KM curves; (3) used clinical expert opinion to assess the clinical plausibility of model extrapolations. Standard parametric distributions, including the

exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma distributions were tested.

For PFS and OS outcomes, the company also produced log-cumulative hazard plots and Schoenfeld residual plots to visually assess whether proportional hazards (PHs) could be assumed. The Grambsch and Therneau test (a chi-square test) was also conducted to test whether the slope between the Schoenfeld residuals and the survival time was zero (where a significant p-value meant that the null hypothesis of PH was rejected). The EAG discusses the company's approach for each outcome in each population in detail over the next subsections.

4.2.4.1 Overall survival

4.2.4.1.1 Population A – comparison to R-based CIT

Based on the AIC and BIC criteria (Table 53 of the company's response to clarification) provided for the MAIC-adjusted KM OS data from EPCORE™ NHL-1, the lognormal curve was chosen by the company as the best-fitting model to estimate OS for epcoritamab.

The company concluded that PH held between the MAIC-adjusted KM OS data from EPCORE™ NHL-1 and the subset of data from SCHOLAR-1 trial that had been matched to ZUMA-1 data in the publication by Neelapu *et al*. The company's conclusion was based on assessment of the log-cumulative hazard curve (Figure 29 of company's response to clarification questions) and on the Schoenfeld residual curve (Figure 30 of company's response to clarification questions). The company added that the Grambsch and Therneau test of OS was consistent with the finding as the p-value of [redacted] suggested that the PH assumption cannot be rejected.

The company applied a HR of [redacted] to the OS epcoritamab curve to generate the R-based CIT OS curve.

4.2.4.1.2 Population A – comparison to Pola + BR

The company did not update its original base case approach to estimating the OS (or PFS) outcomes for the comparison of epcoritamab with Pola + BR. Based on the AIC and BIC criteria (Table 40 of the CS) provided for the MAIC-adjusted KM OS data from EPCORE™ NHL-1 to the Sehn *et al*. data, and on clinical expert opinion, the generalised gamma curve was chosen by the company to estimate OS for epcoritamab.

During clarification, the EAG requested that the company fitted the epcoritamab and the Pola + BR OS curves independently given the company's own assessment that PHs did not hold for OS and the shape of the KM OS curves for both treatments (Figure 15), which clearly shows a crossing of OS curves. The company did not comply with the EAG's request and instead maintained that a "piecewise HR approach" was the appropriate method to estimate the OS curve for Pola + BR, with a HR of [redacted] applied to the first [redacted] months of the model to the OS epcoritamab curve, and with a HR of [redacted] applied after that to generate the Pola + BR OS curve.

Figure 15. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to Pola + BR with two or more prior lines of therapy (reproduced from Figure 14 of the CS appendices)

4.2.4.1.3 Population B – comparison to axi-cel

Based on the AIC and BIC criteria (Table 60 of the company's response to clarification) provided for the MAIC-adjusted KM OS data from EPCORE™ NHL-1, and on clinical expert opinion, the lognormal curve was chosen by the company as the best-fitting model to estimate OS for epcoritamab.

The company concluded that PH did not hold between the MAIC-adjusted KM OS data from EPCORE™ NHL-1 and the ZUMA-1 trial data. During clarification, the EAG requested that the company fitted the epcoritamab and the axi-cel OS curves independently given the shape of the KM OS curves for both treatments (Figure 16), which clearly shows a crossing of OS curves. The company did not comply with the EAG's request and instead decided to estimate the axi-cel OS curve by applying a single HR to the epcoritamab OS curve of [redacted]) throughout the entire model horizon. The company reported that it considered a "piecewise HR approach" with a HR of [redacted] applied to the first [redacted] months of the model to the OS epcoritamab curve, and with a HR of [redacted] applied after that to generate the axi-cel OS curve, as discussed in Section 3.5.3. Nonetheless, the company considered that the HRs generated for OS for after [redacted] was, "*implausibly low and would therefore generate clinically implausible results for axi-cel if applied in the cost-effectiveness model*."

Figure 16. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, no prior CAR-T therapy epcoritamab population (reproduced from Figure 16 of the company's response to clarification question A14)

[redacted]

4.2.4.2 EAG critique

4.2.4.2.1 Population A – comparison to R-based CIT

As discussed in Sections 2.3.1.2 and 3.4.2.1 (and Key Issue 2, Table 3), the EAG is concerned with the use of the Neelapu *et al.* source and considers that the Crump *et al.* publication of the observed KM OS data for R-based CIT from SCHOLAR-1 should have been used instead.[17] Nonetheless, the EAG notes that the OS curves in the Neelapu *et al.* and the Crump *et al.* publications seem to present a fairly similar proportion of patients alive for the timepoints where both publications have data available (Table 46).

Furthermore, the EAG is not sure if the log-cumulative hazard curves (Figure 29, company's response to clarification questions) can confirm that the PH assumption holds, as concluded by the company. The EAG notes that even though the company concluded that based on a Grambsch and Therneau p-value the PH assumption could not be rejected, when the PHs assumption is violated, standard Cox models (and thus the Grambsch and Therneau test) might produce unreliable estimates.[40]

Therefore, the EAG is concerned with the company's assumption of PHs between OS outcomes for epcoritamab and R-based CIT, not only because the company carries the same assumption for PFS outcomes (based on OS outcomes), but also due to a potential underestimation in the OS (and by default PFS) curve for R-based CIT. Table 46 reports the proportion of patients alive estimated in the model for R-based CIT compared to the observed survival data in SCHOLAR-1 in the Neelapu *et al.* and the Crump *et al.* publications. From month 30, the economic model starts to underpredict survival comparatively to Neelapu *et al.*, with long-term predictions considerably and consistently underestimating survival in the model for over 5 years when compared to the observed data in Crump *et al*.

Table 46. Landmark OS estimates for R-based CIT compared with SCHOLAR-1 OS data

Treatment	Data source	Month					
		12	24	30	60	120	180
R-based CIT	Subgroup of patients in SCHOLAR-1 matched to ZUMA-1 (Neelapu *et al.)*	26%	20%	19%	NR	NR	NR
	SCHOLAR-1 (Crump *et al.)**	25%	21%	20%	18%	15%	15%
	Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Based on EAG visual inspection of the KM curves presented in Crump et al.

Abbreviations: KM, Kaplan-Meier; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy.

The EAG is also concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population A. This issue is directly related to the company's assumptions around the proportion of patients who enter LTR at 2 years in the epcoritamab arm of the model (discussed in detail in Section 4.2.4.2) given that the OS curve converged (and became the same) as the PFS curve at about 8 years in the model.

Overall, the EAG considers that the OS curve estimated for R-based CIT is likely to considerably underpredict OS in the long-term model for this treatment. This directly impacts the estimated PFS curve for R-based CIT, given the company's simplistic approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve. This, combined with a potential overestimation of the OS (and PFS) curve for epcoritamab, leads to a likely overestimation of the cost-effectiveness of epcoritamab vs R-based CIT.

4.2.4.2.2 Population A – comparison to Pola + BR

As discussed in Sections 2.3.1.2 and 3.4 and 3.5.2, the EAG is concerned with company's approach to conducting the MAIC to estimate the relative treatment effectiveness of epcoritamab vs Pola + BR. The EAG is also particularly concerned with the company's approach of applying 2 different HRs to the epcoritamab OS curve to estimate a Pola + BR OS curve, before and after [redacted] in the model. The EAG has not seen enough evidence to justify the existence of PHs before and after this timepoint in the model (even if a different HR would apply). Crucially, the company's approach considerably underestimates the proportion of patients alive in the Pola + BR arm of the model after month 12, compared to the observed data available from Sehn *et al.* (Table 47).

Table 47: Landmark OS estimates for Pola + BR compared with Sehn *et al.* OS data

Treatment	Data source	Month					
		3	6	12	24	60	120
	Pola + BR (Sehn *et al.)**	90%	78%	50%	40%	NR	NR
	Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Based on EAG visual inspection of the KM curves presented in Sehn et al.

Abbreviations: KM, Kaplan-Meier; OS, overall survival; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine.

The EAG also notes that at 35 years in the model, when patients would be 90 years old, there are [redacted] of patients alive, which contrasts with the [redacted] estimated for the same population in the epcoritamab curve vs R-based CIT. At 25 years in the model, there are approximately [redacted] of patients estimated to be alive in the epcoritamab arm, which might reflect a more plausible survival prediction than that obtained for the comparison with R-based CIT. This issue is directly related to the company's assumptions around the proportion of patients who enter LTR at 2 years in the epcoritamab arm of the model (discussed in detail in Section 4.2.4.2) given that the OS curve converged (and became the same) as the PFS curve at about 6 years in the model (Figure 17).

The EAG also notes that for the Pola + BR arm, the company took the minimum between the PFS and the OS curves, after the point of crossing of the curves (Figure 17). This approach is inconsistent with the company's approach for epcoritamab, where the maximum between the PFS and the OS curves was taken at the point of crossing. The company's approach for Pola + BR, assumes that the PFS curve becomes the OS curve at the point of crossing which is contradictory to the company's assumption that LTR patients have a higher probability of survival than patients who had a progression (and were included in the OS curve previously, therefore partially dictating the trajectory of the OS curve). The EAG changed this in the company's model, so that when the PFS and OS curves for Pola + BR crossed, the OS curve turned into the PFS curve, as per the assumption for epcoritamab (Figure 18).

Overall, the EAG considers that the OS curve estimated for Pola + BR is likely to considerably underpredict OS in the long-term model for this treatment, which leads to a potential overestimation of the cost-effectiveness of epcoritamab vs Pola + BR.

Figure 17. OS curves used in the company's base case for epcoritamab and Pola + BR

[redacted]

Figure 18. OS curves used in the company's base case for epcoritamab and Pola + BR (corrected)

[redacted]

4.2.4.2.3 Population B – comparison to axi-cel

As discussed in Sections 2.3.1.2, 3.4 and 3.5.3, the EAG is concerned with company's approach to conducting the MAIC to estimate the relative treatment effectiveness of epcoritamab vs axi-cel. The EAG is also concerned with the company's use of a single HR to estimate the OS axi-cel curve as it is clearly methodologically flawed when the underlying KM curves cross. The company's approach is likely to underestimates the proportion of patients alive in the axi-cel arm of the model after month 30 and increasingly until month 60, compared to the observed data available from the latest data cut available for ZUMA-1 (Table 48).

Nonetheless, the EAG notes that using the company's "piecewise HR" approach would have led to clinically implausible low survival values in the axi-cel curve as stated by the company and as confirmed in Table 48. The EAG notes that this is not an acceptable justification to use a single HR to model the OS curve for axi-cel, but instead a reinforcement of the EAG's view that the OS curves for epcoritamab and axi-cel should have been modelled independently.

The EAG identified the same error in the axi-cel arm of the model as that identified for Pola + BR (described in Section 4.2.4.2.2), in that the company took the minimum between the PFS and the OS curves, after the point of crossing of the curves, instead of taking the maximum between the PFS and the OS curves at the point of crossing (as done for the epcoritamab arm - Figure 19). The EAG changed this in the company's model, so that when the PFS and OS curves for axi-cel crossed, the OS curve turned into the PFS curve, as per the assumption for epcoritamab (Figure 20). The corrected landmark figures are also provided in Table 48, showing an approximation (but still and underestimation) to the observed survival estimated in ZUMA-1.

Table 48: Landmark OS estimates for axi-cel compared with ZUMA-1 OS data

Treatment	Data source	Month					
		6	12	24	30	60	120
Axi-cel	ZUMA-1[14]	79%	61%	NR	NR	NR	NR
	ZUMA-1, 5-year data cut*	79%	61%	50%	48%	45%	NR
	Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's base case model corrected by the EAG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Company's scenario using "piecewise" HR approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Based on EAG visual inspection of the KM curves presented in ZUMA-1

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; NR, not reported; OS, overall survival.

The EAG is also concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population B (Figure 19).

Overall, the EAG considers that the OS curve estimated for axi-cel is likely to underpredict OS in the long-term model for this treatment, and that the OS curve for epcoritamab is likely to be overestimated, which leads to a potential overestimation of the cost-effectiveness of epcoritamab vs axi-cel.

Figure 19. OS curves used in the company's base case for epcoritamab and axi-cel

[redacted]

Figure 20. OS curves used in the company's base case for epcoritamab and axi-cel (corrected for crossing of OS and PFS curves)

4.2.4.2.4 Summary

The EAG has serious concerns with the MAICs undertaken to estimate the relative treatment effect of epcoritamab on OS outcomes. Furthermore, the EAG considers the company's approach of jointly fitting survival curves unfit for purpose when the underlying KM curves cross for each treatment's outcome.

Overall, the EAG considers that the cost-effectiveness of epcoritamab is overestimated for every comparison in the model:

1. The OS curve for R-based CIT is likely to considerably underpredict OS in the long-term model for this treatment. This directly impacts the estimated PFS curve for R-based CIT, given the company's approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve. This, combined with a potential overestimation of the OS (and PFS) curve for epcoritamab, leads to a likely overestimation of the cost-effectiveness of epcoritamab vs R-based CIT.
2. The OS curve estimated for Pola + BR is likely to considerably underpredict OS in the long-term model for this treatment, which leads to a potential overestimation of the cost-effectiveness of epcoritamab vs Pola + BR.

3. The OS curve estimated for axi-cel is likely to underpredict OS in the long-term model for this treatment, and in addition, the OS curve for epcoritamab is likely to be overestimated, which leads to a potential overestimation of the cost-effectiveness of epcoritamab vs axi-cel.
4. The overestimation of OS in the model is intrinsically related to the overestimation of PFS in the model (given the convergence of the curves so early in the model), which is discussed in the next section in detail.

The EAG also recommends that the company produces state occupancy traces for the company's base case corrected for the error identified in the model (described in Section 4.2.2.1) for all comparators and all populations.

4.2.4.3 Progression-free survival

4.2.4.3.1 Population A – comparison to R-based CIT

Based on the AIC and BIC criteria (Table 55 of the company's response to clarification) provided for the MAIC-adjusted KM PFS data from EPCORE™ NHL-1, the generalised gamma curve was chosen by the company as the best-fitting model to estimate PFS for epcoritamab.

Even though it was not explicitly stated in the company's updated submission after clarification, the company used the HR derived from jointly fitting the OS curves for epcoritamab and R-based CIT of [redacted] to the PFS epcoritamab curve to generate the R-based CIT PFS curve.

4.2.4.3.2 Population A – comparison to Pola + BR

The company did not update its original base case approach to estimating the PFS outcomes for the comparison of epcoritamab with Pola + BR. Based on the AIC and BIC criteria (Table 42 of the CS) and clinical expert opinion, the generalised gamma curve was chosen by the company to estimate OS for epcoritamab.

As discussed in the OS section, during clarification, the EAG requested that the company fitted the epcoritamab and the Pola + BR OS and PFS curves independently given the company's own assessment that PHs did not hold and the shape of the KM OS curves for both treatments (Figure 21), which clearly shows a crossing of PFS curves. The company did not comply with the EAG's request and instead maintained that a "piecewise HR approach" was the appropriate method to estimate the PFS curve for Pola + BR, with a HR of [redacted]

[redacted] applied to the first [redacted] months of the model to the PFS epcoritamab curve, and with a HR of [redacted] applied after that to generate the Pola + BR PFS curve.

Figure 21. Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (reproduced from Figure 15 in the CS appendixes).
[redacted]

4.2.4.3.3 Population B – comparison to axi-cel

Based on the AIC and BIC criteria (Table 62 of the company's response to clarification) provided for the MAIC-adjusted KM OS data from EPCORE™ NHL-1, the generalised gamma curve was chosen by the company as the best-fitting model to estimate PFS for epcoritamab.

During clarification, the EAG requested that the company fitted the epcoritamab and the axi-cel PFS curves independently given the shape of the KM PFS curves for both treatments (Figure 22), which clearly shows a crossing of PFS curves. The company did not comply with the EAG's request and instead decided to estimate the axi-cel PFS curve by applying a single HR to the epcoritamab PFS curve of [redacted]) throughout the entire model horizon. For OS, the company reported that it considered a "piecewise HR approach" applying two different HRs; one for the first [redacted] months of the model to the OS epcoritamab curve, and another after that to generate the axi-cel OS curve. Nonetheless, the company considered that the HRs generated for OS for after [redacted] was, "*implausibly low and would therefore generate clinically implausible results for axi-cel if applied in the cost-effectiveness model*."

Figure 22. Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population (reproduced from Figure 13 of the CS)

[redacted]

4.2.4.4 EAG critique

4.2.4.4.1 All populations – epcoritamab curves

During clarification, the EAG noted its concern around the company's estimated PFS survival curves in both populations given that these provided a considerably bad visual fit to the end of the KM PFS data (Figure 23 and Figure 24 for population A; and Figure 25 for population B). Crucially, the EAG noted its concern that the KM PFS data from EPCORE™ NHL-1 dropped to [redacted] at 21 months, whereas the company's base case extrapolations assumed that a considerably high proportion of patients was progression-free in the epcoritamab arm at the same time point. The company's updated model assumes that at 24 months, about [redacted] and [redacted] of patients in population A, in the epcoritamab arm , for the comparison with R-based CIT and Pola + BR, respectively; and [redacted] of patients in population B are progression-free in the epcoritamab arm.

Given the lack of evidence presented to substantiate the company's assumptions, the EAG asked the company to provide any evidence available to justify the proportion of progression-free patients on the epcoritamab arms of the model. The company reported that data from a more recent data-cut of EPCORE™ NHL-1 exist ([redacted]), which further support that the [redacted] is not representative of the treatment effect of epcoritamab. The EAG notes that these data are meant

to be shared with the EAG in August 2023. The company also mentioned that clinical expert opinion provided to the company considered it implausible for PFS with epcoritamab to be [redacted] based on extensive experience of disease biology for patients in complete response. Clinical expert opinion provided to the company also, "*estimated a plausible range of 10–40% progression-free at two years and 5–35% progression-free at five years*" as a minimum-maximum range, with the "*most likely value*" estimated to be "*a range of 30–35% and 20–30% of patients progression-free at two and five years, respectively*".

The EAG notes that, while it might agree with the company's view that it is unlikely that all epcoritamab patients have progressed at 21 months, this does not provide any further information on what the plausible proportion of PFS patients is in that point in time, when there are no observed PFS data. The EAG reiterates that the company's updated model assumes that at 24 months, [redacted] of patients in population B are progression-free in the epcoritamab arm; which is above the range considered most likely plausible by the company's own experts for epcoritamab vs R-based CIT (population A) and for epcoritamab vs axi-cel (population B).

Figure 23. Updated long-term PFS extrapolations for epcoritamab: population A, for the comparison against R-based CIT

[redacted]

Figure 24. Updated long-term PFS extrapolations for epcoritamab: population A, for the comparison against Pola + BR

[redacted]

Figure 25. Updated long-term PFS extrapolations for epcoritamab: population B

[redacted]

The EAG acknowledges the small number of patients at risk in the PF KM epcoritamab curves from about month 17 (with an average of [redacted] of patients at risk in the KM curves for both populations, which broadly equated to [redacted] patients in each population); however, the EAG reinforces its view that the extrapolated curves used by the company are unsubstantiated and result in a potential

overestimation of PFS for epcoritamab. During clarification, the company also added that the drops around [redacted] and [redacted] in the PFS KM curves are due to the timing of assessments in the trial and that patients who did not progress or die during the trial period were censored at their last evaluable tumour assessment, which explains the concentration of censoring observed in the PFS KM curve around these times.

4.2.4.4.2 Population A – comparison to R-based CIT

As discussed in Sections 2.3.1.2 and 3.4.2.1 (and Key Issue 2, Table 3), and in Section 4.2.4.2.1, the EAG is concerned with the use of the Neelapu *et al.* source and considers that the Crump *et al.* publication of the observed KM OS data for R-based CIT from SCHOLAR-1 should have been used instead. Furthermore, given the EAG's uncertainty around the validity of the PH assumption for OS, the EAG is also concerned with the appropriateness of assuming PHs for PFS. Nonetheless, the EAG acknowledges that SCHOLAR-1 did not report PFS data, therefore making it impossible to validate the PFS predictions in the model for R-based CIT. However, given the EAG's concerns around the underestimation of the OS curve for R-based CIT compared to the observed data in SCHOLAR-1, it is likely that the same concerns would apply for PFS.

Furthermore, the EAG is concerned with the company's approach of assuming that the HR derived for OS outcomes is the same as the HR for PFS outcomes between epcoritamab and R-based CIT – the company's assumption relies on the OS gain for epcoritamab being proportionately the same as the PFS gain associated with the treatment. Therefore, during clarification, the EAG asked that the company used the HR between the OS and PFS KM curves for epcoritamab for the unadjusted, DLBCL population, no prior CAR-T from EPCORE™ NHL-1 – by applying this HR to the OS SCHOLAR-1 curve derived for R-based CIT the company could estimate a PFS curve for R-based CIT. This method still relied on the assumption that the relationship between OS and PFS outcomes for epcoritamab is the same as that for OS and PFS for R-based CIT; however, it wouldn't assume that the proportional gain observed for epcoritamab for OS is the same as the PFS gain in relation to R-based CIT. The company did not conduct the scenario as it deemed inappropriate to assume that, "*the relationship between OS and PFS for epcoritamab is the same as that for R-based CIT*", given that, "*epcoritamab is considerably more effective at inducing complete response than R-based CIT*". The EAG acknowledges the company's point; however, notes that both options are based on strong, unverifiable assumptions, with the company's assumption potentially favouring epcoritamab and the

EAG's assumption being more conservative. Therefore, the EAG recommends that the company undertakes the scenario requested at TE.

Even though the EAG's experts agreed that progression-free R/R LBCL patients at 2 years after the end of treatment with R-based CIT could be considered to enter LTR, it was noted that the proportion of patients who would reach this status would be low with R-based CIT – one expert suggested that virtually no patients would reach the 2-year mark without a progression event, while the second expert indicated this proportion to be closer to 10% or 15% of patients. A study by Mounier *et al*. 2013, reported in TA883, showed that approximately 20% of patients receiving R-based CIT were progression-free at 2 years, with 15% of patients potentially plateauing from 4 years to 6 years.[35] Nonetheless, the EAG caveats the results in the Mounier *et al*. study by the fact that only 63% of patients in the study received previous rituximab treatment and that most patients were on their second-line treatment. Overall, given the lack of a robust source of data to estimate PFS for R-based CIT in third line R/R LBCL, the EAG considers that the company's extrapolation (Figure 26), which predicts that approximately 3% of patients on R-based CIT enter LTR at 2 years, might be underestimated.

Figure 26. Long-term PFS extrapolations for R-based CIT

4.2.4.4.3 Population A – comparison to Pola + BR

As discussed in Sections 2.3.1.2 and 3.4 and 3.5.2, the EAG is concerned with company's approach to conducting the MAIC to estimate the relative treatment effectiveness of epcoritamab vs Pola + BR. The EAG is also particularly concerned with the company's approach of applying 2 different HRs to the epcoritamab PFS curve to estimate a Pola + BR PFS curve, before and after [redacted] in the model. The EAG has not seen enough evidence to justify the existence of PHs before and after this timepoint in the model (even if a different HR would apply). Crucially, the company's approach slightly overestimates PFS in the first [redacted] of the model and considerably underestimates the proportion of patients alive in the Pola + BR arm of the model after that point (and in the long-term model), compared to the observed data available from Sehn *et al.* (Table 49).

As explained in Section 4.2.4.2.2, the EAG corrected the PFS curve for Pola + BR so that when the PFS and OS curves for Pola + BR crossed, the OS curve turned into the PFS curve (instead of the other way around), as per the assumption for epcoritamab (Figure 27 and Table 49). The EAG correction does not improve sufficiently on the underestimation of the estimated PFS curve compared to the observed KM PFS data for Pola + BR, given that the curves only crossed at 33 months in the model.

Overall, the EAG considers that the PFS curve estimated for Pola + BR considerably underpredicts PFS in the long-term model for this treatment, which leads to a potential overestimation of the cost-effectiveness of epcoritamab vs Pola + BR.

Table 49. Landmark PFS estimates for Pola + BR compared with Sehn PFS data

	Data source	Month					
		3	6	12	18	24	60
Pola + BR	Pola + BR (Sehn *et al.)**	70%	58%	36%	30%	30%	NR
	Company's base case model corrected by the EAG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Based on EAG visual inspection of the KM curves presented in Sehn et al.

Abbreviations: EAG, External Assessment Group; KM, Kaplan-Meier; NR, not reported; PFS, progression-free survival; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine.

Figure 27. PFS curves used in the company's base case for epcoritamab and Pola + BR (corrected)

[redacted]

4.2.4.4.4 Population B – comparison to axi-cel

As discussed in Sections 2.3.1.2, 3.4 and 3.5.3, the EAG is concerned with company's approach to conducting the MAIC to estimate the relative treatment effectiveness of epcoritamab vs axi-cel. The EAG is particularly concerned with the company's use of a single HR to estimate the OS axi-cel curve as it is clearly methodologically flawed when the underlying KM curves cross. The EAG notes that using the "piecewise HR" approach would have also not improved on the predicted PFS in the company's base case vs the observed values in ZUMA-1 (Table 50).

The company's approach slightly underestimates the proportion of patients in the PFS curve in the axi-cel arm of the model after month 24; however, the EAG is less concerned with this than with the other comparators, where the underestimations are much more considerable (Table 50). Furthermore, when the EAG corrected the axi-cel curves in the model for the crossing issue (as described in Section 4.2.4.2.2), the long-term PFS predictions in the company's model are slightly closer to those observed in ZUMA-1 for month 60 (Table 50).

Overall, the EAG considers that the PFS curve estimated for axi-cel might be a reasonable prediction of PFS for this treatment, with the main problem in this comparison being the likely overestimation of the PFS epcoritamab curve, therefore leading to a potential overestimation of the cost-effectiveness of epcoritamab vs axi-cel.

Table 50: Landmark PFS estimates for axi-cel compared with ZUMA-1 PFS data

Treatment	Data source	Month					
		6	12	24	30	60	120
Axi-cel	ZUMA-1[14]	51%	42%	NR	NR	NR	NR
	ZUMA-1, 5-year data cut*	51%	42%	40%	40%	32%	NR
	Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's base case model corrected by the EAG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's scenario using "piecewise" HR approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Based on visual inspection of the KMs given in the publication done by the EAG

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; NR, not reported; PFS, progression-free survival.

Figure 28. Long-term PFS extrapolations for axi-cel - corrected

[redacted]

4.2.4.4.5 Summary

The EAG has serious concerns with the MAICs undertaken to estimate the relative treatment effect of epcoritamab on PFS outcomes. Furthermore, the EAG considers the company's approach of jointly fitting survival curves unfit for purpose when the underlying KM curves cross for each treatment's outcome.

Overall, the EAG is concerned that the company's base case PFS epcoritamab curves are not robust enough to be considered in the cost-effectiveness model. The lack of observed data to substantiate what proportion of epcoritamab patients could be progression-free at 2 years; combined with the company's assumption that the proportion of patients in the PFS epcoritamab curves dictate the proportion of patients who enter LTR; and crucially; the EAG's clinical experts' view that progression-free epcoritamab patients should not be considered to enter LTR at 2 years after initiation of treatment (as discussed in Section 4.2.4), mean that the company's approach to estimating PFS for epcoritamab appears to be fundamentally flawed. This affects costs in the model and patients' survival as the company's LTR assumption means that patients in the extrapolated PFS curve at 2 years begin to incur the SMR-adjusted background mortality; and the convergence of the OS and PFS curves. The EAG's conclusion is that PFS and OS for epcoritamab patients is therefore overestimated, and unsubstantiated in the model.

The EAG considers that the cost-effectiveness of epcoritamab is overestimated for every comparison in the model:

1. The proportion of patients on R-based CIT entering LTR at 2 years might be underestimated; and the proportion of epcoritamab patients entering LTR in this comparison is overestimated (and above what was deemed plausible by the company's clinical experts).
2. The proportion of patients on Pola + BR entering LTR at 2 years is considerably underestimated; even though the proportion of epcoritamab patients entering LTR in this comparison is plausible according to the company's clinical experts.
3. The proportion of patients on axi-cel entering LTR at 2 years might be a reasonable prediction of PFS for this treatment; with the main problem in this comparison being the overestimation of the PFS epcoritamab curve, with the main problem in this comparison being the likely overestimation of the PFS epcoritamab curve, according to the proportion deemed plausible by the company's clinical experts.

These issues can be (at least partially) mitigated by the following actions, which the EAG recommends the company undertakes at TE:

1. The more mature PFS data cut which will be available in August and will likely help inform the plausible probability of patients in the PFS curve at later stages past 20 months in the model.
2. Independently fitting OS and PFS curves for each comparator in the model for each comparator.
3. Allowing the model to have a flexible option, whereby the time at which patients enter the LTR assumption can be selected for different points in time for each comparator and for epcoritamab in each comparison.
4. Allowing for the PFS curves to be dictated by the parametric curves fitted to the more mature epcoritamab data (i.e., allowing for the removal of the LTR assumption in the model for epcoritamab only).

In order to help understand the impact of reducing the proportion of LTR patients in the epcoritamab curves, the EAG has conducted some exploratory analysis. Nonetheless, the EAG notes that these analyses are uncertain as the company's model lacks transparency and ease of manipulation, which made it impossible to remove the LTR assumption from the epcoritamab curve alone. This means that the EAG still had to assume that the PFS curves plateau at 2 years for epcoritamab, which the EAG considers to be a highly uncertain assumption. The EAG also had to fix the comparator PFS curves, as it considers these to already be potentially underestimated in the model (or to provide a reasonable prediction). Therefore, the EAG's approach indirectly changed the HRs used by the company to generate PFS curves. Even though the EAG notes that the MAIC HRs are fundamentally flawed in the company base case analysis, the EAG reiterates that this approach lacks methodological robustness and is only intended as an exploratory analysis of uncertainty. Results of the EAG's analysis are provided in Section 6.

For population A, for the comparison of epcoritamab with R-based CIT the EAG used the company's lognormal model, which was the second best-fitting model according to AIC and BIC statistics for epcoritamab. The lognormal curve provided a proportion of patients in remission at 2 years of approximately [redacted] (instead of approximately [redacted] as in the company's base case model), which is likely to be more plausible in population A (Figure 29). Nonetheless, the EAG notes that the analysis undertaken does not resolve the crucial issue of the R-based CIT PFS curve being potentially

underestimated, therefore the EAG analysis is still likely to overestimate the cost-effectiveness of epcoritamab vs R-based CIT.

Figure 29. EAG exploratory analysis for PFS extrapolations for epcoritamab: population A, for the comparison against R-based CIT

[redacted]

For population A, for the comparison of epcoritamab with Pola + BR the EAG did not undertake any additional analysis. This is because the proportion of progression-free patients at 2 years in the epcoritamab arm is [redacted], which is more reflective of the company's clinical experts' view of a plausible estimate. Nonetheless, the EAG notes that: 1) this does not mean that [redacted] is accurate, only that it has face validity compared to the rest of the epcoritamab curves in the company's base case; and crucially 2) the Pola + BR is severely underestimated in the long-run, therefore the cost-effectiveness of epcoritamab vs Pola + BR is overestimated in the company's analysis.

For population B, the EAG chose the company's lognormal model, which the EAG acknowledges was the third best-fitting model according to AIC and BIC statistics. Nonetheless, the lognormal curve provided a proportion of patients in remission at 2 years below [redacted] and is more aligned with the company's clinical experts view of this proportion being between 30–35%, even if still slightly above the experts' prediction (Figure 30). The EAG acknowledges that this approach implies that epcoritamab leads to a higher proportion of patients being in the PFS state than axi-cel over the first

25 months (and for the remaining of the model); which is contradictory to the underlying KM data for both treatments, which shows that axi-cel might offer a PFS advantage over epcoritamab in the first 3 months of treatment. Therefore, the EAG notes that this analysis is still likely to overestimate the relative treatment effectiveness for epcoritamab. This issue could be resolved if the company provides the independently fitted curves as requested by the EAG.

Figure 30. EAG exploratory analysis for PFS extrapolations for epcoritamab: population B

[redacted]

4.2.4.5 Time to treatment discontinuation

For population A, the time to treatment discontinuation (TTD) survival curves were fitted to the epcoritamab MAIC-adjusted KM TTD data from EPCORE™ NHL-1 to the SCHOLAR-1 subgroup and to the Sehn *et al.* population, for the comparison with R-based CIT and Pola + BR, respectively. The epcoritamab TTD survival curves for population B were fitted to the MAIC-adjusted KM TTD data from EPCORE™ NHL-1 to ZUMA-1.

For population A, the company chose the generalised gamma distribution to model TTD for epcoritamab. This was the fourth best fitting curve according to AIC and BIC statistics; however, the

company chose this curve given the company's clinical experts' opinion that the epcoritamab TTD curve should be similar in shape, although below, the PFS curve. The company's clinical experts added that epcoritamab patients would be expected to mostly remain on treatment until progression with a small probability of discontinuation due to toxicity and noted that in EPCORE™ NHL-1 only [redacted] of patients discontinued due to AEs. For this reason, the company chose to extrapolate the TTD data with the generalised gamma model as this was the parametric model used for PFS.

For population A, in the comparison with Pola + BR, the company also chose the generalised gamma distribution to model TTD for epcoritamab, which was the worst fitting curve according to AIC and BIC statistics. The best-fitting curves were the lognormal followed by the log-logistic and the exponential curves. The company reported that two clinical experts concluded that the generalised gamma extrapolation would provide the most clinically plausible extrapolation, while one clinician concluded that the lognormal or log-logistic extrapolations were the most clinically plausible. The company chose the generalised gamma based on the feedback that the TTD curve should have the same shape as the PFS curve, which was modelled with a generalised gamma distribution for this comparison.

For population B, the company chose the Gompertz distribution to model TTD for epcoritamab. This was the third best fitting curve; however, the company reported choosing this curve given the same rationale that that the epcoritamab TTD curve should be similar in shape, although below, the PFS curve. Nonetheless, the EAG notes that the company used a generalised gamma to model PFS for epcoritamab in population B, so the EAG is unsure how the company's justification holds for this population.

The company's clinical experts advised that R-CIT is well tolerated, with most patients completing eight cycles of chemotherapy and only discontinuing treatment due to disease progression. In line with the advice provided, the company assumed that the R-based CIT TTD curve was equal to PFS for the treatment.

For Pola + BR, the company also assumed that TTD was equal to the PFS curve for the treatment.

As the recommended treatment regimen for axi-cel is a single dose administered via IV, no TTD curve for this treatment was modelled.

4.2.4.6 EAG critique

The EAG is concerned with the company's choice of models to fit the TTD KM data for epcoritamab, particularly in the discrepancy with the rationale for choosing the TTD distributions for population A and population B (i.e., the criteria to have same distribution as that used for the epcoritamab PFS curves). The EAG notes that after 2 years in the model, the TTD and the PFS curves all take roughly the same shape (regardless of the underlying distribution used to model the curves) given that patients in the PFS and TTD curve enter LTR and not only are assumed to not progress but also start incurring the same probability of death (that of the general population mortality increased by the SMR) – see an example, Figure 31, where the different TTD curves fitted in population A (comparison with R-based CIT) broadly follow the same trajectory as the PFS curve from 2 years.

Figure 31. Population A, example of the company's different TTD curves fitted

4.2.4.6.1 Population A – comparison to R-based CIT

For population A, the EAG is concerned that the company's choice of the generalised gamma curve provides a bad visual fit to the underlying KM (fourth best fitting curve out of seven). Figure 32 shows the epcoritamab PFS and TTD base case curves used by the company, together with the TTD

KM curve; and the best-fitting TTD Gompertz curve. The latter provides a considerably better visual fit to the underlying TTD KM data, particularly from month 12 onwards.

Even though the TTD Gompertz converges to the PFS curve, overall, the EAG considers that it provides a better estimation of the underlying TTD curve than the company's generalised gamma, while still providing a difference in mean TTD and mean PFS of [redacted] (vs [redacted] in the company's base case analysis). Arguably, using the Gompertz curve is more representative of the company's expectations of very few discontinuations for epcoritamab that using the generalised gamma, considering the differences in mean TTD and mean PFS. Therefore, the EAG has conducted a scenario analysis where the best-fitting Gompertz curve was used to model TTD for epcoritamab vs R-based CIT.

The EAG notes that in its exploratory analysis, described in Section 4.2.4.4.5, where a lognormal curve is used to model PFS for epcoritamab in population A (comparison with R-based CIT), the difference in mean TTD and mean PFS is less than [redacted], which might potentially underestimate discontinuations in the model for epcoritamab, therefore providing a conservative scenario. Nonetheless, the EAG notes that the company's assumption for TTD with R-based CIT was to equal it to the PFS curve (i.e., implicitly assuming no discontinuations due to toxicity or AEs). However, the EAG's clinical experts noted that the assumption that no patients will discontinue treatment aside from disease progression is clinically implausible, which means that the company's assumption is likely to overestimate the costs of treatment for R-based CIT.

During clarification, the EAG pointed the company to the findings by Cazelles *et al*.[41] where 10% of patients were reported to discontinue treatment with R-based CIT due to toxicity. The EAG also noted that this estimate was [redacted] with the discontinuation rate for epcoritamab reported in the EPCORE™ NHL trial of [redacted]. Therefore, during clarification the EAG requested that the company changed the assumption that TTD and PFS were the same for R-based CIT. The company refused to undertake the scenario requested by the EAG as it considered that, "*the vast majority of patients,* […] *will only discontinue treatment with R-based CIT upon progression*".

Therefore, the EAG scenario using the lognormal distribution for PFS and the Gompertz distribution for TTD for epcoritamab vs R-based CIT might help counterbalance the potential bias introduced by the company's assumptions, and lack of exploratory analysis around the latter.

Figure 32. Population A, TTD and PFS fitted curves, together with TTD and PFS KM data

4.2.4.6.2 Population A – comparison to Pola + BR

For the comparison of epcoritamab with Pola + BR, the fitted TTD curve for epcoritamab was equalled to the PFS curve from approximately [redacted] months given that the fitted PFS curve crossed the TTD curve at that point in time. The early crossing of the curves is related with the PFS curve for epcoritamab in this comparison being considerably lower than the other PFS epcoritamab curves used in population A (R-based CIT) or population B (see discussion in Section 4.2.4.4.2. The EAG notes the company's inconsistency and lack of acknowledgment of the fact that in this population, TTD is assumed to be the same as PFS from [redacted] months in the company's base case, therefore assuming that no discontinuations occur beyond this point. Given the company's choice was based on the worst-fitting curve (the generalised gamma), the EAG conducted a scenario analysis using the Gompertz model, which was the fourth best-fitting model according to AIC and BIC statistics and provided a better visual fit to the KM curve up to month 15 (Figure 33). Results are provided in Section 6. The EAG notes that all other curves (including the best-fitting ones) provided implausibly low TTD tails.

Figure 33. Population B, TTD and PFS KM data

[redacted]

4.2.4.6.3 Population B – comparison to axi-cel

For population B, the Gompertz curve offers the more conservative scenario compared to the best-fitting curves, which were all below the Gompertz, while still providing a good visual fit to the underlying KM TTD curve (Figure 34). Even though the PFS curve is modelled with a generalised gamma, using the latter distribution for TTD would result in an implausible low TTD curve.

The mean TTD and mean PFS in the company's base case is [redacted], respectively. Considering the company's expectation that epcoritamab is well tolerated and very few patients discontinue due to AEs or toxicity, the EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation is likely be too high.

The EAG notes that in its exploratory analysis, described in Section 4.2.4.4.5, where a lognormal curve is used to model PFS for epcoritamab in population B, the difference in mean TTD and mean PFS is [redacted], which is more representative of the company's expectations of very few discontinuations for epcoritamab.

Figure 34. Population B, TTD (Gompertz) and PFS (generalised gamma) fitted curves for epcoritamab

Figure 35. Population B, TTD (Gompertz) and PFS (lognormal) fitted curves for epcoritamab

Overall, the EAG notes the lack of consistency in the company's approach in choosing the TTD curves. The EAG accepts that as a result of conducting 3 different MAICs and adjusting the epcoritamab outcomes to 3 different studies for each comparator, all epcoritamab TTD (and OS and PFS) curves will be different. Nonetheless, there is a lack of consistency in the company's approach in accepting that TTD and PFS curves for epcoritamab might (or may not) be the same; therefore, implicitly assuming different levels of toxicity for epcoritamab in each of the comparator analysis.

The EAG notes that the KM curves for epcoritamab in each comparison all show some deviation from the PFS curves, with the highest one seen for population B (Figure 36 to Figure 38), although the EAG anticipates that the more mature TTD and PFS data might help to better inform the relationship between PFS and TTD KM and fitted curves.

Finally, the EAG notes that company's assumption for R-based CIT and Pola + BR of assuming that patients never discontinue due to toxicity is highly unlikely to be plausible, considering the toxicity of these treatments. The EAG notes that the company's assumption biases the cost-effectiveness results in favour of epcoritamab. Therefore, the EAG recommends that the company reconsiders this assumption for both treatments during TE.

Figure 36. KM PFS and TTD curves for epcoritamab – population A, vs R-based CIT

Figure 37. KM PFS and TTD curves for epcoritamab – population A, vs Pola + BR

[redacted]

Figure 38. KM PFS and TTD curves for epcoritamab – population B

[redacted]

4.2.5 Health-related quality of life

4.2.5.1 Health state utility values

To derive utility values for each health state, linear mixed models (LLM) for repeated measures were used to analyse the EQ-5D-3L data collected in the EPCORE™ NHL-1 trial. In the trial, EQ-5D-3L data were collected at cycles 1,3,5,7,9 and at the end of treatment. For the LLM analysis, three models were fitted that used one, two or three combinations of covariates (health state; health state and treatment status; or health state, treatment status and interaction between health state and treatment status). All models were run using the random intercept model to control for the difference in utilities between patients. After consideration, the company deemed that the utility values derived using one covariate (health state) were the most appropriate, given these provided the lowest AIC and BIC scores and that NICE has expressed previous preference to pool health state utility values across treatment arms.

The company derived utility values from the overall LBCL population and the DLBCL (no prior CAR-T) population which are summarized in Table 51. Even though this was not explicitly stated, in the company's updated model, the company used the utilities derived from the DLBCL (no prior CAR-T) population in both comparisons for population A, and used the utilities derived from the overall LBCL population for population B.

The company also accounted for the natural deterioration of HRQoL associated with ageing by adjusting the utility values used in the economic model as advised in NICE DSU TSD 12,[42] based on Ara and Brazier[43].

Patients in LTR continued to experience the utility value associated with being in the PFS state while alive.

Table 51. Utility values derived from EPCORE™ NHL-1 using linear mixed models (adapted from Table 56 in the CS).

Health state	Utility value	SE
DLBCL, no prior CAR-T – used in population A		
Pre-progression	[redacted]	[redacted]
Post progression	[redacted]	[redacted]
LBCL (overall population) – used in population B		
Pre-progression	[redacted]	[redacted]

Post progression	[redacted]	[redacted]

Abbreviations: CAR-T therapy, chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; SE, standard error.

4.2.5.2 EAG critique

The EAG notes that the pre-and post-progression health state utilities derived from the ZUMA-1 trial (0.72 and 0.65 for the pre-and post-progression health states, respectively) and previously accepted in TA559 and TA649 were slightly lower than the ones derived from the EPCORE™ NHL-1 trial, but generally aligned.

The EAG notes that the population used to derive utilities for population A does not seem to have been limited in the same way as the subgroup of patients used in the effectiveness analysis, as the company did not mention CAR-T eligibility in this population. Therefore, the EAG assumes that the company included all patients who had DLBCL and had received no prior CAR-T treatment. As discussed in Sections 2.3.1.2, 3.4.2.1 and 3.4.2.2 (and Key Issue 6, Table 7), the EAG is unsure whether the data used in MAICs for population A were reflective of a group ineligible for intensive treatments; however, the EAG's preference is that the populations used to derive the utility and the effectiveness estimates are the same, therefore, the EAG recommends that the company provides the analysis requested in Key Issue 6 (Table 7) for the MAIC and that the utility estimates are derived from the respective population (i.e., patients not previously treated with CAR-T and ineligible to receive CAR-T subsequently) at TE.

For population B, the EAG is satisfied with the use of the LBCL population (instead of the DBCL population); however, would have preferred to have restricted the population further to no prior CAR-T, eligible to receive future CAR-T. Therefore, in order to have consistency between the populations used to derive the utility and the effectiveness estimates in population B, the EAG recommends that the company provides the estimates utilities in the LBCL, no prior CAR-T, eligible to receive future CAR-T population during TE.

4.2.5.3 Adverse events

Total QALY loss due to adverse events (AEs) was applied during the first cycle of the model. Adverse events' disutility values were calculated as the product of the utility decrements and the duration of events reported in Table 52. Adverse event rates are presented in Section 3.3.3, with the rates from

the overall LBCL population used in the company's base case. Disutilities were obtained from previous NICE submission where available and assumptions made by the company were applicable.

Table 52. Adverse event-related utility decrements applied in the cost-effectiveness model. Reproduced from Table 58 in the CS.

Adverse event	Utility decrement	SE	Source	Days	Source
Anaemia	0.250	0.025	NICE TA649[29] and NICE TA306[44]	16	NICE TA649[29]
B-cell aplasia	0.370	0.037	NICE ID3795 (now NICE TA883)[8]	365	NICE TA559 (now NICE TA872)[5, 45]
CRS	0.772	0.077	Assumed equal to the utility associated with the progression-free health state, in line with NICE TA559[45]	4	NICE TA559 (now NICE TA872)[5, 45]
Febrile neutropenia	0.150	0.015	NICE TA559[45]	6	NICE TA559 (now NICE TA872)[5, 45]
Hypokalaemia	0.090	0.009	NICE ID3795 (now NICE TA883)[8]	72	NICE ID3795 (now NICE TA883)[8]
ICAN	0.772	0.077	Assumed to be the same as CRS	17	NICE TA559 (now NICE TA872)[5, 45]
Leukopenia	0.090	0.009	NICE TA649[29]	14	NICE TA306[44]
Lymphopenia	0.090	0.009	NICE ID3795 (now NICE TA883)[8]	34	NICE ID3795 (now NICE TA883)[8]
Neutropenia	0.090	0.009	NICE TA649[29]	15	NICE TA306[44]
Neutrophil count decreased	0.090	0.009	Assumed to be the same as neutropenia	15	Assumed to be the same as neutropenia
Pneumonia	0.200	0.020	NICE TA649 and NICE TA559[45]	15	NICE ID3795 (now NICE TA883)[8]

Rash	0.250	0.025	Assumed to be the same as anaemia	16	Assumed to be the same as anaemia
Thrombocytopenia	0.110	0.011	NICE TA649[29]	23	NICE TA306[44]

Abbreviations: CRS, cytokine release syndrome; ICAN, immune effector cell-associated neurotoxicity syndrome; SE, standard error.

4.2.6 Resource use and costs

4.2.6.1 Intervention and comparators' costs and resource use

Drug acquisition costs were calculated by combining dosing regimens with relative dose intensity (Table 53), which were sourced from the electronic market information tool (eMIT), the British National Formulary (BNF) or directly from the company (Table 54).[46, 47] The EAG notes that most of comparator treatments have patient access schemes (PASs) agreed with NHS England (NHSE), therefore a confidential appendix containing the results of the analysis using the PASs will be provided by the EAG after TE.

In the economic model, drug acquisition costs for epcoritamab, R-based CIT and Pola + BR were applied in line with either treatment stopping rules or when patients discontinued treatment, depending on whichever of the two occurred first. Patients who progressed moved on to receive subsequent treatments in the model.

The company costed R-based CIT drug acquisition costs using rituximab combined with gemcitabine and oxaliplatin (R-GemOx) as a proxy for all R-based chemotherapies. This approach was considered appropriate by an advisory board of UK clinical and economic experts organised by the company. Administration costs for R-based CIT and Pola + BR were also included in the model (Table 55).

To reflect the one-time nature of treatment with axi-cel, drug acquisition, administration and monitoring costs were applied as a one-time cost at the beginning of the model.

Costs for the different administration methods were obtained from the National Schedule of Reference Costs 2019–2020[48] (Table 56). All costs in the model were inflated to 2021 cost year.

During clarification, the EAG noted that the CS lacked sufficient detail around how the administration and monitoring cost for axi-cel were estimated in the model. The company clarified that a cost of £41,101 for axi-cel was taken from Slide 4 of the Public Committee Slides from the

third appraisal committee meeting for TA872 (confirmed by the budget impact template from NHS England).[5] The company reported that it understood this to be the agreed NHSE cost for the first 100 days following CAR-T use thus, this cost should be used in all ongoing and future appraisals that included CAR-T therapies. The company understood that this cost included:

- Axi-cel leukapheresis costs;
- Hospitalisation costs for conditional chemotherapy;
- Weighted average cost of CRS;
- Hospitalisation costs for axi-cel administration;
- Axi-cel costs for weighted average cost of allogenic SCT;
- Training costs;
- Medical resource use costs for the first three months (~100 days);
- Hypogammaglobulinemia costs for the first three months (~100 days).

The company added that to prevent any double counting, the cost of CRS was removed from the one-time administration cost of axi-cel in the model. The company took the one-time administration cost of axi-cel calculated as £41,101 and subtracted the cost of CRS as an AE in the model, multiplied by the rate of CRS in the model (£3,560×13%), totalling a cost of administration for axi-cel of £40,638. To this, the company added an extra monitoring cost for axi-cel (see Table 55).

Table 53. Drug dosage inputs applied in the cost-effectiveness model (adapted from table 60 in the CS).

Treatment	Admin route	Admin frequency	Dose intensity	Vial sharing	Reference
Epcoritamab	SC	Cycle 1: 0.16 mg day 1, 0.8 mg day 8, 48 mg day 15 and 22 Cycle 2 and 3: 48 mg day 1, 8, 15, and 22 Cycle 6-9: 48 mg day 1 and 15 Cycle 10+: 48 mg day 1	[redacted]	No	EPCORE™-NHL 1 CSR[21]
Rituximab	IV	375 mg/m2 day 1 up to 8 cycles	100%	No	Mounier N, *et al.* 2013[35]
Gemcitabine	IV	1,000 mg/m2 day 1 up to 8 cycles	100%	No	
Oxaliplatin	IV	100 mg day 1 up to 8 cycles	100%	No	
Axi-cel	IV	One time administration	NA	NA	NICE TA559 (now NICE TA872)[5, 45]

Polatuzumab vedotin	IV	1.8 mg/kg day 1 of a 21-day cycle, up to 6 cycles	No	No	NICE TA649[29]
Bendamustine	IV	90 mg/m2 day 1 and 2 of a 21-day cycle, up to 6 cycles	No	No	
Rituximab	IV	375 mg/m2 day 1 of a 21-day cycle, up to 6 cycles	No	No	

Abbreviations: admin, administration; axi-cel, axicabtagene ciloleucel; CIT, chemoimmunotherapy; IV: intravenous; N/A: not applicable; NICE: National Institute for Health and Care Excellence; SC: subcutaneous.

Table 54. Drug acquisition costs (adapted from Table 61 in the CS.)

Treatment	Dose	Cost per package	Reference
Epcoritamab	1 x 4 mg	[redacted]	AbbVie data on file
		PAS price: [redacted]	
	1 x 48 mg	[redacted]	AbbVie data on file
		PAS price: [redacted]	
Rituximab	2 x 100 mg	£314.33	BNF[47]
	2 x 500 mg	£1,571.67	BNF[47]
Gemcitabine	1 x 200 mg	£3.42	eMIT 2022[46]
	1 x 1000 mg	£8.59	eMIT 2022[46]
Oxaliplatin	1 x 50 mg	£13.49	eMIT 2022[46]
	1 x 200 mg	£21.52	eMIT 2022[46]
Polatuzumab	1 x 30 mg	£2,370.00	BNF[47]
	1 x 140 mg	£11,060.00	BNF[47]
Bendamustine	5 x 25 mg	£28.75	eMIT 2022[46]
	5 x 100 mg	£77.70	eMIT 2022[46]
Rituximab	2 x 100 mg	£314.33	BNF[47]
	2 x 500 mg	£1,571.67	BNF[47]
Axi-cel	-	£280,451	Drug acquisition cost: Yescarta 40million–200million cells/68ml dispersion for infusion bags (Gilead Sciences Ltd).

Abbreviations: BNF, British National Formulary; eMIT, Electronic market information tool; PAS, patient access scheme.

Table 55. Administration costs in the model

Treatment	Administration and/or monitoring	Reference
R-based CIT	One-off administration cost: £5,660.02	NICE TA559 (now NICE TA872) inflated to 2021 cost year[5, 45]
Pola + BR	£502.74 and £358.62, respectively, for the delivery of the delivery of first and subsequent chemotherapies	SB13Z and the SB15Z codes, inflated to 2021 cost year
Axi-cel	One-off administration cost: £40,638 One-off monitoring cost: £1,489 Total: £42,127	One-time administration cost: NICE TA872[5] One-time monitoring cost: NICE TA559 (now TA872), inflated to 2021 cost year[5, 45]

Abbreviations: axi-cel, axicabtagene ciloleucel; CIT, chemoimmunotherapy; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; R, rituximab.

Table 56. Other drug administration costs (reproduced from Table 63 in the CS).

Administration method	Costs	Reference
IV	£358.62	SB15Z (National Schedule of Reference Costs 2019-20) inflated to 2021 cost year[48]
SC	£298.46	SB12Z (National Schedule of Reference Costs 2019-20) inflated to 2021 cost year[48]
Oral	£221.52	SB11Z (National Schedule of Reference Costs 2019-20) inflated to 2021 cost year[48]

Abbreviation: IV: intravenous; SC: subcutaneous.

4.2.6.2 EAG critique

The EAG disagrees with the company's addition of monitoring costs to the axi-cel administration cost. The company's model states that, "*the monitoring cost accounts for excess bed days which accrue due to the AEs associated with the treatment of axi-cel*". Nonetheless, the description of axi-cel administration costs provided by the company already includes costs for managing CRS (the most serious AE associated with treatment) and crucially, the final appraisal determination document and the committee slides in TA872 read, "*the company submitted a further analysis using a CAR T-cell therapy delivery cost of £41,101* [and] *removing all other costs relevant to the delivery of CAR-T for the first 100 days following infusion*." Also, it stated that, "*NHSE have accepted this* [£41,101] *as a*

total cost for the first 100 days and recommend NICE consider this in all ongoing CAR-T appraisals". Therefore, the EAG conducted a scenario analysis where a total cost of £40,638 for the administration of axi-cel was used in the model (which excluded the costs of CRS). The results of the EAG analysis are reported in Section 6.

The EAG notes that the company assumed 8 cycles of treatment with R-based CIT in the model. Nonetheless, the EAG's clinical experts explained that several centres in the UK only allow a maximum of 6 cycles of treatment with R-based CIT. Therefore, the EAG has conducted a scenario analysis in the model where a maximum of 6 cycles of R-based CIT is given. The results of the EAG analysis are reported in Section 6.

The EAG considers the company's approach to costing administration of chemotherapies in the R-based CIT and the Pola + BR treatment combinations is inconsistent. For Pola + BR, the company used the SB13Z and the SB15Z code to reflect the delivery of first and subsequent chemotherapies (£502.74 and £358.62, respectively); however, the company applied an administration cost of £5,660 (£5,063 updated with inflation) for R-based CIT. In TA559, where the company states the administration cost for R-based CIT was taken from, the company costed the administration of a basket to BSC treatments (of which R-based CIT was part) at £5,063, based on the hospital admission of nonelective long-stay HRGs for malignant lymphoma. The EAG in TA559 criticised the company's approach and noted this cost should be replaced with the SB14Z and the SB15Z code to reflect the delivery of first and subsequent chemotherapies.

Due to the difficulty in navigating the cost calculations in the company's model and time restraints, the EAG could not conduct a scenario analysis where the costs of administrating R-based CIT according to the SB14Z and the SB15Z were applied every cycle. Instead, the EAG conducted a simplified analysis where the total cost of £5,063 was replaced by £3,015 (1 first administration of chemotherapy followed by 7 rounds of subsequent administrations); or £2,297 for the scenario where only 6 doses of R-based CIT were administered in the model. The results of the EAG analysis are reported in Section 6.

Nonetheless, the EAG notes that this analysis is likely to overestimate treatment costs as not all patients would have received all rounds of treatment (as some patients will have died in the model before the end of treatment). Therefore, the EAG recommends that the company conducts the more accurate scenario analysis during TE.

Finally, the EAG is unsure why all costs in the model were inflated to the 2021 cost year and recommends that during TE the company inflates all relevant costs to the most recent cost year.

4.2.6.3 Subsequent treatments

After progressing on 3rd line treatments in the model, patients were assumed to receive one line of subsequent treatments. The proportion of patients receiving each subsequent treatment was informed by the company's clinical expert opinion (Table 57) with populations A and B receiving the same proportion of treatments. Costs for subsequent treatments are outlined in Table 58.

Table 57. Proportion of patients receiving subsequent treatments for each preceding treatment (reproduced from Table 64 in the CS).

Treatment at entry	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	No active treatment
Epcoritamab	52.5%	5%	25%	0.5%	3%	13.5%
R-based CIT	46%	10%	26%	1.5%	1.5%	15%
Pola + BR	49%	7%	26%	1.0%	2.5%	15%
Axi-cel	52%	0%	32%	1%	5%	10%
Reference	Company's clinical expert interviews					

Abbreviations: Allo, allogenic; auto, autologous; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; R, rituximab; SCT, stem cell transplant.

Table 58. Costs and administrations of subsequent treatments.

Subsequent treatment	Cost per administration	Number of administrations per model cycle	Mean time on treatment (months)
R-based CIT	£1,214	1.00	8.00
CAR-T therapy	£321.089 (£280,451 plus one-off administration cost: £40,638)	1.00	1.00
Radiotherapy	£3,673	10.00	1.00
Autologous SCT	£28,398	1.00	1.00
Allogenic SCT	£81,718	1.00	1.00

Abbreviations: axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; ID: identification; NICE: National Institute for Health and Care Excellence; R: rituximab; SCT, stem cell transplant; TA: technology appraisal.

4.2.6.4 EAG critique

The EAG consulted with its clinical experts to validate the proportions assumed by the company who expressed that in clinical practice, previous treatment would be taken into consideration when providing further treatment, therefore rendering the company's assumption of the same subsequent treatments in both populations implausible. For example, patients previously treated with epcoritamab would have differing future treatments depending on if they were eligible to receive CAR-T therapy (i.e., if patients were part of population A or B). Additionally, the EAG's experts noted that 4th line therapy for those previously treated with a rituximab-based combination should be palliative chemotherapy (and not include subsequent rituximab as assumed by the company) with a mix of oral chemotherapy, radiotherapy and no active treatment. As a result, during clarification, the EAG requested the company to conduct a scenario analysis using the proportion of patients receiving subsequent treatments as outlined in Table 59. The company refused to conduct the EAG's requested analysis as it considered that, "*the subsequent treatment assumptions used in the submitted base case are appropriate*".

The EAG conducted the scenario analysis and reports the results in Section 6; however, due to time constraints, for the R-based CIT and Pola + BR patients receiving subsequent palliative chemotherapy, the EAG undertook the simplifying assumption of removing the costs of rituximab from the R-based CIT combination used in the model as a subsequent treatment. It is likely that these patients would get different chemotherapies from GemOx, therefore, the EAG recommends that the company conducts the scenario analysis requested by the EAG at TE.

Table 59. EAG preferred subsequent treatment proportions.

Treatment at entry	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	Allo-SCT	No active treatment
Epcoritamab (population A)	30%	11%	25%	1%	3%	30%

Epcoritamab (population B)	30%	30%	25%	1%	3%	12%
R-based CIT	30%*	8%	30%	0%	2%	30%
Pola + BR	30%	8%	30%	0%	2%	30%
Axi-cel	9%	0%	32%	1%	5%	53%

*Additional chemotherapy following treatment with R-based CIT would be palliative and not R-based.
Abbreviations: Allo, allogenic; auto, autologous; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; R, rituximab; SCT, stem cell transplant.

The EAG finds the company's costing of administration for subsequent events in the model to be inconsistent with the administration costs applied for 3rd line treatments. Even though it is not clear in the model (or reported in the CS), the EAG investigated the model and concluded that the administration cost for all subsequent treatments (CAR-T therapy, radiotherapy, autologous SCT, and allogenic SCT) was applied, and assumed to be £358.62, the cost of a subsequent administration of chemotherapy based on the SB15Z code. Nonetheless, the EAG requests that the company clarifies and justifies its approach at TE.

4.2.6.5 Health-state utility costs and resource use

An overview of the disease management-related resource use and costs by health state and treatment discontinuation status are provided in Table 60. In addition to the disease management costs detailed in Table 60, patients in the PD health state were also assumed to incur a one-off cost of disease follow up due to their disease progressing. Table 61 summarises the resource use and unit cost of disease follow up applied in the model. Terminal care-related resource use and associated costs are reported in Table 62. Resource use frequencies were referenced from NICE TA306, which in turn sourced all the resource use from clinical expert opinion.[29, 44, 45]

While epcoritamab patients were assumed to be on treatment until progression or unacceptable toxicity, the company considered that the resource use incurred by epcoritamab patients would decrease over time while patients were on treatment. To incorporate this assumption into the model, the company used a threshold of [redacted], after which progression-free epcoritamab patients on treatment would be considered to incur the "PFS off-treatment" resource use detailed in Table 60. This threshold was used by the company under the justification that it reflects median PFS in for patients who achieved partial response (PR) or complete response (CR) in the DLBCL

population of EPCORE™ NHL-1. After 2 years, all patients in the PFS state in every treatment arm of the model (including epcoritamab) were assumed to stop incurring any disease management or other follow-up costs, as these were considered to be in LTR.

Unit costs were sourced from NHS reference costs or available published literature with costs inflated to 2021, where applicable.[48]

Table 60. Disease management health care resource use and cost by health state and treatment discontinuation. Reproduced from Table 66 in the CS).

Resource	Value	Resource use by health state, per model cycle		
		PFs on-treatment	PFs off-treatment	PD
Residential care (days)	[redacted]	2.99	0.75	-
Day care (days)	[redacted]	1.12	0.28	1.87
Home care (days)	[redacted]	4.67	1.17	9.33
Hospice (days)	£168.86	0.05	-	0.93
Oncologist (number of visits)	[redacted]	1.67	-	0.33
Haematologist (number of visits)	[redacted]	0.78	0.19	1.00
Nurse (number of visits)	[redacted]	4.00	1.00	-
Palliative care team (number of visits)	£157.13	-	-	1.33
Specialist nurse (number of visits)	[redacted]	0.67	0.17	2.50
GP (number of visits)	[redacted]	2.00	-	3.33
District nurse (number of visits)	[redacted]	1.50	0.38	4.00
CT scan (number of visits)	[redacted]	0.31	0.31	0.03
Full blood count (number of visits)	[redacted]	3.33	3.33	1.00
LDH (number of visits)	[redacted]	2.00	2.00	0.33

Liver function (number of visits)	[redacted]	3.33	3.33	1.00
Renal function (number of visits)	[redacted]	3.33	3.33	0.33
Immunoglobulin (number of visits)	[redacted]	0.67	0.67	0.33
Calcium phosphate (number of visits)	[redacted]	0.67	0.67	1.00

Abbreviations: CT, computerised tomography; GP, general practitioner; LDH, lactate dehydrogenase; PD, progressed disease; PF, progression-free.

Table 61. Resource use and unit cost of disease follow up for patients with progressive disease (reproduced from Table 67 in the CS).

Resource	Costs per patient	Use (% of patients)
ECG	£147.66	67%
MUGA	£511.56	33%
CT-scan	£111.11	17%
MRI	£151.01	7%
PET-CT	£511.56	57%
Bone marrow biopsy	£624.12	0%

Abbreviations: CT: computed topography; ECG: electrocardiogram; MUGA: multigated acquisition; MRI: magnetic resonance imaging; PET: positron emission tomography.

Table 62. Terminal care related resource use and cost. Reproduced from Table 68 in the CS.

Resource	Costs per patient	Use (% of patients)
CT-scan	£111.11	33%
MRI	£151.01	7%

Abbreviations: CT, computer topograpy; MRI, magnetic resonance imaging.

4.2.6.6 EAG critique

The EAG has several concerns with the company's implementation of disease management costs in the model. Firstly, investigations of the company's model led the EAG to the conclusion that for R-based CIT; Pola + BR; and axi-cel; all patients incurred the "PFS on-treatment" for the initial 2 years of the model, after which progression-free patients started incurring no costs as these were

considered to be in LTR. This is inconsistent with the company's approach to estimating follow-up costs for epcoritamab where patients incurred a "PFS off-treatment" follow-up cost after [redacted] months in the model. The company's approach is biased in favour of epcoritamab and is unjustified, as patients who finished their comparator treatments (before 2 years) and were in the PFS state should have incurred the "PFS off-treatment" lower costs.

Therefore, the EAG has conducted an exploratory analysis where R-based CIT; Pola + BR; and axi-cel patients incurred lower resource use costs before 2 years. Ideally, the EAG would have changed the company's assumption to reflect the "PFS on-treatment" for the duration of treatment with each comparator. However, due to time restraints and the difficulty in making changes to the company's model separately for each comparator (to reflect different treatment durations), the EAG had to run a simplified approach where all patients in the comparator treatment were assumed to incur the "PFS off-treatment" from the beginning of the model. This assumption is reasonable for axi-cel (given this is a one-off treatment), although for R-based CIT and Pola + BR, ideally patients would have incurred "PFS on-treatment" costs for 8 (or 6) and 4 doses of treatment, respectively. Therefore, the EAG recommends that the company adapts their model to be more flexible, so that each treatment arm can incur the resource use for the on- and off-treatment costs for the correct amount of time.

Furthermore, the EAG disagrees with the company's assumption that after [redacted] in the PFS state epcoritamab patients would move to the off-treatment resource as assumed in the model. The company justified this approach based on it reflecting median PFS for patients who achieved partial response (PR) or complete response (CR) in the DLBCL population of EPCORE™ NHL-1. The EAG does not understand how median PFS would dictate resource use for patients on epcoritamab treatment – the EAG's clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued, meaning that the resource use estimated by the company for epcoritamab for the progression-free, on treatment period should be observed for as long as treatment is given in the model. However, in contrast to this, epcoritamab patients in the model are assumed to incur less resource uses after what seems a poorly-defined threshold of [redacted] and crucially, patients stop incurring any costs when entering LTR even though they would continue to be on treatment. The EAG notes that the company's base case approach is biased in favour of epcoritamab and artificially underestimates the disease management costs associated with the treatment, without a plausible clinical explanation.

The EAG therefore requested that the company conducted a scenario analysis where patients on treatment with epcoritamab experienced the same resource use from cycle 0 to end of treatment in the model. The company refused to conduct this analysis. Therefore, the EAG conducted an exploratory analysis where the follow-up costs (PFS on-treatment costs) were incurred for epcoritamab while patients were on treatment. Due to lack of transparency in the company's model, the EAG cannot ensure that the implementation of this assumption in the model does not contain errors. Therefore, the EAG recommends that the company includes this option in the model as requested by the EAG at TE.

The EAG was also concerned that some resources lacked clarity around what was included in their costs leading to potentially double counting of some services. This was the case for residential care, day care, home care and hospice care. For example, the PSSRU[49] source used by the company to cost day care, included 1 working hour of a band 7 nurse. However, the company also included time with a specialist nurse; district nurse; and nurse time separately. During clarification, the company stated that the district nurse resource use is considered to be community-based health care, while the specialist nurse and nurse resource use are hospital-based health care. However, the cost associated with the district nurse, specialist nurse and nurse time are all based on the National Schedule of Reference Costs 2019-20 (N02AF), in line with previous NICE TAs in R/R LBCL. The EAG is unclear how this avoids double counting of resources in the model.

The company's justification for other queries about double counting of resources in the model was generally that, "*all cost categories and cost sources used in the model are aligned with previous NICE appraisals in R/R LBCL (such as TA649, TA306 and TA559).*" And, "*TA649 does not include a detailed explanation of what is included in these two resource use categories, but they are both part of professional and social services.".* The EAG is not satisfied that the cost sources used to cost resource use in the model are not double counting resources in the model.

The EAG's clinical experts also considered that a multigated acquisition scan (MUGA) would not be used in UK clinical practice, and that patients would be unlikely to see an oncology consultant when a haematologist would be sufficient. Furthermore, the EAG's experts noted that in UK clinical practice only CT scans of 3 or 3+ areas with contrast would be used (cost codes RD26Z and RD27Z) for R/R LBCL patients. Therefore, the EAG requested the company removed/changed these resources in the model accordingly. The company provided these as scenario analysis during clarification and the impact on the final ICER was minimal.

4.2.6.7 *Adverse reaction costs and resource use*

Adverse events were costed as a one-off cost and were assumed to occur within the first cycle of the model for patients receiving each treatment (Table 63). Costs were informed using previous HTA submissions and NHS reference costs inflated to the 2021 cost year.[48]

Table 63. AE costs in the economic model. Reproduced from Table 69 in the CS.

Adverse event	Cost per event	SE
Anaemia	£328.40	£32.84
B-cell aplasia	£2,600.02	£260.00
CRS	£3,560.40	£356.04
Febrile neutropenia	£1,884.72	£188.47
Hypokalaemia	£1,456.44	£145.64
ICAN	£3,560.40	£356.04
Leukopenia	£476.74	£47.67
Lymphopenia	£1,533.37	£153.34
Neutropenia	£384.55	£38.46
Neutrophil count decreased	£384.55	£38.46
Pneumonia	£904.16	£90.42
Rash	£384.55	£38.46
Thrombocytopenia	£381.86	£38.19

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; ICAN, immune effector cell-associated neurotoxicity syndrome.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 64 presents the cost-effectiveness results of the company's updated probabilistic base case for epcoritamab vs R-based CIT, while Table 65 provides the equivalent deterministic results. Table 66 and Table 67 report the equivalent results for the comparison of epcoritamab and Pola + BR. The company applied a severity modifier of 1.2 to the incremental QALYs in their updated base case for the comparison of epcoritamab with R-based CIT and Pola + BR.

Table 68 and Table 69 report the probabilistic and deterministic ICERs for the comparison of epcoritamab and axi-cel, respectively, where no severity modifier was used.

As noted at the beginning of Section 4, the probabilistic ICERs reported by the EAG slightly differ from those reported by the company in Tables 39, 37, and 43 of the company's response to clarification questions. This is because the EAG had to re-run the probabilistic ICERs for all comparisons given that the company originally included discounted life-years gained in their probabilistic ICERs (instead of undiscounted life-years). Furthermore, there was a reporting mistake in the probabilistic ICER for epcoritamab vs Pola + BR, which the EAG corrected.

The company's probabilistic and deterministic results are broadly similar, with the exception of the ICERs for epcoritamab vs Pola + BR, where the probabilistic ICER is approximately £2,600 higher than the deterministic ICER.

Table 64. Company's base case probabilistic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
R-based CIT	£85,009	[redacted]	1.005	[redacted]	[redacted]	[redacted]	[redacted]	£19,260	£16,050

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 65. Company's base case deterministic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
R-based CIT	£82,610	[redacted]	0.900	[redacted]	[redacted]	[redacted]	[redacted]	£18,598	£15,498

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 66. Company's probabilistic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		

Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	£141,171	[redacted]	1.803	[redacted]	[redacted]	[redacted]	[redacted]	£7,584	£6,320

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 67. Company's deterministic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	£138,794	[redacted]	1.488	[redacted]	[redacted]	[redacted]	[redacted]	£4,892	£4,077

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 68. Company's base case probabilistic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£375,814	[redacted]	3.799	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 69. Company's base case deterministic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£370,344	[redacted]	3.842	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company's updated cost-effectiveness scatter plots and cost-effectiveness acceptability curves for epcoritamab against R-based CIT are provided in Figure 22 and Figure 23 of the company's clarification response, with the equivalent figures for the comparison with axi-cel being presented in Figure 24 and 25 of the company's clarification response, respectively. The company did not provide the equivalent figures for the comparison with Pola + BR.

5.2.2 Deterministic sensitivity analysis

The company conducted a one-way deterministic sensitivity analysis to assess the sensitivity of the model to individual parameter uncertainty. Each parameter was varied by 95% CIs where applicable and by ±10% where these values were unavailable. Results for the comparison of epcoritamab vs R-based CIT and axi-cel are provided in Figure 26 and Figure 27 of the company's clarification response. The company did not provide the equivalent figures for the comparison with Pola + BR.

5.2.3 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. Results of all scenario analyses conducted by the company are presented in Table 51 and Table 52 of the company's clarification response. The company did not provide the equivalent figures for the comparison with Pola + BR.

Overall, the EAG notes that the company's sensitivity analyses are based on the structural and methodological flaws identified by the EAG throughout the report. Therefore, the EAG considers that the results of the analyses are highly uncertain and do not help mitigate any uncertainty in relation to the company's deterministic (and probabilistic) base case results. The EAG recommends that the company re-runs all of these scenarios once the EAG's recommendations have been implemented in the company's model and that the company runs all of the analyses for the comparison of epcoritamab vs Pola + BR.

6 Additional economic analysis undertaken by the EAG

As explained throughout the report, the EAG considers that the cost-effectiveness of epcoritamab is overestimated for every comparison in the model and that the company's base case model is fundamentally flawed. Due to this, and to time constraints, the EAG only presented deterministic ICERs in Section 6. The analyses conducted by the EAG are meant to help depict the potential impact of the EAG's changes to the model (with the main concern being around reducing the proportion of LTR patients in the epcoritamab curves); however, they do not provide ICERs robust enough to become alternative base case results.

For the same reason, and due to there being three comparator treatments, which required the EAG to have three separate model versions (due to the already discussed lack of flexibility in the company's model to change assumption separately for each comparator), the EAG provides the impact of the changes made to the model cumulatively (i.e., the EAG did not implement each change to the model separately, but instead presents the impact of changing assumptions in a cumulative way).

At the end of this section the EAG lists all the recommended changes to the company's model to be conducted at TE that would help mitigate the uncertainty in the company's model results.

6.1 Model corrections

The EAG corrections were explained throughout the report. These consisted of the following:

- Taking the minimum between the PFS and the OS epcoritamab curves when the PFS curve dropped below the OS curve for all populations, to avoid having a proportion of patients who start to progress late in the model (which is in direct contradiction with the company's intended assumption of no further progression after 2 years in the model for PFS patients). The EAG reiterates the fact that this was a simplistic correction due to time constraints, and one that relies on manually doing this for each comparator treatment, which needs to be run separately (but not allowed to run simultaneously) in the company's base case model. Ideally, this would be automated via embedded formulae, to avoid mistakes and to allow for this error to be automatically corrected for each comparator. The EAG, therefore, recommends that the company implements this at TE.
- Correcting the PFS curve for Pola + BR and for axi-cel, separately, so that when the PFS and OS curves crossed, the OS curve turned into the PFS curve (instead of the other way around as assumed in the company's model) and to make it consistent with the assumption made by the company for epcoritamab.

Table 70 presents the cost-effectiveness results of the company's deterministic results with the EAG correction. Table 71 provides the equivalent results for Pola + BR and Table 72 reports the results for axi-cel. The EAG corrections had a small impact on all the ICERs.

Table 70. Company's base case deterministic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
R-based CIT	£82,608	[redacted]	0.90	[redacted]	[redacted]	[redacted]	[redacted]	£18,516	£15,430

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 71. Company's deterministic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	£137,552	[redacted]	2.05	[redacted]	[redacted]	[redacted]	[redacted]	£8,355	£6,962

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 72. Company's base case deterministic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£369,767	[redacted]	4.28	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

The exploratory analysis conducted by the EAG were explained throughout the report. These consisted of the following:

1. For population A, for the comparison of epcoritamab with R-based CIT the EAG used the company's lognormal model for PFS, which was the second best-fitting model according to AIC and BIC statistics for epcoritamab. The lognormal curve provided a proportion of patients in remission at 2 years of approximately [redacted] (instead of approximately [redacted] as in the company's base case model).
2. For population B, the EAG chose the company's lognormal model, which the EAG acknowledges was the third best-fitting model for PFS for epcoritamab according to AIC and BIC statistics. Nonetheless, the lognormal curve provided a proportion of patients in remission at 2 years below [redacted] and is more aligned with the company's clinical experts view of this proportion being between 30–35%.
3. The EAG has conducted a scenario analysis where the best-fitting Gompertz curve was used to model TTD for epcoritamab vs R-based CIT.

4. The EAG conducted a scenario analysis using the Gompertz model, which was the fourth best-fitting model according to AIC and BIC statistics and provided a better visual fit to the KM curve up to month 15 for epcoritamab vs Pola + BR.
5. A total administration cost of £41,101 for axi-cel was used in the model, excluding the costs of CRS, therefore totalling £40,638 (as opposed to the company's cost of £42,127).
6. Assuming a maximum of 6 cycles of R-based CIT (instead of 8).
7. The EAG conducted a simplified analysis where the total administration cost of R-based CIT of £5,063 was replaced by £2,297 (1 first administration of chemotherapy followed by 5 rounds of subsequent administrations).
8. The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model (as per Table 59 in the report). For the R-based CIT patients receiving subsequent palliative chemotherapy, the EAG undertook the simplifying assumption of removing the costs of rituximab from the subsequent R-based CIT combination used in the model.
9. The EAG has conducted an exploratory analysis where R-based CIT; Pola + BR; and axi-cel patients incurred the "PFS off-treatment" costs before 2 years in the model, while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years.
10. The EAG conducted an exploratory analysis to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS and assumed that epcoritamab patients stay on the "PFS on-treatment" follow-up costs while on treatment.

Results of the EAG's exploratory analysis are provided in Table 73, Table 74 and Table 75 for the comparison of epcoritamab with R-based CIT Pola + BR; and axi-cel; respectively.

For all the analyses, the biggest driver of the EAG's exploratory analysis is the removal of the assumption that epcoritamab patients stop incurring follow-up costs in the NHS at 2 years from the model. This is followed by changing the assumption that epcoritamab patients start incurring the "PFS off-treatment" follow-up costs from [redacted] in the model to assuming epcoritamab patients incur "PFS on-treatment" follow-up costs for 2 years (or while on treatment for scenario analysis 10), as per clinical expert opinion provided to the EAG. For this scenario, the EAG also reduced the follow-up costs for comparator treatments from "PFS on-treatment" to "PFS off-treatment". The EAG, again, caveats its simplifying approach of doing the latter from the first cycle in the model and notes that the company should implement this scenario appropriately in the model during technical

engagement, given the model's current lack of flexibility of allowing such a scenario analysis for comparator treatments (and only allowing it for epcoritamab).

The EAG notes that the assumption of R-based CIT patients receiving 6 or 8 cycles of treatment in the model has a minimal impact on the ICER, therefore, the EAG conducted all subsequent scenario analysis after scenario 6 assuming that R-based CIT is given for 6 cycles of treatment, instead of presenting twice as many analyses for both options of treatment duration.

For population A, for the comparison to R-based CIT, the EAG's exploratory ICER amounts to £47,454 per QALY gained, with a severity modifier of 1.2 applied. Given the mean age of population A and the sex distribution at baseline ([redacted] respectively, in the company's base case), and the total QALY gain for R-based CIT in the EAG's final exploratory ICER of 0.900 QALYs, the severity modifier of 1.2 is applicable to the QALY gain generated in the analysis.

For population A, for the comparison to Pola + BR, the EAG's exploratory ICER amounts to £101,875 per QALY gained, with no severity modifier applied. Given the mean age of population A and the sex distribution at baseline ([redacted] respectively, in the company's base case), and the total QALY gain for Pola + BR in the EAG's final exploratory ICER of 2.053 QALYs, no severity modifier is applicable to the QALY gain generated in the analysis.

For population B, the EAG's exploratory ICER amounts to £15,432 per QALY gained, with no severity modifier applied. Given the mean age of population A and the sex distribution at baseline ([redacted] respectively, in the company's base case), and the total QALY gain for R-based CIT in the EAG's final exploratory ICER of 4.280 QALYs, no severity modifier is applicable to the QALY gain generated in the analysis. The EAG notes that axi-cel is subject to a confidential PAS, which is not included in the results presented in the EAG report.

The EAG notes that the age and sex distribution at baseline in the company's model was derived from the MAIC-adjusted populations (see Section 3.4.1). Therefore, if the MAICs are updated as suggested by the EAG in Section 1.3, it is likely that these parameters will change.

Table 73. Results of the EAG's exploratory analyses – R-based CIT

	Results per patient	Epcoritamab	R-based CIT	Incremental value	Incremental value with severity modifier
0	Company's corrected base case				

	Total costs (£)	[redacted]	£82,608	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£18,516	£15,430
1	Using company's lognormal model for PFS				
	Total costs (£)	[redacted]	£82,608	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£23,431	£19,526
3	Using the Gompertz curve to model TTD				
	Total costs (£)	[redacted]	£82,608	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£22,797	£18,998
6	Assuming a maximum of 6 cycles of R-based CIT (instead of 8)				
	Total costs (£)	[redacted]	£82,305	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£22,874	£19,062
7	The EAG conducted a simplified analysis where the total administration cost of R-based CIT of £5,063 was replaced by £2,297 (1 first administration of chemotherapy followed by 5 rounds of subsequent administrations).				
	Total costs (£)	[redacted]	£78,942	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£23,732	£19,777
8	The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.				
	Total costs (£)	[redacted]	£68,579	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£29,554	£24,629
9	R-based CIT patients incurred the "PFS off-treatment" costs before 2 years in the model while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years				
	Total costs (£)	[redacted]	£63,944	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£33,675	£28,063
10	The EAG conducted an exploratory analysis as a proxy to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS.				
	Total costs (£)	[redacted]	£63,944	[redacted]	[redacted]
	QALYs	[redacted]	0.900	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£56,945	£47,454

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

Table 74. Results of the EAG's exploratory analyses – Pola + BR

	Results per patient	Epcoritamab	Pola + BR	Incremental value
0	Company's corrected base case			
	Total costs (£)	[redacted]	£146,295	[redacted]
	QALYs	[redacted]	2.05	[redacted]
	ICER (£/QALY)	-	-	£8,355
4	Using the Gompertz curve to model TTD			
	Total costs (£)	[redacted]	£137,552	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£7,580
8	The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.			
	Total costs (£)	[redacted]	£136,527	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£21,197
9	Pola + BR patients incurred the "PFS off-treatment" costs before 2 years in the model while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years			
	Total costs (£)	[redacted]	£123,383	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£43,102
10	The EAG conducted an exploratory analysis as a proxy to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS.			
	Total costs (£)	[redacted]	£123,383	[redacted]
	QALYs	[redacted]	2.053	[redacted]
	ICER (£/QALY)	-	-	£101,875

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.

Table 75. Results of the EAG's exploratory analyses – axi-cel

	Results per patient	Epcoritamab	Axi-cel	Incremental value
0	Company's corrected base case			
	Total costs (£)	[redacted]	£369,767	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	8.536
2	Using company's lognormal model for PFS			
	Total costs (£)	[redacted]	£369,767	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	7.706

5	A total administration cost of £41,101 for axi-cel was used in the model, excluding the costs of CRS, therefore totalling £40,638.			
	Total costs (£)	[redacted]	£368,278	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	7.657
7	The EAG used the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.			
	Total costs (£)	[redacted]	£363,470	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	5.290
9	Axi-cel patients incurred the "PFS off-treatment" costs before 2 years in the model while epcoritamab patients stay on the "PFS on-treatment" costs for 2 years			
	Total costs (£)	[redacted]	£350,927	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NHB	-	-	4.407
10	The EAG conducted an exploratory analysis as a proxy to remove the assumption that epcoritamab patients at 2 years stop incurring follow-up costs in the NHS.			
	Total costs (£)	[redacted]	£350,927	[redacted]
	QALYs	[redacted]	4.280	[redacted]
	ICER (£/QALY)	-	-	£15,432
	NHB	-	-	0.479

Abbreviations: axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year.

6.3 Conclusions of the cost effectiveness sections

The EAG has serious concerns with the MAICs undertaken to estimate the relative treatment effect of epcoritamab on OS and PFS outcomes compared to the relevant comparators in populations A and B. Furthermore, the EAG considers the company's approach of jointly fitting survival curves unfit for purpose when the underlying KM curves cross for PFS and OS outcomes for epcoritamab and Pola + BR; and epcoritamab and axi-cel, respectively.

Overall, the EAG is concerned that the company's base case PFS epcoritamab curves are not robust enough to be considered in the cost-effectiveness model. The lack of observed data to substantiate what proportion of epcoritamab patients could be progression-free at 2 years; combined with the company's assumption that the proportion of patients in the PFS epcoritamab curves dictate the

proportion of patients who enter LTR; and crucially; the EAG's clinical experts' view that progression-free epcoritamab patients should not be considered to enter LTR at 2 years after initiation of treatment, mean that the company's approach to estimating PFS for epcoritamab appears to be fundamentally flawed.

In order to help understand the impact of reducing the proportion of LTR patients in the epcoritamab curves, the EAG has conducted some exploratory analysis. Nonetheless, the EAG notes that these analyses are uncertain as the company's model lacks transparency and ease of manipulation, which made it impossible to remove the LTR assumption from the epcoritamab curve alone. This means that the EAG still had to assume that the PFS curves plateau at 2 years for epcoritamab, which the EAG considers to be a highly uncertain assumption. The EAG also had to fix the comparator PFS curves in order to provide a reasonable prediction, as it considers these to already be potentially underestimated in the model. Therefore, the EAG's approach indirectly changed the HRs used by the company to generate PFS curves. Even though the EAG notes that the MAIC HRs are fundamentally flawed in the company base case analysis, the EAG reiterates that this approach lacks methodological robustness and is only intended as an exploratory analysis of uncertainty.

For population A, for the comparison to R-based CIT, the EAG's exploratory ICER amounts to £47,454 per QALY gained, while for the comparison to Pola + BR, the EAG's exploratory ICER amounts to £101,875 per QALY gained. For population B, the EAG's exploratory ICER amounts to £15,432 per QALY gained; however, the EAG notes that axi-cel is subject to a confidential PAS, which is not included in the results presented in the EAG report.

The results of the EAG's exploratory analysis need to be further caveated by the fact that these analyses did not address the EAG's concerns around the following issues, contributing to the overestimation of the cost-effectiveness of epcoritamab in the model:

1. The OS curve for R-based CIT is likely to considerably underpredict OS in the long-term model for this treatment. This directly impacts the estimated PFS curve for R-based CIT, given the company's approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve.
2. The OS curve estimated for Pola + BR is likely to considerably underpredict OS in the long-term model for this treatment.

3. The OS curve estimated for axi-cel is likely to underpredict OS in the long-term model for this treatment.
4. The proportion of patients on R-based CIT entering LTR at 2 years might be underestimated.
5. The proportion of patients on Pola + BR entering LTR at 2 years is considerably underestimated.

As discussed through the report, the EAG has several recommendations for the additional analyses to be undertaken by the company at TE. These will help to resolve some of the fundamental flaws in the company's base case analysis and (at least partially) mitigate some of the uncertainty in the company's (and the EAG's) results. These consist of:

1. Exploring whether alternative sources of data for R-based CIT that resolve issues raised with SCHOLAR-1 exist and could be used in the MAIC vs R-based CIT, or using Crump *et al.* rather than Neelapu *et al.* as the source of SCHOLAR-1 data (see Key Issue 2, Table 3);
2. Clarifying how applicable the population from EPCORE™ NHL-1 analysed for MAICs vs R-based CIT and Pola + BR is in terms of ineligibility for intensive treatments and providing scenarios where the analysed EPCORE™ NHL-1 used in the MAIC represents a group that is not eligible for intensive treatments (see Key Issue 6, Table 7);
3. Updating all MAICs so that all reported baseline characteristics are adjusted for, given the concerns described by the EAG about unanchored MAICs (see Key Issue 7, Table 8);
4. Ensuring that data from the most recent data-cut is used in any updated MAICs (see Key Issue 8, Table 9);
5. Exploring the impact on results for the MAIC vs axi-cel when IWG criteria are applied to EPCORE™ NHL-1 IPD for PFS assessment rather than Lugano, given this was the criteria used in the ZUMA-1 study (see Key Issue 10, Table 11);
6. Correcting the model to avoid a proportion of patients progressing late in the model (which is in direct contradiction with the company's intended assumption of no further progression after 2 years in the model for PFS patients). This correction should be automated via embedded formulae, to avoid mistakes and to allow for this error to be automatically corrected for each comparator.
7. Correcting the PFS curve for Pola + BR and for axi-cel, separately, so that when the PFS and OS curves crossed, the OS curve turned into the PFS curve (instead of the other way around as currently assumed in the company's model) and to make it consistent with the assumption made by the company for epcoritamab.

8. Including a scenario analysis where the HR between the OS and PFS KM curves for epcoritamab for the unadjusted, DLBCL population, no prior CAR-T from EPCORE™ NHL-1 is used to estimate a PFS curve for R-based CIT.
9. Using the more mature PFS data cut which will be available in August to help inform the plausible probability of patients in the PFS curve at later stages past 20 months in the model, and potentially re-fitting OS and PFS curves for epcoritamab.
10. Independently fitting OS and PFS curves for each comparator in the model.
11. Allowing for the removal of the LTR assumption in the model for epcoritamab only (i.e., allowing for the PFS curves for epcoritamab to be dictated by the parametric curves fitted to the more mature epcoritamab data).
12. Allowing the model to have a flexible option, whereby the time at which patients enter the LTR assumption can be selected for different points in time for each comparator and for epcoritamab in each comparison.
13. Including a scenario analysis where patients on treatment with epcoritamab experience the same resource use (the "PFS on treatment" resource use) from cycle 0 to end of treatment in the model.
14. Including a scenario analysis where patients on comparator treatments experience the "PFS on treatment" resource use while on treatment; and the "PFS off treatment" resource use after the end of treatment and before 2 years in the model.
15. Using utility estimates derived from DLBCL patients not previously treated with CAR-T and ineligible to receive CAR-T subsequently for population A.
16. Using estimates derived from the DBCL, no prior CAR-T, eligible to receive future CAR-T for population B.
17. Including a scenario analysis where the costs of administrating R-based CIT are based on the SB14Z and the SB15Z cost codes.
18. Including a scenario analysis where the proportion of patients receiving subsequent treatments is based on the EAG's clinical experts' opinion and where rituximab is excluded from the subsequent regimens given to R-based CIT and Pola + BR patients.
19. The EAG finds the company's costing of administration for subsequent events in the model to be unclear and inconsistent with the administration costs applied for 3rd line treatments. Therefore, the EAG requests that the company clarifies and justifies its approach for estimating these in the model.

20. Including an option in the model where the assumption that R-based CIT and Pola + BR never discontinue due to toxicity is varied.
21. Inflating all relevant costs in the model to the most recent cost year.

The EAG also recommends that the company produces state occupancy traces for the company's base case for all populations.

7 Severity modifier

As outlined in the NICE methods guide,[6] "*the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS*". The thresholds of QALY weightings for severity are reported in Table 76.

Table 76. QALY weighting for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Abbreviations: QALY, quality-adjusted life-year

The company calculated the absolute and proportional QALY shortfall using a published calculator by Schneider *et al*. 2021.[50] The tool calculates the expected total QALYs for the general population matched to baseline age and sex distribution included in the economic model. The source of the general population EQ-5D data used in the calculator is from a study by Hernandez *et al*. 2020.[51] Table 77 presents the summary features of the QALY shortfall analysis with regards to sex and baseline mean age used in the model. The company's model reports that the latter were obtained through the MAIC-adjusted population characteristics for each comparator, respectively.

Table 77. Summary of preferred assumptions for general population QALY shortfall estimates

Factor	Population A (R-based CIT)	Population A (Pola + BR)	Population B
Sex distribution - % female	[redacted]	[redacted]	[redacted]
Baseline mean age - years	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life-year; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; R-based CIT, rituximab-based chemoimmunotherapy.

To calculate the absolute and proportional QALY shortfall using the calculator, the company used the base case total QALYs estimated for each comparator arm, as reported in Table 78.

Table 78. Company's QALY shortfall analysis

Category	Estimated total QALYs in company's base case	Proportional shortfall	QALY weight to be applied
Population A (R-based CIT)	[redacted]	93.72%	1.2

Population A (Pola + BR)	[redacted]	87.24%	1.2
Population B	[redacted]	73.19%	1

Abbreviations: QALY, quality-adjusted life-year; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; R-based CIT, rituximab-based chemoimmunotherapy.

7.1.1 EAG critique

The EAG considers the Schneider *et al*. calculator an appropriate tool to estimate absolute and proportional QALYs. The EAG notes that the company used a weight of 1.2 in the incremental QALYs used to estimate the ICERs for Population A (for R-based CIT and Pola + BR), which is appropriate, considering the baseline characteristics and the total QALY estimation in the company's base case analyses. Importantly, if the company updates the MAICs as requested by the EAG at TE, the baseline characteristics in the model are likely to change (together with the total QALY estimation).

Nonetheless, the EAG's exploratory analysis produced different total QALYs for the comparator arms (with the exception of the comparison with R-based CIT). The EAG's QALY shortfall calculation is presented in Table 79.The EAG notes that the applicability of the severity modifier is dependent on the underlying assumptions changed in the EAG's exploratory analysis.

Table 79. EAG's QALY shortfall calculation

Category	Estimated total QALYs in company's base case	Proportional shortfall	QALY weight to be applied
Population A (R-based CIT)	[redacted]	93.72%	1.2
Population A (Pola + BR)	[redacted]	82.32%	1
Population B	[redacted]	70.12%	1

Abbreviations: QALY, quality-adjusted life-year; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; R-based CIT, rituximab-based chemoimmunotherapy.

8 References

1. National Institute for Health and Care Excellence (NICE). Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [ID1684]: In development [GID-TA10580], 2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10580. Date accessed: May 23.
2. National Institute for Health and Care Excellence (NICE). Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma: Technology appraisal guidance [TA874]. , 2023. Available from: https://www.nice.org.uk/guidance/ta874. Date accessed: May 23.
3. AbbVie Advisory Board. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). 2022.
4. AbbVie Data on File. Epcoritamab for Treating Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL). UK Medical Advisory Board - Meeting Report. 2023.
5. National Institute for Health and Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies: Technology appraisal guidance [TA872], 2023. Available from: https://www.nice.org.uk/guidance/ta872. Date accessed: Jun 23.
6. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual, 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Date accessed: May 23.
7. National Institute for Health and Care Excellence (NICE). Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments: Final scope, 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10931/documents/final-scope. Date accessed: May 2023.
8. National Institute for Health and Care Excellence (NICE). Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma: Technology appraisal guidance [TA883], 2023. Available from: https://www.nice.org.uk/guidance/ta883. Date accessed: May 23.
9. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Reagan PM, Miklos DB, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. *Blood advances* 2021; **5**: 4149-55.
10. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2020; **38**: 155-65.
11. Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. *Blood advances* 2022; **6**: 533-43.
12. EUnetHTA. PTJA06 – Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, 2020. Available from: https://www.eunethta.eu/ptja06/ Date accessed: Dec 22.
13. Liebers N, Duell J, Fitzgerald D, Kerkhoff A, Noerenberg D, Kaebisch E, et al. Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas. *Blood Adv* 2021; **5**: 2707-16.
14. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol* 2019; **20**: 31-42.
15. AbbVie Data on File. Epcoritamab Draft SmPC. 8 November 2022.
16. AbbVie Data on File. Epcoritamab EPCORE™ NHL-1 - Statistical Analysis Plan, Expansion Part, aNHL Cohort. 2022.

17. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017; **130**: 1800-8.
18. Centre for Reviews and Dissemination (CRD). Systematic reviews: CRD's guidance for undertaking reviews in health care, 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Date accessed: May 23.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.
20. AbbVie Data on File. Included and excluded studies lists from clinical SLR. March 2023.
21. AbbVie Data on File. EPCORE™ NHL-1 CSR. January 2022.
22. Clinicaltrials.gov. A Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in R/R DLBCL (EPCORE™ DLBCL-1). Available from: https://clinicaltrials.gov/ct2/show/NCT04628494. Date accessed: Jun 23.
23. Scottish Intercollegiate Guidelines Network (SIGN). Search Filters. Available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/. Date accessed: Jun 23.
24. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins J. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022, 2022. Available from: www.training.cochrane.org/handbook. Date accessed: May 23.
25. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2019; **25**: 625-38.
26. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; **26**: 2767-78.
27. AbbVie Data on File. Clinical Trial Protocol. A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma. 2020.
28. AbbVie Data on File. EPCORE™ NHL-1 Data Tables. 2022.
29. National Institute of Health and Care Excellence (NICE). Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma. www.nice.org.uk/guidance/ta649: National Institute of Health and Care Excellence,, 2020 23 September 2020. Report No.
30. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplantation* 2016; **51**: 51-7.
31. Jacobson CA, Locke FL, Miklos DB, Vose JM, Lin Y, Budde LE, et al. Outcomes of Patients (Pts) in ZUMA-9, a Multicenter, Open-Label Study of Axicabtagene Ciloleucel (Axi-Cel) in Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL) for Expanded Access and Commercial Out-of-Specification (OOS) Product. *Blood* 2020; **136**: 2-3.
32. Czuczman MS, Trněný M, Davies A, Rule S, Linton KM, Wagner-Johnston N, et al. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Clinical Cancer Research* 2017; **23**: 4127-37.
33. Faria R, Hernandez Alava M, Manca A, Wailoo AJ. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data., 2015. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Date accessed: Jun 23.

34. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE, 2016. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Date accessed: Jun 23.
35. Mounier N, El Gnaoui T, Tilly H, Canioni D, Sebban C, Casasnovas R-O, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica* 2013; **98**: 1726.
36. Pettengell R, Sebban C, Zinzani PL, Derigs HG, Kravchenko S, Singer JW, et al. Monotherapy with pixantrone in histologically confirmed relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: post-hoc analyses from a phase III trial. *British Journal of Haematology* 2016; **174**: 692-9.
37. Pettengell R, Długosz-Danecka M, Andorsky D, Belada D, Georgiev P, Quick D, et al. Pixantrone plus rituximab versus gemcitabine plus rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation: a phase 3, randomized, multicentre trial (PIX306). *British Journal of Haematology* 2020; **188**: 240-8.
38. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D, et al. Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. *Blood Adv* 2022; **6**: 2920-6.
39. Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). *Ann Oncol* 2017; **28**: 1436-47.
40. Lin RS, León LF. Estimation of treatment effects in weighted log-rank tests. *Contemp Clin Trials Commun* 2017; **8**: 147-55.
41. Cazelles C, Belhadj K, Vellemans H, Camus V, Poullot E, Gaulard P, et al. Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation. *Leuk Lymphoma* 2021; **62**: 2161-8.
42. Ara R, Wailoo AJ. NICE DSU Technical Support Document 12: The use of health state utility values in decision models, 2011. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/utilities. Date accessed: Aug 22.
43. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value in Health* 2011; **14**: 539-45.
44. National Institute for Health and Care Excellence (NICE). Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma: Technology Appraisal Guidance [TA306]. Available from: https://www.nice.org.uk/guidance/ta306 Date accessed: Nov 22.
45. National Institute for Health and Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies: Technology Appraisal Guidance [TA559], 2019. Available from: https://www.nice.org.uk/guidance/ta559. Date accessed: May 23.
46. Department of Health and Social Care. eMIT national database. Drugs and pharmaceutical market information tool, 2023. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
47. BNF. British National Formulary. 2021. Available from: https://bnf.nice.org.uk/. Date accessed.
48. NHS. National Cost Collection for the NHS. 2021., 2021. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Date accessed: Feb 23.
49. Burns A, Curtis L. Unit Costs of Health and Social Care 2021. 2021. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/. Date accessed: Dec 22.

50. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. 2021.
51. Hernandez Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. 2020.

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 7 July 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 1: Factual inaccuracies

Major inaccuracies

Issue 1 Justification for timepoint at which epcoritamab patients switch to PFS 'off-treatment' resource use

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG incorrectly state that the Company's assumption that after [redacted] in the PFS state epcoritamab patients move to the PFS 'off-treatment' resource use is based on "median PFS". Page 41: "*The company justified this approach based on it reflecting median PFS in the trial*." Page 175: "*the EAG disagrees with the company's assumption that after [redacted] in the PFS state epcoritamab patients would move to the off-treatment resource as assumed in the model. The company justified this approach based on it reflecting "median PFS" in the trial."* Page 175: "*the EAG does not understand how median PFS would dictate resource use for*	The EAG report should state that this timepoint is informed by median PFS **for patients who achieved partial response (PR) or higher** in the DLBCL population of EPCORE™ NHL-1. Relatedly, when comparing the timepoint of [redacted] to median PFS in population A and population B in the model (page 175), it should be clearly stated that these endpoints are not directly comparable (one is median PFS for patients in PR or higher and the others are median PFS for all patients). Furthermore, the EAG report should state that the Company justified this approach based on feedback from UK clinical experts and the fact that patients who are progression-free beyond this point have surpassed the median PFS for patients receiving epcoritamab who are in PR and most progression-free patients beyond this timepoint are in complete response (CR), rather than just "based on it reflecting '*median PFS*'". Please can the text be amended as follows:	It is incorrect to state that the timepoint at which patients in the epcoritamab arm in the PFS health state switch to the PFS 'off-treatment' resource use ([redacted]) is median PFS from the trial; it is median PFS for patients with DLBCL in PR or higher from the trial. The inaccurate description in the EAG report invalidates the Company's justification for using this to inform the timepoint. Moreover, it is inaccurate to state that the Company justified the timepoint of 4.1 months based on it reflecting median PFS alone. In response to Clarification Question (CQ) B30, the Company provided extensive justification for the selection of this timepoint, including gathering additional clinical validation on this assumption. This justification should be fairly highlighted in the EAG report.	The EAG made the following changes to the text: "*The company justified this approach based on it reflecting median PFS in for patients who achieved partial response (PR) or complete response (CR) in the DLBCL population of EPCORE™ NHL-1*." Furthermore, the EAG deleted the sentence "*The EAG highlights that median PFS in the model is [redacted] months in population A and [redacted] months in population B*." from the report as it agrees that the estimates are not comparable. Nonetheless, the EAG maintains its view that it does not understand how median PFS (even that achieved by PR or CRs) should dictate

patients on epcoritamab treatment"	Page 41: "*The company justified this approach based on it reflecting median PFS* ***for patients with DLBCL who have achieved PR or higher*** *in the trial* ***and based on feedback from UK clinical experts****."* Page 175: "*The company justified this approach based on it reflecting "median PFS"* ***for patients with DLBCL who have achieved PR or higher*** *in the trial, arguing that patients who are progression-free beyond this point are likely to be in CR,* ***and based on feedback from UK clinical experts****."* Page 175: "*the EAG does not understand how median PFS* ***for patients with DLBCL who have achieved PR or higher*** *would dictate resource use for patients on epcoritamab treatment"*		resource use for patients on epcoritamab treatment as the EAG's clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued. Accordingly, the EAG did not make further changes to the report.

Issue 2 EPCORE™ NHL-1 population used to inform utility values for population A

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 38, the EAG report states that "*The population used to derive utilities for population A does not seem to have been limited in the same way as the subgroup of patients used in the effectiveness analysis, given that the company did not mention CAR-T eligibility for this population in the utility analysis*".	The statements that the population used to derive utilities for population A is not limited in the same way as the population used in the effectiveness analysis should be removed. Alternatively, if the EAG are concerned that the population informing the efficacy data and the utility data in base case analysis A are not limited by CAR-T eligibility, this statement should be rephrased to focus on this, rather	As stated in Document B (Section B.3.4.1, Table 56), the utility values used in base case analysis A are informed by the DLBCL no prior CAR-T population of EPCORE™ NHL-1. This population is aligned with the population from epcoritamab used in the MAIC informing the updated base case analysis A (DLBCL no prior CAR-	Not a factual inaccuracy, no change required. The EAG reports clearly states that, "*the EAG assumes that the company included all patients who had DLBCL and had received no prior CAR-T treatment*."

This is further discussed on page 163: "*The EAG notes that the population used to derive utilities for population A does not seem to have been limited in the same way as the subgroup of patients used in the effectiveness analysis, as the company did not mention CAR-T eligibility in this population*"	than a lack of alignment between the source of efficacy data and utility data.	T). As such, it is inaccurate to state that the population used to derive utilities for population A is not limited in the same way as the subgroup used to inform efficacy data in the analysis.	

Issue 3 Inaccurate description of the Company's assumptions used for patients in long-term remission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In numerous instances, the EAG report states that patients in long-term remission are assumed to not use any healthcare resources. Page 41: *"patients stop incurring any follow-up costs when entering LTR even though they would continue to be on treatment"* Page 173: *"After 2 years, all patients in the PFS state in every treatment arm of the model (including epcoritamab) were assumed to stop incurring any disease management or other*	Please can this be amended to acknowledge that patients in long-term remission are assumed to not use any health resources, apart from those associated with ongoing treatment administration: Page 41: *"patients stop incurring any follow-up costs, **apart from costs associated with the administration of treatment,** when entering LTR even though they would continue to be on treatment"* Page 173: *"After 2 years, all patients in the PFS state in every treatment arm of the model (including epcoritamab) were assumed to stop incurring **~~any~~** disease management or other follow-up costs **apart from costs associated with the administration of treatment**, as these were considered to be in LTR"*	As stated in the Document B (Section B.3.2.2), and further clarified in response to Clarification Question B30, once patients enter long-term remission, they are "assumed to use no healthcare resources beyond those required for treatment administration after 24 months". The EAG report should clearly explain that for patients in long-term remission, no healthcare resources are assumed to incur, **except those required for treatment administration**.	Not a factual inaccuracy, no change required. The EAG report clearly states that patients remain on treatment beyond LTR.

follow-up costs, as these were considered to be in LTR" Page 175: *"all patients incurred the "PFS on-treatment" for the initial 2 years of the model, after which progression-free patients started incurring no costs as these were considered to be in LTR."* Page 176: *"patients stop incurring costs when entering LTR even though they would continue to be on treatment"*. Page 183: *"Patients in LTR were also assumed to not use any healthcare resources"* This is an inaccurate description of the assumptions adopted for patients in long-term remission, as patients continue to incur resource use associated with administration of treatment.	Page 175: *"all patients incurred the "PFS on-treatment" for the initial 2 years of the model, after which progression-free patients started incurring no costs,* ***apart from costs associated with the administration of treatment,*** *as these were considered to be in LTR."* Page 176: *"patients stop incurring costs when entering LTR,* ***apart from costs associated with the administration of treatment****"* Page 183: *"Patients in LTR were also assumed to not use any healthcare resources,* ***apart from costs associated with the administration of treatment****"*		

Minor inaccuracies

Issue 4 Inaccurate description of the Company's response to clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 83 of the EAG report states "*some values lacked overall face validity due to lack of consistency across similar events (lymphopenia, leukopenia, neutropenia and neutrophil count decrease, based on feedback from the EAG's clinical experts). The EAG asked the company to clarify this as part of CQ B24 but the company did not comment on this*." This is an inaccurate description of the questions asked during Clarification Questions, and thereby an inaccurate description of the Company's response.	Please can this be amended as follows: *"some values lacked overall face validity due to lack of consistency across similar events (lymphopenia, leukopenia, neutropenia and neutrophil count decrease, based on feedback from the EAG's clinical experts). The EAG asked the company to clarify* ***the incidence rates used for these AEs*** *as part of CQ B2****6*** ~~***but the company did not comment on this***~~*.* ***The Company confirmed that those reported in the Company Submission (for R-based CIT, axi-cel and Pola + BR) and updated in response to CQ B24 (for epcoritamab) are the correct values used for these AEs****."*	The Company acknowledge that there were multiple versions of the response to the clarification questions, which could have resulted in this misunderstanding. The Company would be happy to discuss and resolve this query with the EAG as part of technical engagement. The Company believe that there is a typographical error in the EAG report, whereby the EAG refer to CQ B24 instead of CQ B26. In addition, the EAG did not ask the Company to clarify why the incidence rates for lymphopenia, leukopenia, neutropenia and neutrophil count decrease are different (within each treatment arm). In CQ B26, the EAG asked the Company to "*confirm the incidence rates used*" for these AEs, and the Company responded to confirm these incidence rates. It is therefore inaccurate to state that the Company did not comment on the lack of consistency between these AEs, as the Company were not aware of being asked to comment on this.	The EAG has made the changes requested by the company.

Issue 5 Inaccurate reporting of data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93, Section 3.3.4 states *"[median value for the 3 prior treatments group was not provided for OS]".* This is inaccurate reporting of the data provided to the EAG during Clarification Questions.	Please can this be amended as follows (including correction of the results and addition of AIC highlighting): *"[median value for the 3 prior treatments group was* [redacted] *for OS]"*	The EAG incorrectly states that the Company did not provide the median OS for the subgroup of patients that had received 3 prior treatments. The Company did provide this, but the median OS in this subgroup was [redacted], as reported in Clarification Question A1, Figure 6.	The EAG has made the change requested by the company.

Issue 6 Inaccurate description of the functionality in the Company's CEM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 151, Section 4.2.3 states that the EAG recommend the Company update the CEM to allow "*the model to have a flexible option, whereby the time at which patients enter the LTR assumption can be varied by the user and crucially, can be selected for different points in time for each comparator and for epcoritamab in each comparison*". This is an inaccurate description of the	Please can this be amended as follows: "*the model to have a flexible option, whereby the time at which patients enter the LTR assumption* ~~*can be varied by the user and crucially,*~~ *can be selected for different points in time for each comparator and for epcoritamab in each comparison*".	The Company acknowledge that the time at which patients enter long-term remission cannot currently be selected for different points for each treatment arm, however it is inaccurate to state that the Company's CEM does not allow for the time at which patients enter long-term remission to be varied by the user. This can be varied on the 'Survival tab' of the Clarification Questions CEM, with	The EAG has made the changes requested by the company.

functionality included in the Company's CEM.		the same change applying to all comparators.	

Issue 7 Inaccurate description of an error identified in the CEM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 175, Section 4.2.5, the EAG report highlights that on investigation of the CEM, the EAG identified an error in the CEM that was not identified during Clarification Questions. The EAG report then states that "*The company's approach is biased in favour of epcoritamab and is unjustified, as patients who finished their comparator treatments (before 2 years) and were in the PFS state should have incurred the "PFS off-treatment" lower costs."* This is inaccurately portrayed as an intentional approach by the Company that biases in favour of epcoritamab, rather than an unintentional error.	Please can this be amended as follows: "*This* ***error*** *is inconsistent with the company's approach to estimating follow-up costs for epcoritamab where patients incurred a "PFS off-treatment" follow-up cost after* [redacted] *in the model.* ***This error results in bias*** *in favour of epcoritamab* ~~***and is unjustified***~~*, as patients who finished their comparator treatments (before 2 years) and were in the PFS state should have incurred the "PFS off-treatment" lower costs."* In addition, it should be made clear that this error was identified by the EAG following Clarification Questions, so the Company did not yet have the opportunity to rectify this error in the CEM.	This is an error in the model, rather than an intentional assumption adopted by the Company. It should therefore be phrased as such in the EAG report, so as not to suggest that the Company have intentionally biased the analyses in favour of epcoritamab. Insofar as further corrections to this error are required, the Company will undertake this as part of technical engagement.	Not a factual inaccuracy, no change required. Nonetheless, the EAG thanks the company for clarifying that the issue identified by the EAG is based on an error and asks that the company corrects this during TE.

Issue 8 Unclear description of EAG exploratory analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 188 of the EAG report states that the EAG conducted the following exploratory analysis: "*A total administration cost of £41,101 for axi-cel was used in the model, excluding the costs of CRS, therefore totalling £40,638.*"	Please can this be amended to include further details regarding this exploratory analysis and how it differs from the assumption used in the Company's base case.	As this is the same assumption used in the Company's base case analysis, there is a lack of clarity regarding what the EAG's exploratory analysis involves.	The EAG made the following changes to the text, "*A total administration cost of £41,101 for axi-cel was used in the model, excluding the costs of CRS, therefore totalling £40,638 (as opposed to the company's cost of £42,127).*"

Typographical errors

Issue 9 Typographical and data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 5 and page 67, the EAG report states "pixanthrone"	Please can this be amended to "pixantrone" in all instances throughout the EAG report.	Typographical error	The EAG has corrected this throughout the report.
Page 31, Section 1.3 states *"At least one potentially important prognostic factor highlighted by the EAG's clinical experts (refractory to last anti-lymphoma treatment) was not reported in Sehn et al., meaning it could not be adjusted for and it is unclear whether there are any important differences compared to EPCORE™ NHL-1 in the MAIC"*	Please can this be amended as follows: *"At least one potentially important prognostic factor highlighted by the EAG's clinical experts (refractory to last anti-lymphoma treatment) was not reported in* ***ZUMA-1****, meaning it could not be adjusted for and it is unclear whether there are any important differences compared to EPCORE™ NHL-1 in the MAIC"*	Typographical error Issue 10 of the EAG report is discussing the limitations associated with ZUMA-1	The EAG thanks the company for highlighting this and has made the correction.

		for the MAIC versus axi-cel. As such, the Company believe that this sentence should be referring to ZUMA-1, rather than Sehn *et al.*	
Page 34, Section 1.3, states *"The OS curve for epcoritamab in all compassions is likely to be overestimated, particularly for the comparison with R-based CIT and axi-cel, where there is approximately an average of* [redacted] *of epcoritamab patients alive at the age of 90"*	Please can this be amended as follows: *"The OS curve for epcoritamab in all compassions is likely to be overestimated, particularly for the comparison with R-based CIT and axi-cel, where there is approximately an average of* [redacted] *of epcoritamab patients alive at the age of 90"*	Typographical error Due to typographical errors in the proportion of patients in the epcoritamab arm alive in the comparisons versus R-based CIT and axi-cel included in EAG report (documented below), the average calculated is incorrect. The average of	Not a factual inaccuracy, no change required. The [redacted] is the rounded equivalent estimate of [redacted]

		[redacted] and [redacted] is [redacted]	
The EAG report states that in the Company's updated model, [redacted] of patients in population B are progression-free in the epcoritamab arm: Page 34, Section 1.3 *states "The company's base case model assumes that at 24 months, about* [redacted] *of patients are progression-free in population A, for R-based CIT and Pola + BR, respectively;* [redacted] *of patients in population B are progression-free in the epcoritamab arm."* Page 43, Section 1.4 states *"Nonetheless, the lognormal curve provided a proportion of patients in remission at 2 years below* [redacted] *and is more aligned with the company's clinical experts view of this proportion being between 30–35%."* Page 146, Section 4.2.4.4 states *"The company's updated model assumes that at 24 months, about* [redacted] *and* [redacted] *of patients in population A, for R-based CIT and Pola + BR, respectively; and* [redacted] *of patients in population B are progression-free in the epcoritamab arm."* Page 147. Section 4.2.4.4 states *"The EAG reiterates that the company's updated model*	Please can this be amended to [redacted] In addition, when reported on page 156 of the EAG report, please can the confidentiality highlighting be amended to mark this value as AIC, as these data are not publicly available.	Typographical error The correct data are reported in the Company's Clarification Questions CEM.	The EAG has made the changes requested by the company.

assumes that at 24 months, about [redacted] and [redacted] of patients in population A; and [redacted] of patients in population B are progression-free in the epcoritamab arm;" Page 156, Section 4.2.4.4 states *"Nonetheless, the lognormal curve provided a proportion of patients in remission at 2 years below [redacted] and is more aligned with the company's clinical experts view of this proportion being between 30–35%, even if still slightly above the experts' prediction (Figure 30)."*			
In the EAG report (including pages 38, 39, 168, 169 and 196), the report states that cost codes SB14Z and SB15Z are used to cost the administration of Pola + BR.	Please can this be amended to cost codes **SB13Z** and SB15Z.	Typographical error The correct source is reported in Appendices, Appendix P.6, Table 160.	The code SB14Z was replaced by SB13Z in the following instances: Table 17; Table 55; page 173; where referring to the company's approach of costing the first administration of Pola+BR. Nonetheless, the EAG maintains its recommendation that the company includes a scenario analysis where the costs of administrating R-based CIT (and Pola+BR) are based on the SB14Z cost code for first administration and

			the SB15Z code for subsequent treatment administrations (as in TA559), unless the company can justify why these treatments should not be considered to be given as conventional chemotherapy to outpatients.
Page 58, Section 2.3.1 states *"double or triple hit lymphomas ([redacted] based on central laboratory analysis) may be higher than expected"*	Please can this be amended as follows: *"double or triple hit lymphomas ([redacted] based on central laboratory analysis) may be higher than expected"*	Typographical error The correct data are reported in Document B, Section B.2.3.2.	The EAG has not made the requested change as data in Table 8 of the CS (Section B.2.3.2 highlighted by the company) supports the figure of [redacted] when the number with double-hit ([redacted]) and triple-hit ([redacted]) are summed, of a total of [redacted] analysed at the central laboratory for LBCL. The EAG has added the number analysed to the report.
Page 61, Section 2.3.1 states "*which may limit the applicability of these analyses to those with no prior CAR-T treatment. Given when those with prior CAR-T use are removed from the analyses, a proportion with fourth line treatments and beyond remain in the analysis, the EAG considers this limitation to be specific to those with no prior*	Please can this be amended as follows: "which may limit the applicability of these analyses to those with ~~no~~ prior CAR-T treatment. Given when those with prior CAR-T use are removed from the analyses, a proportion with fourth line treatments and beyond remain in the analysis, the EAG considers this limitation to be specific to those with ~~no~~ prior CAR-T use rather than	Typographical error This section of the EAG report is discussion limitations associated with excluding	The EAG has made the change suggested by the company throughout the report.

CAR-T use rather than any patient at 4L and beyond (see Key Issue 5, Table 6).”	any patient at 4L and beyond (see Key Issue 5, Table 6).”	patients who had received prior CAR-T therapy from the analysis.	
Page 63, Section 2.31 states *“In addition, the EAG notes that the adjustment of EPCORE™ NHL-1 to Sehn et al. means the adjusted EPCORE NHL-1 population is even worse in terms of some prognostic factors (such as disease stage III-IV, ECOG score 2 and IPI score ≥3),”*	Please can this be amended as follows: *“In addition, the EAG notes that the adjustment of EPCORE™ NHL-1 to Sehn et al. means the adjusted EPCORE™ NHL-1 population is even worse in terms of some prognostic factors (such as disease stage III-IV, ECOG score 2 and IPI score ≥3),”*	Typographical error	The EAG has made the change as requested by the company.
Page 64, Section 2.3.1 states *“While the EAG is less concerned about the effect of excluding forms of LBCL other than DLBCL, the exclusion of those with prior CAR-T treatments may be important, particularly* [redacted] *for this subgroup (see Key issues 4 and 5, Table 5 and Table 6.”*	Please can this be amended as follows: *“While the EAG is less concerned about the effect of excluding forms of LBCL other than DLBCL, the exclusion of those with prior CAR-T treatments may be important, particularly* [redacted] *for this subgroup (see Key issues 4 and 5, Table 5 and Table 6).”*	Typographical error.	The EAG has made the change as requested by the company.
Page 68, Section 2.3.4 states *“this is included as part of Key Issue 3 (Table 4) xx.[1, 2]”*	Please can this be amended as follows: *“this is included as part of Key Issue 3 (Table 4) ~~xx~~.[1, 2]”*	Typographical error. Alternatively, if the EAG intended to include additional information here, please can this be added.	The EAG has made the change as requested by the company.

In Table 30, page 87, Section 3.3.3 the following values are reported for the adverse events for epcoritamab **Epcoritamab[a]** [redacted] Epcoritamab CSR, [redacted][3]; Table 34 of the company's response to CQ B22	The reported values are the Pola + BR adverse events. As such, please can these values be amended as follows: **Epcoritamab[a]** [redacted] Epcoritamab CSR, [redacted][3]; Table 34 of the company's response to CQ B22	Typographical error The AE frequencies reported in the EAG report the values used for the Pola + BR arm, based on NICE TA649.	The EAG has made the changes requested by the company.

Page 97, Section 3.4.1 states "*The mean age for the epcoritamab population when compared to R-based CIT (population A) and axi-cel (population B) is* [redacted] *than that of the overall EPCORE™ NHL-1 population."*	Please can this be amended as follows (including the change of the confidentiality highlighting from CIC to AIC): "*The mean age for the epcoritamab population when compared to R-based CIT (population A) and axi-cel (population B) is* [redacted] ***(for population A and for population B)*** *than that of the overall EPCORE™ NHL-1 population"*	Typographical error	The EAG has located the mean age for the overall population in the CSR and amended Table 31 to include this, and updated the text and highlighting.
Page 103, Section 3.4.2 states *"For PIX306 (comparator of gemcitabine + rituximab), the EAG acknowledges the company's response to CQ B12, which indicates that 67.5% had either no or only one prior treatment."*	Please can this be amended as follows: *"For PIX306 (comparator of gemcitabine + rituximab), the EAG acknowledges the company's response to CQ B1**3** which indicates that 67.5% had either no or only one prior treatment."*	Typographical error	The EAG has made the change requested by the company.
Table 39, page 124, Section 4 and Table 65, page 182, Section 5.1 states [redacted] as the incremental ICER (£/QALY) for the Company's base case deterministic results for epcoritamab vs R-based CIT	Please can this be amended to [redacted].	Typographical error The correct data are reported in Clarification Questions, Table 41, and the Company's Clarification Questions CEM.	The EAG has made the changes requested by the company.

Table 41, page 124, Section 4 and Table 67, page 183, Section 5.1 states the QALYs with severity modifier for the Company's deterministic scenario analysis for epcoritamab vs Pola + BR as [redacted]	Please can this be amended to [redacted]	Typographical error The correct data are reported in the Company's Clarification Questions CEM.	The EAG has made the changes requested by the company.
Page 128, Section 4.2.2 states "*Patients in population A enter the model in the PFS state at a mean age of [redacted] years, while patients in population B enter the model at [redacted] years.*"	Please can this be amended as follows: "*Patients in population A enter the model in the PFS state at a mean age of [redacted] years, while patients in population B enter the model at [redacted] years.*"	Typographical error The values reported are for the original base case analyses. The correct data for the updated base cases are reported in the Company's Clarification Questions CEM. If the EAG are intentionally reporting data for the original base case analyses, this	The EAG has made the changes requested by the company.

<table>
<tr><td></td><td></td><td>should be clearly stated.</td><td></td></tr>
<tr><td>In Table 46, page 137, Section 4.2.4 the landmark OS for R-based CIT compared with SCHOLAR-1 OS data at Month 180 is reported to be [redacted] for the Company's base case model</td><td>Please can this be amended to [redacted]</td><td>Typographical error

The correct data are reported in the Company's Clarification Questions CEM.</td><td>The EAG has made the changes requested by the company.</td></tr>
<tr><td>Page 137, Section 4.2.4 states "The EAG is also concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive."</td><td>Please can this be amended as follows:

"The EAG is also concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive."</td><td>Typographical error

The correct data are reported in the Company's Clarification Questions CEM.</td><td>The EAG has changed the value [redacted] in the text, given that when the number of months is rounded to years in the model, at 35 years, the latter is the estimated survival in the company's model (row 468 in tab "patient distribution").</td></tr>
<tr><td>Table 47, captioned 'Landmark OS estimates for R-based CIT compared with Sehn et al. OS data' page 138, Section 4.2.4 contains the following values:
<table><tr><td rowspan="2">Data source</td><td colspan="6">Month</td></tr><tr><td>3</td><td>6</td><td>12</td><td>24</td><td>60</td><td>120</td></tr></table></td><td>Please can the caption be amended to:

"Landmark OS estimates for Pola + BR compared with Sehn et al. OS data"

Please can the values be amended to the following:
<table><tr><td rowspan="2">Data source</td><td colspan="6">Month</td></tr><tr><td>3</td><td>6</td><td>12</td><td>24</td><td>60</td><td>120</td></tr></table></td><td>Typographical error

The correct data are reported in the Company's Clarification Questions CEM. Additional,</td><td>The EAG has made the changes requested by the company.</td></tr>
</table>

Pola + BR (Sehn *et al.)**	90 %	78 %	50 %	32 %	NR	NR	Pola + BR (Sehn *et al.)**	90%	78%	50%	**40%**	NR	NR	visual inspection of the KM curves presented in Sehn *et al* (2022) suggest that the OS at 24 months is approximately 40%, not 32%.	
Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Company's base case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Page 138, Section 4.2.4 states *"At 25 years in the model, there are approximately [redacted] of patients estimated to be alive in the epcoritamab arm, which might reflect a more plausible survival prediction than that obtained for the comparison with R-based CIT."*							Please can this be amended as follows: *"At 25 years in the model, there are approximately [redacted] of patients estimated to be alive in the epcoritamab arm, which might reflect a more plausible survival prediction than that obtained for the comparison with R-based CIT."*							Typographical error The correct data are reported in the Company's Clarification Questions CEM.	The EAG has made the changes requested by the company.
In Table 48, page 141, Section 4.24 the landmark OS estimate for axi-cel based on the Company's base case model is reported to be XXX at Month 120							Please can this be amended to [redacted]							Typographical error The correct data are reported in the Company's Clarification Questions CEM.	The EAG has made the changes requested by the company.

Page 141, Section 4.2.4 states *"The EAG is also concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive."*	Please can this be amended as follows: *"The EAG is also concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive."*	Typographical error The correct data are reported in the Company's Clarification Questions CEM.	The EAG has changed the value [redacted] in the text, given that when the number of months is rounded to years in the model, at 35 years, the latter is the estimated survival in the company's model (row 468 in tab "patient distribution").
Page 146, Section 4.2.4.4 states *"The company's updated model assumes that at 24 months, about [redacted] and [redacted] of patients in population A, for R-based CIT and Pola + BR, respectively; and [redacted] of patients in population B are progression-free in the epcoritamab arm."*	For clarity, please can this be amended as follows: *"The company's updated model assumes that at 24 months, about [redacted] and [redacted] of patients* ***in the epcoritamab arm*** *in population A, for R-based CIT and Pola + BR, respectively; and [redacted] of patients in population B are progression-free in the epcoritamab arm."*	The current phrasing of this sentence is unclear as it suggests that the [redacted] and [redacted] reported are the proportion of patients receiving R-based CIT and Pola + BR that are progression-free. This should be amended to clearly state that the values reported are for the epcoritamab arm, in the	The EAG has made the changes requested by the company.

		comparison versus R-based CIT and Pola + BR, respectively.	
Page 150, Section 4.2.4 states *"the EAG caveats the results in the Mounier et al. study by the fact that only 50% of patients in the study received previous rituximab treatment and that most patients were on their second-line treatment"*	Please can this be amended as follows: *"the EAG caveats the results in the Mounier et al. study by the fact that only **63**% of patients in the study received previous rituximab treatment and that most patients were on their second-line treatment"*	Typographical error Based on the publication by Mounier et al. (2013), 63% of patients received prior treatment with rituximab.[4]	The EAG has made the changes requested by the company.
Page 163, Section 4.2.4 states "*in order to have consistency between the populations used to derive the utility and the effectiveness estimates in population B, the EAG recommends that the company provides the estimates utilities in the DBCL, no prior CAR-T, eligible to receive future CAR-T population during TE*."	Please can this be amended as follows: "*in order to have consistency between the populations used to derive the utility and the effectiveness estimates in population B, the EAG recommends that the company provides the estimates utilities in the **LBCL**, no prior CAR-T, eligible to receive future CAR-T population during TE*."	Typographical error The population used to inform the updated base case analysis B efficacy data is the LBCL, no prior CAR-T, CAR-T eligible population. The Company assume that the EAG are requesting the utilities based	The EAG has made the changes requested by the company.

		on the LBCL, no prior CAR-T, CAR-T eligible population.	
Table 51, page 166, Section 4.2.5 the title is *"Table 51. Utility values derived from EPCORE NH-1 using linear mixed models (adapted from Table 56 in the CS)"*	Please can this be amended as follows: *"Table 51. Utility values derived from EPCORE™ NH**L**-1 using linear mixed models (adapted from Table 56 in the CS)"*	Typographical error	The EAG has made the changes requested by the company.
In Table 57, page 174, Section 4.2.6.3 the percentage of patients receiving no active treatments as subsequent treatments is reported as [redacted] for Pola + BR	Please can this be amended to [redacted]	Typographical error The correct data are reported in Document B Appendix P, Table 161.	The EAG has made the changes requested by the company.
Page 185, Section 6.1.1 states "*However, at month 384 (approximately 32 years in that's n41. The modelled difference in the curves implies that a proportion of patients starts progressing at 32 years in the model, which is in direct contradiction with the company's intended assumption of no further progression after 2 years in the model for PFS patients"*	Please can this sentence be revised, as it is currently unclear.	Typographical error	The EAG could not find the sentence referred to by the company in the EAG report.
In Table 77, page 197, Section 7 the baseline mean age for Population A (Pola + BR) is reported as XXX	Please can this be amended to [redacted]	Typographical error The correct data are reported in	The EAG has made the changes requested by the company.

		Document B Appendix P, Table 132.	

References

1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood advances 2021;5:4149-4155.
3. AbbVie Data on File. EPCORE™ NHL-1 Data Tables. 2022.
4. Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica 2013;98:1726.
5. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol 2023;41:2238-2247.
6. AbbVie Data on File. EPCORE™ NHL-1 CSR. January 2022.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 16 August 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	On behalf of AbbVie, [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AbbVie Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Executive summary AbbVie are grateful for the opportunity to be able to respond to each of the Key Issues raised by the External Assessment Group (EAG). Since the original Company Submission (CS), further data have become available from a more recent data cut of the EPCORE™ NHL-1 trial, with approximately [redacted] additional follow-up (median follow-up: [redacted]). With this additional follow-up, ORR for patients with diffuse large B-cell lymphoma (DLBCL) was [redacted] ([redacted]; 95% confidence interval [CI]: [redacted]), with median progression-free survival (PFS) being [redacted] (95% CI: [redacted]). Of note, the median PFS among those with a best response of complete response (CR) was[redacted]. The overall survival (OS) was [redacted] (95% CI: [redacted]) months. AbbVie have provided these new data as part of this response, which further strengthen the benefits of epcoritamab already observed in the EPCORE™ NHL-1 trial, and addresses some of the uncertainty raised by the EAG. In particular, all clinical data from the [redacted] data cut are presented in Appendix A, and all indirect treatment comparisons (ITCs) and economic

analyses have been updated to be based on the most recent data cut, as presented in Appendix B and C, respectively.

Some of the Key Issues raised by the EAG demonstrate considerable overlap and in these circumstances, one response has been used to address multiple Key Issues.

The critiques raised by the EAG focus around three key areas:

- **Population**, including the use of subpopulations from EPCORE™ NHL-1 in the matching adjusted indirect comparisons (MAICs) and the generalisability of the available data to patients with prior chimeric antigen receptor T-cell (CAR-T) therapy experience
- **Comparisons** of epcoritamab versus comparators, including the appropriateness of the MAICs conducted, estimates of long-term outcomes and application of the long-term remission assumption
- **Costs** applied in the cost-effectiveness model (CEM), including subsequent treatments and resource use estimates for the epcoritamab arm

An overview of the EAG's Key Issues grouped into the three focus areas (population, comparisons and costs) and how they related to each comparator included within the submission is presented in Table 1.

Table 1: Overview of EAG's Key Issues, grouped into the three focus areas and how they relate to each comparator

Comparator	Population	Comparisons	Costs
R-based CIT	1, 5, 6 and 15	2, 3, 7, 8, 11–13	14, 16–18
Pola + BR	1, 4–6 and 15	7, 8, 9, 11–13	14, 16–18
Axi-cel	1	7, 8, 10, 11–13	14, 16–18

		Abbreviations: axi-cel: axicabtagene ciloleucel; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R-based CIT: rituximab-based chemoimmunotherapy. ***Anticipated licensed indication for epcoritamab*** Since development of the CS, epcoritamab is now anticipated to be licenced for the treatment of [redacted]. As a result, AbbVie have updated the base case analyses to align with the anticipated licensed population. [redacted] [redacted] ***Updated cost-effectiveness results*** As detailed throughout the responses, AbbVie have updated the base case analyses in response to the EAG's concerns and conducted a number of scenario analyses. These updates and scenario analyses are detailed throughout the responses to each Key Issue, and the corresponding results are presented in the ***Summary of changes to the company's cost-effectiveness estimate(s)*** Section, with a top line summary of the key results in Table 2. Numerous scenario analyses were conducted to explore any uncertainty associated with the base case assumptions. The results of all scenarios for population A are between approximately £25,500 and £34,000, with only two scenario analyses being above £30,000, whilst all scenarios for population B demonstrate that epcoritamab is dominant over axicabtagene ciloleucel (axi-cel).

<table>
<tr>
<td></td>
<td></td>
<td>
Table 2: Base-case probabilistic results (epcoritamab PAS price)
<table>
<tr><th rowspan="2">Technologies</th><th colspan="3">Incremental</th><th rowspan="2">NHB at £20,000</th><th rowspan="2">NHB at £30,000</th></tr>
<tr><th>Costs (£)</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="6">Population A: ineligible for, or choose not to receive, intensive therapies</td></tr>
<tr><td>Epcoritamab versus R-based CIT</td><td>[redacted]</td><td>[redacted]</td><td>£26,915</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="6">Population B: eligible for intensive therapies</td></tr>
<tr><td>Epcoritamab versus axi-cel</td><td>[redacted]</td><td>[redacted]</td><td>Epcoritamab is dominant</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: axi-cel: axicabtagene ciloleucel; CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.
</td>
</tr>
<tr>
<td>1. The population in the decision problem may be broader than that covered by the trial, which was limited to those that failed prior autologous stem cell transplant and had ECOG scores 0-2</td>
<td>No</td>
<td>
UK clinical experts confirmed the generalisability of the EPCORE™ NHL-1 population to all patients with R/R DLBCL in the UK.

The EAG raised concerns that there are some differences between the population included in the original decision problem for this appraisal and the population included in the pivotal clinical trial for epcoritamab, EPCORE™ NHL-1. As highlighted in the CS, Document B, during an AbbVie-organised advisory board held in July 2022, UK clinical experts confirmed that data from EPCORE™ NHL-1 are generalisable to all patients with R/R DLBCL after two or more prior therapies in the UK.[1] The population of interest in the submission is also in line with the National Institute for Health and Care Excellence (NICE) final scope and the full anticipated licensed indication.
</td>
</tr>
</table>

2. Issues associated with the paper used to inform data for SCHOLAR-1 in the MAIC vs R-based CIT	No	**AbbVie recognise the limitations associated with SCHOLAR-1 and Neelapu *et al.* as a source of efficacy data for rituximab-based chemoimmunotherapy (R-based CIT), however, maintain that SCHOLAR-1 is an appropriate source to derive efficacy estimates for R-based CIT for this decision problem. A comparison of OS outcomes based on Neelapu *et al.* with historical OS outcomes for R-based CIT demonstrate that survival estimates from Neelapu *et al.* are a reasonable estimate, and potentially optimistic , for the survival of patients receiving R-based CIT.** ***Selection of SCHOLAR-1 to provide efficacy data for R-based CIT*** As highlighted in the CS, Document B, and further discussed in response to CQ A15, the sources of efficacy evidence for all comparators were identified via a systematic literature review (SLR) which identified clinical evidence for patients initiating third line therapies and beyond (3L+) for R/R large B-Cell lymphoma (LBCL), including R/R DLBCL. Further criteria were then applied to identify the most appropriate studies to inform comparative efficacy estimates. In instances where the included study could not provide appropriate information, real-world evidence (RWE) that could serve these purposes were considered for that comparator instead. Based on the SLR and additional inclusion criteria, a number of potential data sources providing comparative efficacy evidence for R-based CIT were identified, as presented in Table 3. Prior to submission, AbbVie conducted extensive feasibility assessments to explore the appropriateness of each source of efficacy data for R-based CIT, through which SCHOLAR-1 was identified as the most appropriate source of efficacy for R-based CIT. **Table 3: Overview of R-based CIT studies included in the clinical SLR and reason for exclusion from the MAICs**
3. Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used	Yes	

Data type	Source	Reason for exclusion from the MAICs
CORAL trial	Van den Neste, 2016[2]	Insufficient information on baseline characteristics available
CORAL trial combined with HMRN RWE data	NICE TA567[3]	Insufficient information on baseline characteristics available
COTA RWE data	Hamadani (2022)[4, a]	Insufficient information on baseline characteristics available
Sehn *et al.* 3L+ (synthetic data)[a]	EUnetHTA submission for Pola + BR[b] Sehn *et al.* (2019) and Sehn *et al.* (2022) extension study[5,c]	Comparator (i.e., bendamustine plus rituximab) not relevant to the decision problem (as outlined in CS, Document B, Section B.1.3.4)

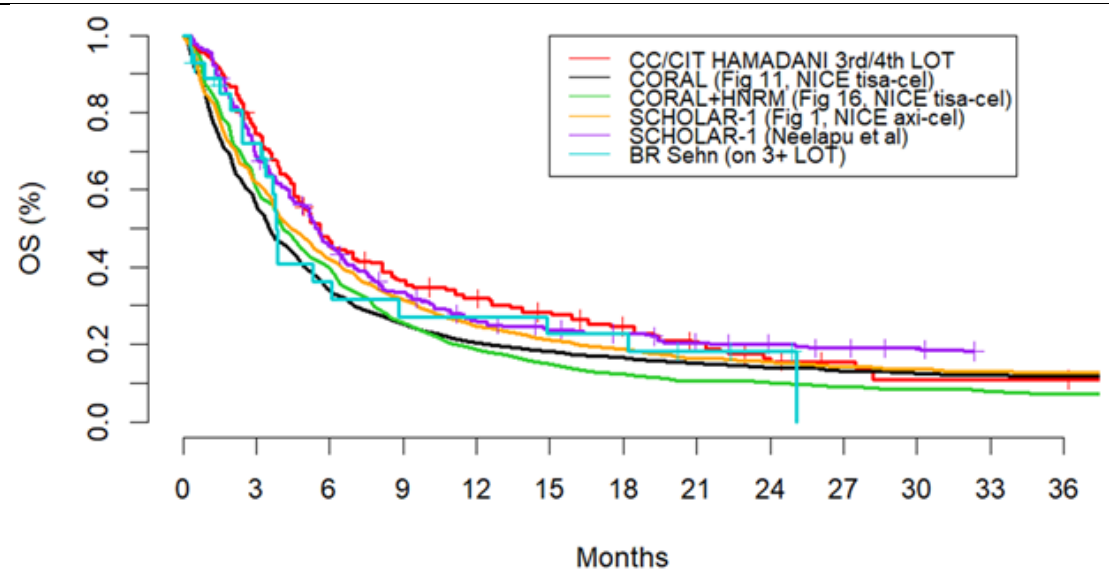
[a] Hamadani (2022) is a pooled cohort from the CORAL extension studies. As such, limitations associated with CORAL also apply to Hamadani (2022); [b] In line with the approach used in the CS, data from the EUnetHTA submission were used to inform baseline characteristics of the 3L+ population receiving BR; [c] In line with the approach taken for the 3L+ Pola + BR data used in the CS, synthetic OS and PFS KM curves for BR were derived for a population who had received two or more prior lines of therapy from the data published on BR by Sehn *et al.*

Abbreviations: 3L+: third therapy line and beyond; HMRN: haematological malignancy research network; KM: Kaplan Meier; MAIC: matching-adjusted indirect comparison; NA: not applicable; NR: not reported; Pola +BR: polatuzumab vedotin, bendamustine and rituximab; RWE: real-world evidence; SLR: systematic literature review.

Limitations associated with Crump et al. (2017) and selection of Neelapu et al. (2021) as the source of SCHOLAR-1 data

		The EAG shared apprehensions regarding the paper used to source the SCHOLAR-1 data; specifically, the EAG expressed a preference for the Crump *et al.* (2017) paper to be used instead of Neelapu *et al.* (2021). AbbVie maintain that conducting this MAIC using data from Neelapu *et al.* (2021) for SCHOLAR-1 (n=340), as opposed to the Crump *et al.* (2017) for SCHOLAR-1 (n=636), is the most suitable approach. This is because, of the 636 patients included in the analysis presented by Crump *et al.* (2017), 28% of patients received only one prior line of therapy, which is not representative of the decision problem in this submission.[7] Whereas, although it is not explicitly stated within the paper to be exclusively a 3L+ population, the data reported in the secondary Neelapu *et al.* (2021) publication have been cited as representative for patients who have received two or more prior lines of therapy.[6] Therefore, it is more appropriate to use this data set compared with the Crump *et al.* (2017) data to align with the decision problem in this submission as closely as possible. The EAG also raised concerns regarding the fact that the population included in Neelapu *et al.* (2021) represents a population that is more comparable to ZUMA-1, as propensity score matching had been performed. However, AbbVie would like to highlight that in the Neelapu *et al.* (2021) ITC, it was the ZUMA-1 population that was reweighted to match SCHOLAR-1 (as is common practice for ITCs), rather than the SCHOLAR-1 population that was adjusted.[6] Moreover, as part of the NICE evaluation of axi-cel as a treatment for DLBCL and PMBCL [TA872] in which an ITC of axi-cel (based on ZUMA-1) versus R-based CIT (based on SCHOLAR-1) was presented, the Neelapu *et al.* (2020) population (N=340) was further filtered to ensure the SCHOLAR-1 population was comparable to the ZUMA-1 population, resulting in a sample size of 133 and suggesting that the Neelapu *et al.* (2020) population is not a population that is comparable to ZUMA-1.[7] ***Limitations associated with SCHOLAR-1***

		The EAG raised a number of specific concerns related to SCHOLAR-1 as a source of efficacy evidence for R-based CIT, including that SCHOLAR-1 includes those with refractory disease only (rather than a mix of relapsed and refractory disease). Whilst criteria were applied to identify patients from SCHOLAR-1 that were refractory to **any** line of therapy, AbbVie would like to highlight that patients were not refractory to **all** lines of therapy and 21% of patients in the Neelapu *et al.* (2021) dataset still relapsed within 12 months of autologous stem cell transplant, which is comparable to the high proportion of refractory patients in the EPCORE™ NHL-1 trial.[8, 9] The EAG suggested that the overrepresentation of patients with refractory disease rather than relapsed disease may underestimate survival outcomes for R-based CIT compared with a mixed population. However, following adjustment, the baseline characteristics of the SCHOLAR-1 and EPCORE™ NHL-1 populations were well balanced, as presented in Appendix B.1.1.1. Moreover, AbbVie have conducted a comparison of the survival estimates for patients with R/R DLBCL receiving R-based CIT based on a number of historical sources (Figure 1). This clearly demonstrates that the survival estimates for SCHOLAR-1 from Neelapu *et al.* (2021) are an appropriate estimate of survival for patients receiving R-based CIT, as supported by UK clinical experts, and fall at the upper-end of the range observed. **Figure 1: OS in historical controls in R/R DLBCL**



Abbreviations: 3+; third-line and beyond; axi-cel: axicabtagene ciloleucel; DLBCL: diffuse large B-cell lymphoma; LOT: line of treatment; NICE: National Institute for Health and Care Excellence; OS: overall survival; R/R: relapsed/refractory; tisa-cel: tisagenlecleucel.

The EAG also questioned whether the population included in the Neelapu *et al.* (2021) paper was limited to patients with DLBCL only, and therefore whether it was necessary for the MAIC versus SCHOLAR-1 to be limited to the DLBCL population from EPCORE™ NHL-1. In light of the anticipated license indication for epcoritamab, AbbVie consider the MAIC using the DLBCL population from EPCORE™ NHL-1 as the most relevant, whilst also noting DLBCL was the most common diagnosis in the SCHOLAR-1 data set.

Additionally, AbbVie have conducted a MAIC versus SCHOLAR-1 (based on Neelapu *et al.* [2021]) in which the LBCL, no prior chimeric antigen receptor therapy (CAR-T) population from EPCORE™ NHL-1 is used to inform the efficacy estimates of epcoritamab. The results from

		this MAIC are consistent with the DLBCL population. The detailed results of this MAIC are presented in Appendix B.2. AbbVie maintain that SCHOLAR-1 represents the most suitable source of efficacy data for R-based CIT for this decision problem, and the limitations of SCHOLAR-1 should not be considered to be a significant source of uncertainty for the comparison of epcoritamab versus R-based CIT. Moreover, this data source has also been used and accepted in other NICE appraisals in R/R LBCL, namely in the appraisal for axi-cel as a treatment for R/R DLBCL and PMBCL after two or more systemic therapies [TA559].[10]
4. The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population	Yes	**The MAIC using data from Sehn *et al.* 3L+ is highly likely to bias against epcoritamab. AbbVie have conducted additional MAICs using UK real-world data on polatuzumab vedotin, bendamustine and rituximab (Pola + BR) at 3L+ from Northend *et al.* which demonstrates a [redacted] treatment benefit for epcoritamab versus Pola + BR.** Pola + BR is only a relevant treatment option for a minority of patients with R/R LBCL after two or more lines of therapy. As such, AbbVie do not consider Pola + BR to be a relevant comparator. Regardless, in response to the issues raised by the EAG, AbbVie have conducted a number of MAICs of epcoritamab versus Pola + BR using data from the subgroup of patients from the Northend *et al.* real-world data that have received two or more prior therapies (hereafter referred to as Northend *et al.* 3L+). Moreover, AbbVie have also provided additional supportive MAICs in which epcoritamab is fully adjusted to comparator populations. More information related to these MAICs are presented in Appendix B, with a response to these Key Issues provided in Appendix D.
9. Limitations of Sehn *et al.* for the MAIC vs Pola + BR	Yes	

5. Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment	Yes	**The EAG acknowledge that restricting the epcoritamab population to those with no prior CAR-T therapy in the MAICs for population A was necessary. To address the uncertainty associated with the generalisability of these data to patients who have received prior CAR-T, AbbVie have conducted an additional MAIC versus Tomas *et al.*, using the population of patients from EPCORE™ NHL-1 who had received prior CAR-T therapy. This demonstrates epcoritamab is effective for patients with DLBCL that is R/R to CAR-T therapy.** The EAG flagged that results of the MAICs and economic model may not be applicable to patients with prior CAR-T use and that survival results from EPCORE™ NHL-1 [redacted] However, with the additional follow-up in the [redacted] data cut-off, the survival outcomes appear to be consistent after approximately [redacted]. Although EPCORE™ NHL-1 did include patients who had previously received CAR-T therapy, both Sehn *et al.* (2019) and SCHOLAR-1 did not include patients who had previously received CAR-T therapy.[5, 8] This is due to the changing treatment landscape for R/R LBCL and the introduction of CAR-T therapies after the collection of the Sehn *et al.* (2019) and SCHOLAR-1 data. Therefore, as highlighted by the EAG, limiting the epcoritamab population to patients that had not received prior CAR-T was necessary to align the epcoritamab population with populations included in comparator studies. It would be inappropriate to conduct any analyses in which the epcoritamab population includes patients with prior CAR-T but the comparator populations do not as this would introduce a high degree of uncertainty due to between-study heterogeneity. In response to Key Issues 4 and 9, AbbVie have conducted an additional MAIC for epcoritamab versus Pola + BR, based on data from Northend et al. 3L+, in which the epcoritamab population includes patients that have received prior CAR-T therapy. Further information is provided in Appendix D.

		It is important to note that feedback from clinical experts and published literature indicate that outcomes for patients post CAR-T are poorer than those without prior CAR-T.[1, 11] Therefore, although epcoritamab may initially have [redacted] in patients with prior CAR-T experience when compared with patients that have not received prior CAR-T therapy (DLBCL population; no prior CAR-T, median OS: [redacted]; prior CAR-T, median OS: [redacted]), this decrement is anticipated to be greater for R-based CIT. Evidence of this is supported by the Tomas *et al.* study, a retrospective, observational study conducted in the US and Israel, compared to the SCHOLAR-1 data set;[11] complete response (CR) rates for patients who received chemotherapy post CAR-T therapy in Tomas *et al.* were reported to be 0.0%, whereas CR rates for patients who received chemotherapy (with no prior CAR-T exposure) were reported to be 12.1% in the SCHOLAR-1 study.[11, 12] Although AbbVie acknowledge that these populations may not be comparable and therefore this naïve comparison is subject to uncertainty, this comparison demonstrates that failure on prior CAR-T therapy renders DLBCL more difficult to treat, and a substantial difference in response to R-based CIT is observed for patients who have received prior CAR-T therapy versus no prior CAR-T therapy. To further explore this, AbbVie have conducted additional MAICs of epcoritamab versus CIT, using data from Tomas *et al.*, in a population of patients that have received prior CAR-T therapy.[11] When using the DLBCL, prior CAR-T therapy population from EPCORE™ NHL-1 (epcoritamab received first-line after CAR-T [redacted] and epcoritamab received any-line after CAR-T [redacted]), and adjusting for all clinically important prognostic variables, the results of the MAICs are consistent with the MAIC informing base case analysis A, as presented in Table 4. The unadjusted and adjusted epcoritamab OS Kaplan Meier (KM) curves, alongside the CIT OS KM curve, based on Tomas *et al.*, are presented in Figure 2 for both the DLBCL, epcoritamab received first-line after CAR-T and epcoritamab received any-line after CAR-T populations from EPCORE™ NHL-1. Further details on these MAICs are presented in Appendix B.2.

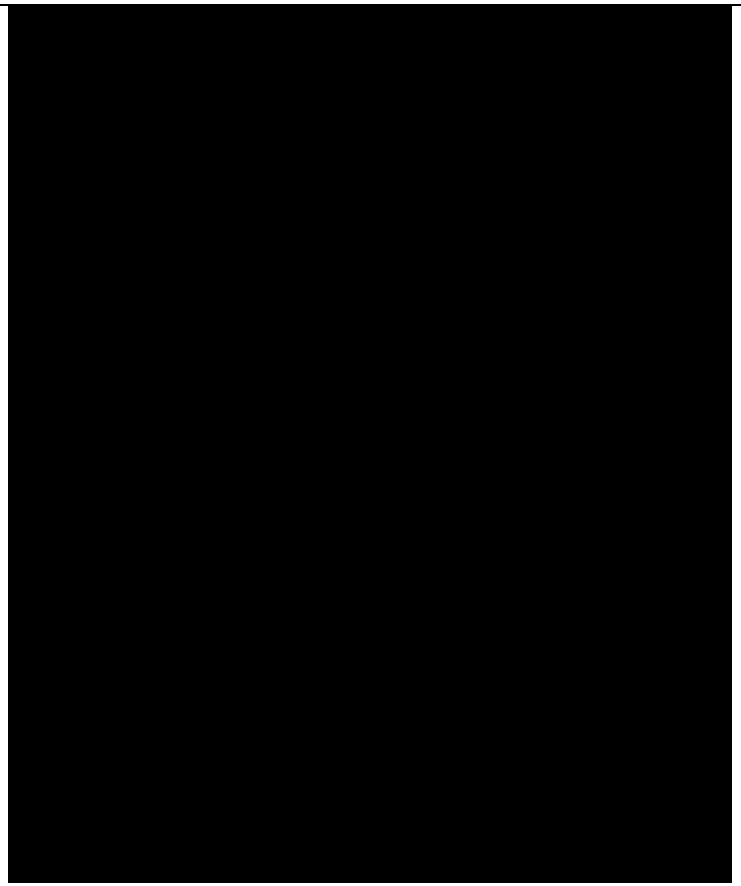
The consistency observed across these analyses demonstrates that epcoritamab is effective for patients with DLBCL that is R/R to CAR-T therapy. As such, the generalisability of the results of population A to patients who have received prior CAR-T should not be considered a significant source of uncertainty.

Table 4: Comparison of MAIC results for epcoritamab versus R-based CIT (no prior CAR-T versus prior CAR-T)

Epcoritamab population	Comparator data source	Adjusted OS HR (95% CI)	
		Before [redacted]	After [redacted]
DLBCL, no prior CAR-T	SCHOLAR-1	[redacted]	
DLBCL, prior CAR-T, epcoritamab 1L after CAR-T[a]	Tomas *et al.*	[redacted]	[redacted]
DLBCL, no prior CAR-T, epcoritamab any-line after CAR-T[a]	Tomas *et al.*	[redacted]	[redacted]

A piecewise HR approach was explored for the MAICs versus Tomas *et al.*
Abbreviations: 1L: first-line; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; OS: overall survival.

Figure 2: Unadjusted and adjusted OS KM curves for epcoritamab versus CIT based on Tomas *et al.* (epcoritamab DLBCL, prior CAR-T populations)

		 The top figure shows the results of the MAIC in which the epcoritamab LBCL, no prior CAR-T, epcoritamab received first-line after CAR-T therapy population is used; the bottom figure shows the results of the MAIC in which the epcoritamab LBCL, no prior CAR-T, epcoritamab received any-line after CAR-T therapy population is used. **Abbreviations**: 1L: first-line; AnyL: any-line; CART: chimeric antigen receptor T-cell therapy; chemo: chemotherapy; HR: hazard ratio; OS: overall survival.

6. It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments	No	**The population used in the MAICs for population A is patients who had DLBCL and had received no prior CAR-T therapy to align with the populations included in the data sources for R-based CIT and Pola + BR. However, as discussed in response to Key Issues 4, 7 and 9, all MAICs are appropriately adjusted to the comparator trials to align with the relevant populations under consideration.** As stated in the CS, Document B, Section B.2.8.2, the epcoritamab population used in the MAICs versus R-based CIT and Pola + BR (based on Sehn *et al.* 3L+) was patients who had DLBCL and had received no prior CAR-T therapy (N=[redacted]) to align with the comparator populations in which patients had not received prior CAR-T. For the MAICs versus Pola + BR based on Liebers *et al.* RW data, the overall DLBCL and LBCL populations were used, whilst for the MAICs versus Pola + BR based on Northend et al. RW data, the DLBCL, no prior autologous stem cell transplant (ASCT) population was used to align more closely with the comparator populations. It is not appropriate or balanced for the epcoritamab population to be restricted to those ineligible for intensive therapies, without applying the same restriction to the comparator populations; if the eligible patients were to be removed, without running the same adjustment for the comparator data sets, bias (of unknown magnitude or direction) would be introduced into the analyses. As AbbVie do not have access to the comparator trials' individual patient data (IPD) to complete such adjustments, it is not appropriate to conduct a MAIC in which the epcoritamab population was limited to those ineligible for intensive therapies specifically. With this considered, AbbVie disagree with the EAG's requested scenario analyses whereby the subgroup of patients ineligible for intensive treatments from EPCORE™ NHL-1 are matched to the comparator studies for R-based CIT and Pola + BR. Regardless, as discussed in response to Key Issues 4, 7 and 9, the MAICs informing the updated analyses versus R-based CIT and Pola + BR are appropriately adjusted to the comparator trials to align with the relevant populations under consideration.

7. Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons	Yes	**AbbVie maintain that the MAICs included in the updated base case, in which all clinically important baseline characteristics are adjusted for, provide the most robust estimates of comparative efficacy. However, in response to the EAG's request, AbbVie have conducted MAICs versus R-based CIT, Pola + BR and axi-cel in which all reported variables are adjusted for. These MAICs are likely to be subject to a high degree of uncertainty and issues associated with over-adjustment, as UK clinical experts confirmed that some variables are correlated.** The EAG have highlighted that some factors reported in the comparator trial populations were not adjusted for in the MAICs versus epcoritamab. As outlined in response to Clarification Question (CQ) A15, the MAICs were conducted in accordance with NICE Decision Support Unit TSD18 and following feedback from UK clinical experts. Moreover, UK clinical experts confirmed that some variables are correlated, such as disease stage and IPI score, so adjusting for both will result in issues associated with collinearity and over-adjustment. As such, AbbVie maintain that the MAICs included in the updated base case provide the most robust estimates of comparative efficacy, maximising larger sample sizes to inform the adjusted hazard ratios (HRs).[8, 13, 14 15] However, in response to the request from the EAG, AbbVie have conducted MAICs versus R-based CIT, Pola + BR and axi-cel in which all reported baseline characteristics are adjusted for. Further details on these MAICs are presented below and in Appendix B.1.1.2 and Appendix B.2. Discussion related to the MAICs versus Pola + BR is presented in Appendix D. ***Epcoritamab versus R-based CIT*** For the comparison of epcoritamab versus R-based CIT, two additional supportive MAICs have been conducted. One MAIC has been conducted in which all reported variables (n=10) are adjusted for, with truncation of weights at 1% and 99% of their distribution (N_{Eff}=[redacted]); when the same variables were adjusted for without truncation, the model did not converge. However, the results of this MAIC were considered clinically implausible by clinical experts, as

the adjusted OS KM curve for epcoritamab showed an [redacted], likely due to the substantially reduced effective sample size. As such, a further MAIC has been conducted in which nine reported variables (as outlined in Appendix B.1) have been adjusted for, with no truncation of the adjustment weights applied (N_{Eff}=[redacted]).

A comparison of the results of the MAIC informing updated base case analysis A (seven variables adjusted for) with the supportive MAICs in which more variables are adjusted for is presented in Table 5. Overall, the results of all MAICs are consistent and suggest that the MAIC informing base case analysis A represents a conservative estimate of the comparative efficacy of epcoritamab versus R-based CIT.

Table 5: Comparison of MAIC results for epcoritamab versus R-based CIT, based on SCHOLAR-1

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted OS HRs (95% CI)
DLBCL, no prior CAR-T	SCHOLAR-1	7; with truncation[a] N_{eff}=[redacted]	[redacted]
		9; no truncation[b] N_{eff}=[redacted]	[redacted]
		10; with truncation N_{eff}=[redacted]	[redacted]

[a]MAIC analysis used to inform base case analysis A. [b] MAIC analysis used to inform scenario analysis A.4.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; OS: overall survival.

Epcoritamab versus axi-cel

A summary of the results of the fully adjusted MAIC using the DLBCL population from EPCORE™ NHL-1 compared with the results of the MAIC informing the updated base case

analysis B are presented in Table 6. The results of the fully adjusted MAIC (10 reported variables adjusted for) using the DLBCL population from EPCORE™ NHL-1 are consistent with the results of the MAIC informing the updated base case analysis of epcoritamab versus axi-cel (in which all clinically important variables are adjusted for [n=8]); in fact, the results of the MAIC in which all reported variables are adjusted for suggest a greater treatment benefit for epcoritamab versus axi-cel ([redacted]). The results of the MAIC using the LBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 were consistent.

Table 6: Comparison of MAIC results for epcoritamab versus axi-cel, based on ZUMA-1

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted OS and PFS HRs (95% CI)
DLBCL, no prior CAR-T, CAR-T eligible	ZUMA-1	8* (N_{eff}=[redacted]	OS: [redacted] PFS: [redacted]
		10 (N_{eff}=[redacted]	OS: [redacted] PFS: [redacted]

*MAIC analysis used to inform base case analysis B.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; OS: overall survival.

Conclusion

The results of the fully adjusted MAICs demonstrate that this methodology has the potential to introduce bias into the analyses. The fully adjusted MAIC versus SCHOLAR-1 produced a clinically implausible [redacted] and the fully adjusted MAICs versus axi-cel produce clinically implausible comparative efficacy estimates [redacted] of epcoritamab, as supported by feedback from UK clinical experts (Table 6).[16]

		Regardless, in order to explore the impact on the cost-effectiveness results of adjusting for all reported variables in the MAICs, a scenario analysis has been conducted in which the comparative efficacy of epcoritamab versus R-based CIT is informed by the MAIC in which nine reported variables have been adjusted for, with no truncation of the adjustment weights applied. When this MAIC is used to inform the cost-effectiveness analysis of epcoritamab versus R-based CIT, the incremental cost-effectiveness ratio (ICER) is decreased versus the base case analysis A, demonstrating that epcoritamab remains a cost-effective use of NHS resources.
8. All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1	Yes	**Further data have become available from a more recent data cut ([redacted]) of the EPCORE™ NHL-1 trial and all ITCs and economic analyses have been updated to be based on the most recent data cut.** All clinical data from the [redacted] data cut are presented in Appendix A, including the subgroup analyses requested as part of CQ A1 and A2, and updated cost-effectiveness results based on the new data-cut and incorporating changes to the base case during technical engagement are presented in the ***Summary of changes to the company's cost-effectiveness estimate(s)*** Section. Relevant discussion related to the results from the [redacted] data cut off and how these results may help to decrease any uncertainty associated with the efficacy of epcoritamab is presented in response to specific Key Issues.
10. Limitations of ZUMA-1 for the MAIC vs axi-cel	No	**AbbVie recognise the presence of some limitations associated with ZUMA-1 as the source of efficacy data for axi-cel and, in order to address some of these limitations, have conducted a MAIC in which the epcoritamab population is fully adjusted to ZUMA-1. Of the remaining uncertainties, the use of the modified intention-to-treat (mITT) population and the difference in PFS definition between EPCORE™ NHL-1 and ZUMA-1 likely introduce bias against epcoritamab.** The EAG raised a number of uncertainties regarding the use of the ZUMA-1 trial in the MAIC of epcoritamab versus axi-cel. Before addressing these concerns, AbbVie would like to

highlight that the MAIC versus axi-cel has now been updated to include the 5-year ZUMA-1 data, which aims to alleviate some of the uncertainties associated with this comparison.

AbbVie agree that the definition used for PFS differs between EPCORE™ NHL-1 and ZUMA-1 (Lugano and International Working Group [IWG] criteria, respectively) trials (Table 7). However, as acknowledged by the EAG, the use of Lugano criteria for epcoritamab instead of IWG criteria is likely to introduce bias against epcoritamab due to increased sensitivity of the Lugano criteria compared with the IWG criteria. For this reason, AbbVie have not provided additional analyses where the IWG criteria are applied to the EPCORE™ NHL-1 population.

Table 7: Definitions of the Lugano and IWG criteria

Criteria	Trial	Outcome definition			
		CR	PR	SD	PD
Lugano[17]	EPCORE™ NHL-1[18]	Complete metabolic and radiologic response	Partial metabolic response or remission	No metabolic response or stable disease	Progressive metabolic disease
IWG[19]	ZUMA-1[20]	Disappearance of all evidence of disease	Regression of measurable disease and no new sites	Failure to attain CR/PR or PD	Any new lesion or increase by 50% of previously involved sites from nadir

Abbreviations: CR: complete response; IWG: International Working Group; PD: progressed disease; PR: partial response; SD: stable disease.

Published data from ZUMA-1 only include patients who were infused with axi-cel rather than all patients approved for treatment

		The EAG raised concerns with the publication used to inform the MAIC of epcoritamab versus axi-cel as the reported data from the mITT population of the ZUMA-1 study only included patients who were infused with axi-cel. AbbVie agree with the EAG that the overall intention-to-treat (ITT) population from ZUMA-1, which includes all patients approved for treatment with axi-cel in the trial, is likely more representative of the efficacy of axi-cel in UK clinical practice. However, AbbVie are not aware of any published data from the ITT population of ZUMA-1 that could be used to inform a MAIC of epcoritamab versus axi-cel. This is because a proportion of patients in the ITT population would experience progression or death in the interval between approval for treatment and infusion with axi-cel (approximately 7 weeks, based on feedback from UK clinical experts, or 56 days based on UK real-world data); however, these patients are removed in the mITT population.[16, 21] As such, the efficacy of axi-cel in UK clinical practice would be expected to be poorer than that observed in the mITT population of ZUMA-1, as stated by UK clinical experts. This is supported by UK real-world data published by Kuhnl *et al.* (2022) which demonstrates that approximately 17% (69/404) of patients approved for treatment with CAR-T therapy were unable to receive the infusion due to either disease progression or death due to disease progression; due to all causes, approximately 35% (104/404) of patients approved for treatment did not receive the infusion.[21] The group of patients who experienced progression or death in the first ~7 weeks of the trial are those with more rapid disease progression and poorer prognosis when compared with patients who remain progression-free after ~7 weeks. As such, as these patients are removed in the mITT population, it is likely that the mITT population represents a fitter population, when compared with the ITT population. As stated by Kuhnl *et al.* (2022), the results of the mITT population will "inherently over-estimate the clinical benefit of CAR-T.[21] Therefore, as the EAG notes, the use of the mITT population in the MAIC of epcoritamab versus axi-cel likely introduces bias against epcoritamab. As no data from the ITT population of ZUMA-1 are published, the uncertainty introduced into the MAIC by using the mITT population represents an unresolvable uncertainty, as highlighted

		by the EAG. However, if it were possible to use data from the ITT population of ZUMA-1 instead of the mITT population, the cost-effectiveness of epcoritamab would be expected to increase. ***Not all prognostic factors were reported in ZUMA-1*** The EAG noted that at least one potentially important prognostic factor (refractory to last anti-lymphoma treatment) was not reported in ZUMA-1, meaning it could not be adjusted for. As highlighted by the EAG, this is a source of uncertainty that is beyond the control of AbbVie. However, adjusting for other related factors (such as primary refractoriness, resistance to two consecutive lines and refractory to second-line treatment) is likely to result in the proportion of patients refractory to last anti-lymphoma treatment in the EPCORE™ NHL-1 and the ZUMA-1 populations being similar. AbbVie have conducted additional supportive analyses in which the epcoritamab population (DLBCL and LBCL) is fully adjusted to the ZUMA-1 population (all reported variables adjusted). Further details on these analyses are presented in Appendix B and they are discussed further in response to Key Issue 7.
11. Implementation of when the long-term remission assumption starts in the model	Yes	**AbbVie have updated the base case approach to use independent modelling, and resultingly re-evaluated each of the OS, PFS and time to treatment discontinuation (TTD) curves used in the model, in line with previous approaches to align with available data and clinical expert input. As a result of this update and following the availability of longer-term data for both epcoritamab and axi-cel, it is no longer necessary to apply long-term remission assumptions in the economic model. Instead, patients entering long-term remission are assumed to be implicitly captured within the modelled survival curves.**
12. Estimation of overall survival in the model	Yes	
13. Estimation of progression-free survival in the model.	Yes	

		Specific concerns raised by the EAG in Key Issues 2, 3, 6, 7, 9 and 10 are outlined in response to each individual Key Issue. This response will therefore focus on the EAG's concerns regarding jointly fitting survival curves and the estimations of OS and PFS. ***Modelling of comparator survival via independent extrapolation*** In response to the EAG's request, AbbVie have updated the base case so that all comparators are modelled via independent extrapolation. Full details on each of the extrapolation choices for both epcoritamab and its comparators are provided in Appendix C. ***Estimation of the relative effect of epcoritamab on OS and PFS versus each comparator*** ***R-Based CIT*** Based on the lognormal extrapolation selected to model OS for R-based CIT in updated base case analysis A, the landmark OS estimates for R-based CIT at 12, 24 and 60 months are [redacted], [redacted] and [redacted], respectively. These are broadly aligned with the observed data from SCHOLAR-1, which show 25.7% and 20.1% of patients are alive at 12 and 24 months, respectively. As observed data are not available from SCHOLAR-1 at 5 years, feedback from UK clinical experts was used to validate the survival estimated at this time point; when asked to provide estimates of OS for R-based CIT at 5 years, the experts estimated a range of 5–10%, with the estimated lower plausible limit being 0%. The long-term survival OS estimates for R-based CIT are therefore aligned with both published survival data from SCHOLAR-1 and feedback from UK clinical experts. Whilst OS is modelled independently for epcoritamab and R-based CIT, in the absence of comparator data for PFS, PFS for R-based CIT continues to be modelled using the OS HR, in line with the original base case approach. As highlighted in response to CQ B12, it is inappropriate to assume that the relationship between OS and PFS for epcoritamab is the same as that for R-based CIT. As such, AbbVie have not conducted the EAG's request to

		perform a scenario analysis where the HR between OS and PFS for R-based CIT is based on that observed in EPCORE™ NHL-1. ***Axi-cel*** Based on the selected base case extrapolations for updated base case analysis B, the landmark OS estimates for axi-cel at 12, 24 and 60 months are [redacted]% [redacted]% and [redacted]%, respectively. Compared to the observed ZUMA-1 5-year data, these estimates are closely aligned at all timepoints, with survival slightly overestimated compared to the observed data between 12 and 24 months. ***Long-term estimates of PFS for epcoritamab*** As outlined in response to Key Issue 8, data from the most recent data cut of EPCORE™ NHL-1 are now available and the cost-effectiveness model, and all associated analyses, have been updated using these data. Detailed clinical effectiveness results, including a PFS KM curve, are presented in Appendix A. With an additional [redacted] of follow-up, the PFS KM curve for the DLBCL population from EPCORE™ NHL-1 no longer demonstrates [redacted] and PFS appears to be [redacted]. When comparing the long-term PFS estimates for epcoritamab in the CEM versus the observed KM data and estimates from UK clinical experts, it is apparent that the epcoritamab PFS estimates are clinically plausible and do not overestimate the likely treatment effect associated with epcoritamab. However, to explore any uncertainty associated with the selected extrapolations, a number of scenario analyses have been conducted varying the OS and PFS extrapolations selected to model epcoritamab in each comparison. ***Long-term assumptions*** *Model corrections to survival estimates*

		AbbVie wish to highlight that the error identified in the model related to the estimation of OS during the long-term remission period has been corrected within the CEM. AbbVie have also produced state occupancy traces following these corrections within the cost-effectiveness model, as requested by the EAG. *Approach to modelling long-term survival* With the additional follow-up from the EPCORE™ NHL-1 trial, AbbVie have updated the base case so that each treatment arm is independently modelled. As a result of this update and due to the availability of longer-term data for both epcoritamab and axi-cel allowing for the extrapolated curves in the model to be better informed, the external long-term remission assumption has been removed for epcoritamab and its comparators. Instead, it is assumed that the long-term remission experienced by patients receiving each treatment, both epcoritamab and comparators where appropriate, is implicitly captured within the selected extrapolation. For epcoritamab specifically, during validation interviews with UK clinical experts, the clinical experts supported that patients receiving treatment who have achieved and sustained a CR for a certain period of time would be assumed to be in long-term remission and would incur decreased resource use whilst remaining on treatment.[16] With the longer duration of follow-up from the EPCORE NHL-1 trial, median PFS in the DLBCL population was [redacted] (95% CI: [redacted]); for patients with DLBCL in CR, median PFS was [redacted], compared with [redacted] and [redacted]) for patients in PR and non-responders, respectively. This supports the fact that patients receiving epcoritamab who have achieved CR demonstrate durable responses to treatment. There were also [redacted] between the [redacted] and [redacted] data-cuts.

		As such, the EAG's concerns regarding the timepoint at which patients receiving each treatment enter long-term remission have not been responded to, as these concerns are resolved by the other updates to the base case analyses.
14. Estimation of time to treatment discontinuation in the model.	Yes	**Updated TTD extrapolations for epcoritamab have been selected based on data from the [redacted] data cut of EPCORE™ NHL-1 and in line with feedback from UK clinical experts.** The EAG expressed concerns regarding the extrapolations selected to model TTD for epcoritamab in the base case analyses. As outlined in response to Key Issue 8, the CEM has been updated using data from the [redacted] data cut of EPCORE™ NHL-1. Selection of the extrapolations to model TTD for epcoritamab has been conducted based on the [redacted] data cut and all information relating to this is provided in Appendix C. In response to the EAG's concern regarding inconsistent selection of TTD extrapolations for population A and population B and in line with feedback from UK clinical experts stating patients are, the exponential extrapolation has been selected to model TTD for epcoritamab in all analyses. Scenario analyses have been conducted varying the extrapolation selected to model TTD for epcoritamab in each comparison. The EAG expressed concerns regarding the assumption that TTD for R-based CIT and Pola + BR is equal to PFS for each treatment. This assumption was adopted in response to feedback from UK clinical experts and due to a lack of published data on the TTD of R-based CIT and Pola + BR in UK clinical practice. AbbVie have been unable to identify any suitable data on the proportion and timing of patients discontinuing treatment with R-based CIT or Pola + BR due to reasons other than progression, and as a result, no scenario analyses have been performed varying this assumption.
15. The population(s) used to derive utilities used in the	No	**The population used to derive utility values for base case analysis A is aligned with the subgroup of patients used to inform the efficacy of epcoritamab. For each analysis, the**

model (in relation to eligibility for CAR-T).		**population used to derive utility values for each analysis are aligned as far as possible with the subgroup of patients used to inform the efficacy of epcoritamab.** The EAG questioned whether the population used to derive utilities for population A has been restricted in the same way as the subgroup of patients used in the effectiveness analysis. AbbVie would like to confirm that the population used to derive the utility values for population A is aligned with the epcoritamab population informing the efficacy estimates (DLBCL, no prior CAR-T population). As such, the utility values for population A are aligned with the EAG's preference that the same populations are used to derive the utility and the effectiveness estimates. The EAG also recommended that AbbVie provides the utility estimates for the MAIC requested in Key Issue 6. As discussed in Key Issue 6, it is not appropriate to conduct a MAIC in which the epcoritamab population is restricted specifically to those ineligible for intensive therapies without applying the same restriction to the comparator populations. Given this, AbbVie consider that the EAG's request for utility estimates based on the subpopulation of patients ineligible for intensive therapies from EPCORE™ NHL-1 is no longer relevant. Prior to submission, AbbVie conducted a range of utility analyses (CS Appendices, Appendix O); the results of these analyses demonstrated high rates of consistency in the estimated utility values. In addition, scenario analysis with HSUV identified from recent NICE appraisals produced consistent cost-effectiveness conclusions. Therefore, this should not be considered as a significant source of uncertainty.
16. Treatment and administration costs of comparators in the model.	Yes	**The EAG raised a number of queries related to the treatment and administration costs of comparators in the model, including the administration costs applied to R-based CIT and Pola + BR, the duration of treatment for R-based CIT and the monitoring costs assumed for axi-cel. Where feasible, AbbVie have updated the base case analyses or conducted scenario analyses in response to these concerns.**

		Model corrections to administration costs and epcoritamab cost Firstly, AbbVie wish to highlight that the errors identified in the model related to the administration costs applied to subsequent treatments have been corrected and incorporated into the updated base case. These corrections include removing intravenous costs for axi-cel as a subsequent treatment and aligning the administration costs for chemotherapy with those used for R-based CIT as a comparator. In addition, the error identified in the model by the EAG during the technical engagement call related to the cost of epcoritamab has also been updated. This correction results in the cost of epcoritamab now currently being incurred in line with the modelled TTD curve. ***Axi-cel administration and monitoring costs*** In the base case analyses, the administration and monitoring costs of axi-cel are the total of a one-time administration cost of £64,990 and an additional one-time monitoring cost of £1,541. As outlined in the CS, Document B, Section B.3.5.1, the one-time monitoring cost accounts for excess bed days which accrue due to the adverse events (AEs) associated with the treatment of axi-cel, in line with AbbVie's interpretation of the approach taken in TA559, which only explicitly specifies costs for CRS management are included in the one-time administration cost tariff. In response to the EAG's concern regarding the monitoring cost applied to axi-cel, a scenario analysis has been conducted where the one-time monitoring cost is removed for axi-cel. The administration cost is still assumed. The results of this scenario analysis demonstrate that epcoritamab is dominant over axi-cel, and therefore remains a cost-effective use of NHS resources. In re-reviewing the costs included in the administration costs in TA599, it became apparent that these costs do not capture the costs of bridging therapy, which is an essential component of treatment for a substantial proportion of patients with axi-cel to provide them with interim

		treatment whilst waiting to receive their infusion. Based on clinical expert input, an additional one-off cost has been added to the model base case for axi-cel, based on a weighted cost of receiving one-cycle of bridging therapy comprising 60%, 17.5% and 7.5% of Pola + BR (the most commonly used chemotherapy for bridging therapy), radiotherapy and steroids, respectively. ***Treatment duration and administration costs for R-based CIT*** In the submitted base case, patients were assumed to receive eight cycles of R-based CIT. However, feedback from the EAG's clinical experts suggested that some centres in the UK only allow a maximum of six cycles of R-based CIT. While the SmPC for rituximab states it is used for up to 8 cycles, AbbVie acknowledge that chemotherapy protocols for R-GemOx suggests six cycles are also common.[22, 23] In response to this, the base case has been updated to assume that patients receive R-based CIT for a total of six cycles, rather than eight cycles, which represents a conservative assumption in terms of the resulting cost-effectiveness of epcoritamab. In addition, in response to the EAG's concern, the base case has been updated so that administration costs of R-based CIT are aligned with the approach adopted for Pola + BR, using cost codes SB14Z and SB15Z. The EAG requested a further scenario analysis in which the cost of rituximab as part of chemotherapy as a subsequent treatment has been removed. Feedback from UK clinical experts stated that rituximab is given as part of chemotherapy as a subsequent treatment. As such, this scenario analysis is not considered relevant to UK clinical practice and no results are presented for this. ***Cost year used for inflation of all costs*** At the time of submission, inflation indices were only available to 2021. As such, where relevant, all costs in the model were inflated to the 2021 cost year. However, in response to

		the request from the EAG and due to subsequent availability of data, all costs in the model have been inflated to the most recent available cost year (2022). This change has been incorporated into the updated base case analyses.
17. Subsequent treatments in the model.	Yes	**AbbVie recognise that a higher proportion of epcoritamab patients may receive subsequent treatment with CAR-T therapy in clinical practice than the assumptions used in the base case. However, it would be inappropriate to conduct a scenario analysis in which an increased proportion of patients in the epcoritamab arm are assumed to receive CAR-T therapy, without reflecting the efficacy benefit associated with subsequent CAR-T therapy. To explore the uncertainty associated with these assumptions, AbbVie have conducted a scenario analysis in which the EAG's preferred subsequent treatment assumptions are adopted and the epcoritamab quality-adjusted life years (QALYs) are adjusted accordingly.** As part of CQ B27, following feedback from UK clinical experts, the EAG requested that alternative subsequent treatment proportions are used in the cost-effectiveness analyses. Notably, the EAG's preferred subsequent treatment proportions assume a substantially higher proportion of patients receive CAR-T therapy after treatment with epcoritamab (11% [population A] and 30% [population B]) compared with the assumptions used in the submitted base case (5%; based on UK clinical expert opinion) and the proportion of patients that received subsequent CAR-T therapy in EPCORE™ NHL-1 ([redacted]%). AbbVie acknowledge that a higher proportion of epcoritamab patients may receive subsequent treatment with CAR-T therapy in clinical practice. However, as highlighted in response to CQ B27, if the proportion of patients receiving CAR-T therapy after epcoritamab is assumed to be substantially higher than the proportion that received CAR-T therapy after epcoritamab in EPCORE™ NHL-1, the increased CAR-T usage would be associated with a clinical benefit which is not reflected in the efficacy data for epcoritamab currently used in the model. As such, to conduct a fair scenario analysis using the EAG's preferred subsequent treatment proportions, the epcoritamab efficacy data would need to be adjusted to reflect the

		efficacy benefit associated with subsequent CAR-T therapy. If a scenario analysis was conducted using the EAG's preferred subsequent treatment assumptions with no adjustments made to the epcoritamab efficacy data, the epcoritamab treatment arm would incur increased costs without incurring the associated efficacy benefits. AbbVie have conducted a scenario analysis using the EAG's preferred subsequent treatment assumptions. In order to reflect the increased efficacy associated with the increased subsequent CAR-T use for the epcoritamab arm, an additional QALY adjustment for the epcoritamab arm has been added. In the absence of suitable published data, the additional QALYs added were based on the difference in total QALYs estimated for R-based CIT and axi-cel in base case analysis A and B, respectively, multiplied by the increased proportion of patients that receive subsequent CAR-T in the model. This results in a total QALY adjustment of [redacted] and [redacted] if applied to population A and population B, respectively. For population A, this scenario analysis results in both increased incremental costs and QALYs, compared to the base case analysis, with an ICER of £30,650; however, this ICER should be interpreted with caution due to the high degree of uncertainty associated with this scenario. For population B, epcoritamab remains dominant over axi-cel, demonstrating that it is a cost-effective use of NHS resources.
18. Disease follow-up costs in the model.	Yes	**Based on feedback from UK clinical experts, it is clinically implausible for patients receiving treatment with epcoritamab to incur the PFS on-treatment resource use estimates for the full duration of their treatment. The timepoint at which epcoritamab patients switch to the PFS off-treatment resource use has been updated based on the [redacted] data cut to [redacted] (median PFS for partial responders). Clinical experts consulted for this appraisal stated disease in complete response requires less intense follow-up. After the [redacted] timepoint, [redacted].** The EAG commented on the company's implementation of follow-up costs in the model. Firstly, AbbVie would like to clarify that the patients in the comparator arms incurring the PFS

		on-treatment resource use for the initial two years was an error in the model; this has now been corrected in the updated base case to ensure that PFS on-treatment resource use costs are applied whilst patients receive treatment, before patients then switch to PFS off-treatment resource use costs. For axi-cel, the PFS on-treatment resource use estimates are incurred for one cycle, in line with the time that patients receive bridging therapy before axi-cel treatment (see response to Issue 16). As discussed in response to CQ B30, AbbVie acknowledge that the dosing of epcoritamab differs from currently available treatments as patients would receive subcutaneous injection epcoritamab until progression or unacceptable toxicity, rather than for a fixed number of infusions. As such, patients in the epcoritamab arm would always be on-treatment according to modelled TTD whilst progression-free. However, the resource use of patients receiving epcoritamab is anticipated to decrease over time once patients have achieved CR, as clearly stated by UK clinical experts.[16] AbbVie accept that the timepoint of reducing the intensity of resource use, based on decreasing follow-up, for patients receiving treatment with epcoritamab is uncertain. However, during extensive validation with multiple UK clinical experts, the clinical experts clearly stated that the timepoint by which most patients are in CR represents an appropriate timepoint for the resource use associated with epcoritamab to decrease. This is because patients are unlikely to require resource use beyond injection service, blood tests, interpretation of blood tests by nurse or pharmacist, and occasional consultant lead contacts after this stage following this timepoint.[16] As such, the EAG's requested scenario analysis in which patients receiving epcoritamab continue to incur the resource use associated with the PFS on-treatment health state for their duration of treatment is a substantial overestimation of the healthcare resource use of these patients and is clinically implausible. AbbVie maintain that the median PFS for patients with DLBCL in partial response is the most appropriate value to inform this timepoint because the majority of patients with progression-free disease will have complete response after this timepoint. As such, based on the [redacted]

		data cut, patients on epcoritamab incur the PFS on-treatment resource use estimates for [redacted], after which they switch to the less intense PFS resource use estimates alongside appropriate administration cost.

Summary of changes to the company's cost-effectiveness estimate(s)

As discussed in Issue 1–18 above, AbbVie have made a number of adjustments to the company's base-case cost-effectiveness estimates following technical engagement; these changes are summarised in Table 8.

Table 8: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Base case analysis A (epcoritamab versus R-based CIT)			
Key Issue 8	All clinical data and ITCs based on June 2022 data cut of EPCORE™ NHL-1	All clinical data and ITCs based on April 2023 data cut of EPCORE™ NHL-1	Change from CQ base case: +£7,982 ICER: £23,480
Key Issue 16	Where relevant, all costs in the model inflated to the 2021 cost year	Where relevant, all costs in the model inflated to the 2022 cost year	
	Model correction to epcoritamab cost [redacted]		
Key Issues 11–14	All comparators modelled via application of a HR to the extrapolated epcoritamab time-to-event data, with a long-term remission applied to patients in PFS 24 months after treatment initiation	All comparators modelled via independent extrapolation. Patients entering long-term remission are assumed to be implicitly captured with the modelled survival curves.	
Key Issue 16	Model corrections to resource use for comparators		+£1,050 ICER: £24,530
	Model corrections to administration costs		+£7 ICER: £24,537
	R-based CIT received for 8 cycles	R-based CIT received for 6 cycles	+£185

			ICER: £24,722
	Administration of R-based CIT based on the approach in TA559	Administration of R-based CIT aligned with the approach adopted for Pola + BR, using cost codes SB14Z and SB15Z	+£1,109 ICER: £25,831
	Costs of bridging therapy prior to axi-cel treatment not considered	Costs of bridging therapy prior to axi-cel treatment included	−£343 ICER: £25,488
Base case analysis A following technical engagement	**Incremental costs:** [redacted]	**Incremental QALYs:** [redacted]	**ICER: £25,488**
Base case analysis B (epcoritamab versus axi-cel)			
Key Issue 8	All clinical data and ITCs based on June 2022 data cut of EPCORE™ NHL-1	All clinical data and ITCs based on April 2023 data cut of EPCORE™ NHL-1	ICER: Dominant
Key Issue 16	Where relevant, all costs in the model inflated to the 2021 cost year	Where relevant, all costs in the model inflated to the 2022 cost year	
	Model correction to epcoritamab cost [redacted]		
Key Issues 11–14 Key Issue 16	All comparators modelled via application of a HR to the extrapolated epcoritamab time-to-event data, with a long-term remission applied to patients in PFS 24 months after treatment initiation	All comparators modelled via independent extrapolation. Patients entering long-term remission are assumed to be implicitly captured with the modelled survival curves.	ICER: Dominant
Key Issue 16	Model corrections to resource use for comparators		ICER: Dominant
	Model corrections to administration costs		ICER: Dominant
	R-based CIT received for 8 cycles	R-based CIT received for 6 cycles	ICER: Dominant
	Administration of R-based CIT based on the approach in TA559	Administration of R-based CIT aligned with the approach adopted	ICER: Dominant

		for Pola + BR, using cost codes SB14Z and SB15Z	
	Costs of bridging therapy prior to axi-cel treatment not considered	Costs of bridging therapy prior to axi-cel treatment included	ICER: Dominant
Base case analysis B following technical engagement	**Incremental costs:** [redacted]	**Incremental QALYs:** [redacted]	**ICER: Dominant**

Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; R-based CIT: rituximab based chemoimmunotherapy; Pola + BR: polatuzumab with bendamustine plus rituximab.

Updated base case following Technical Engagement

Base-case results

Base case analysis A: Patients ineligible for, or chose not to receive, intensive therapies

As outlined in the CS (Section B.2.6), the shortfall for base case population A meets the threshold for applying a severity modifier of 1.2 to the incremental QALYs. Based on the updated model, a severity modifier of 1.2 still applies in this population. As such, this modifier is applied in the base case results for analyses considering the population of patients who are ineligible for, and choose not to receive, intensive therapy. Results of the base case analysis A without a severity modifier applied, and subsequently with the 1.2 severity modifier applied to the QALYs, are presented in the following sections.

With the severity modifier applied, the results of the base case cost-effectiveness analysis demonstrate that epcoritamab is a cost-effective use of NHS resources, when compared with R-based CIT, especially when considered alongside the high level of unmet need in this patient population and innovative nature of epcoritamab. The results of the deterministic and probabilistic analyses demonstrate are a high degree of alignment.

No severity modifier applied

For patients ineligible for, or choose not to receive, intensive therapies, the results of the probabilistic analysis at epcoritamab patient access scheme [PAS] price are presented in Table 9. The probabilistic net health benefit (NHB) associated with epcoritamab at epcoritamab PAS price is presented in Table 10. The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Deterministic results are also provided in Table 11 (at epcoritamab PAS price). The deterministic NHB associated with epcoritamab is presented in Table 12 (at epcoritamab PAS price).

Table 9: Base-case probabilistic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£79,726	[redacted]	0.867	[redacted]	[redacted]	[redacted]	£32,298

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 10: Net health benefit (probabilistic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£79,726	0.867	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 11: Base-case deterministic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£79,708	[redacted]	0.863	[redacted]	[redacted]	[redacted]	£30,586

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 12: Net health benefit (deterministic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£79,708	0.863	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Severity modifier applied

Equivalent probabilistic and deterministic results cost-effectiveness results and NHB are presented in Table 13–Table 16 (at epcoritamab PAS price).

Table 13: Base-case probabilistic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£79,726	[redacted]	0.867	[redacted]	[redacted]	[redacted]	£26,915

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 14: Net health benefit (probabilistic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£79,726	0.867	[redacted]	[redacted]	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 15: Base-case deterministic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£79,708	[redacted]	0.863	[redacted]	[redacted]	[redacted]	£25,488

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years.

Table 16: Net health benefit (deterministic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£79,708	0.863	[redacted]	[redacted]	[redacted]	[redacted]

These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Base case analysis B: Patients eligible for intensive therapies

For patients eligible for intensive therapies, the results of the probabilistic analysis are presented in Table 17 (at epcoritamab PAS price). The probabilistic NHB associated with epcoritamab is presented in Table 18 (at epcoritamab PAS price). The PSA was run for 1000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Deterministic results are also provided in Table 19 (at epcoritamab PAS price). The deterministic NHB associated with epcoritamab is presented in Table 20 (at epcoritamab PAS price). The results of the base case cost-effectiveness analysis demonstrate that epcoritamab is a cost-effective use of NHS resources when compared with axi-cel, [redacted]. The results of the deterministic and probabilistic analyses demonstrate a high degree of alignment.

Table 17: Base-case probabilistic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
Axi-cel	£440,749	[redacted]	5.488	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 18: Net health benefit (probabilistic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
Axi-cel	£440,749	5.488	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 19: Base-case deterministic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
Axi-cel	£442,130	[redacted]	5.566	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 20: Net health benefit (deterministic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
Axi-cel	£442,130	5.566	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Probabilistic sensitivity analysis

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for epcoritamab versus R-based CIT for patients who are ineligible for, or choose not to receive, intensive therapies are presented in Figure 3 and Figure 4, respectively. The equivalent figures for epcoritamab versus axi-cel for patients eligible for intensive therapies are presented in Figure 5 and Figure 6.

Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

Figure 3: Cost-effectiveness scatter plot for epcoritamab versus R-based CIT (epcoritamab PAS price)

Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

Figure 4: Cost-effectiveness acceptability curve for epcoritamab versus R-based CIT (epcoritamab PAS price)

Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

Base case analysis B: Patients eligible for intensive therapies

Figure 5: Cost-effectiveness scatter plot for epcoritamab versus axi-cel (epcoritamab PAS price)

Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 6: Cost-effectiveness acceptability curve for epcoritamab versus axi-cel (epcoritamab PAS price)

Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis was conducted. Where available, each parameter was varied by 95% CIs. For parameters where CIs were not available the input was varied by ±10% of their mean value.

Patients ineligible for, or choose not to receive, intensive therapies

Figure 7: DSA tornado plot for epcoritamab versus R-based CIT (epcoritamab PAS price)

Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

Patients eligible for intensive therapies

Figure 8: DSA tornado plot for epcoritamab versus axi-cel (epcoritamab PAS price)

Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; DSA: deterministic sensitivity analysis; epco: epcoritamab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy; SC: subcutaneous.

Scenario analyses

Probabilistic results at epcoritamab PAS price for all scenario analyses run in response to the EAR are presented in Table 21, with deterministic results presented in Table 22.

Table 21: Scenario analyses probabilistic results (epcoritamab PAS price)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT			[redacted]	[redacted]	£26,915	[redacted]	[redacted]
Scenario analysis A.4	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T fully adjusted to SCHOLAR-1 (10 variables adjusted)	[redacted]	[redacted]	£25,485	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic	[redacted]	[redacted]	£27,330	[redacted]	[redacted]
PFS extrapolation for epcoritamab	Generalised gamma	Lognormal	[redacted]	[redacted]	£33,798	[redacted]	[redacted]
OS extrapolation for R-based CIT	lognormal	Loglogistic	[redacted]	[redacted]	£27,036	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]	£27,720	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma	[redacted]	[redacted]	£28,296	[redacted]	[redacted]
Subsequent treatments	Subsequent treatment proportions based on feedback from UK clinical experts	Subsequent treatment proportions based on EAG's preferred proportions, with epcoritamab efficacy adjusted	[redacted]	[redacted]	£30,650	[redacted]	[redacted]
Base case population B versus axi-cel			[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario analysis B.1	Efficacy data from DLBCL, no prior	Efficacy data from LBCL, no prior CAR-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	CAR-T, CAR-T eligible population	T, CAR-T eligible population					
TTD extrapolation for epcoritamab	Exponential	Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Monitoring cost for axi-cel	A one-time monitoring cost is assumed for axi-cel	The one-time monitoring cost is removed for axi-cel	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Subsequent treatments	Subsequent treatment proportions based on feedback from UK clinical experts	Subsequent treatment proportions based on EAG's preferred proportions, with epcoritamab efficacy adjusted	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: Axi-cel: axicabtagene ciloleucel;; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy.

Table 22: Scenario analyses deterministic results (epcoritamab PAS price)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT			[redacted]	[redacted]	£25,488	[redacted]	[redacted]
Scenario analysis A.4	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T fully adjusted to SCHOLAR-1 (10 variables adjusted)	[redacted]	[redacted]	£23,446	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
OS extrapolation for epcoritamab	Lognormal	Loglogistic	[redacted]	[redacted]	£25,460	[redacted]	[redacted]
PFS extrapolation for epcoritamab	Generalised gamma	Lognormal	[redacted]	[redacted]	£34,335	[redacted]	[redacted]
OS extrapolation for R-based CIT	lognormal	Loglogistic	[redacted]	[redacted]	£25,470	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]	£25,039	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma	[redacted]	[redacted]	£27,182	[redacted]	[redacted]
Subsequent treatments	Subsequent treatment proportions based on feedback from UK clinical experts	Subsequent treatment proportions based on EAG's preferred proportions, with epcoritamab efficacy adjusted	[redacted]	[redacted]	£29,012	[redacted]	[redacted]
Base case population B versus axi-cel			[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario analysis B.1	Efficacy data from DLBCL, no prior CAR-T, CAR-T eligible population	Efficacy data from LBCL, no prior CAR-T, CAR-T eligible population	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Monitoring cost for axi-cel	A one-time monitoring cost is assumed for axi-cel	The one-time monitoring cost is removed for axi-cel	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Subsequent treatments	Subsequent treatment proportions based on feedback from UK clinical experts	Subsequent treatment proportions based on EAG's preferred proportions, with epcoritamab efficacy adjusted	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Results for base case analysis A, include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: Axi-cel: axicabtagene ciloleucel;; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy.

Pola + BR scenario analyses

The results of the scenario analyses in which Pola + BR is considered a relevant comparator are presented in Table 23 (probabilistic) and Table 24 (deterministic). The results of these scenario analyses demonstrate that epcoritamab is a cost-effective use of NHS resources versus Pola + BR.

Table 23: Results of scenario analyses for Pola + BR: ineligible for, or choose not to receive, intensive therapy (probabilistic; with PAS)

Parameter	Scenario			Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis A.1	Comparator efficacy informed by Sehn et al. 3L+ (epcoritamab population: DLBCL, no prior CAR-T adjusted to Sehn et al. 3L+)	Epcoritamab extrapolations OS: generalised gamma PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations OS: loglogistic PFS: gamma	[redacted]	[redacted]	**£13,130**	[redacted]	[redacted]
		Epcoritamab extrapolations OS: **loglogistic**		[redacted]	[redacted]	£9,159	[redacted]	[redacted]

Parameter	Scenario			Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		PFS: Generalised gamma TTD: exponential						
		Epcoritamab extrapolations OS: generalised gamma PFS: Generalised gamma TTD: **gamma**		[redacted]	[redacted]	£17,663	[redacted]	[redacted]
		Epcoritamab extrapolations OS: generalised gamma PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations: OS: **lognormal** PFS: gamma	[redacted]	[redacted]	£13,060	[redacted]	[redacted]
			Pola + BR extrapolations: OS: **generalised gamma** PFS: gamma	[redacted]	[redacted]	£5,119	[redacted]	[redacted]
			Pola + BR extrapolations: OS: loglogistic PFS: **lognormal**	[redacted]	[redacted]	£15,230	[redacted]	[redacted]
Scenario analysis A.2	Comparator efficacy informed by Liebers et al.	Epcoritamab extrapolations OS: lognormal	Pola + BR extrapolations OS: lognormal PFS: lognormal	[redacted]	[redacted]	£15,698	[redacted]	[redacted]

Parameter	Scenario			Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	RWE (epcoritamab population: DLBCL unadjusted)	PFS: Generalised gamma TTD: exponential						
Scenario analysis A.3	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: LBCL unadjusted)	Epcoritamab extrapolations OS: lognormal PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations OS: lognormal PFS: lognormal	[redacted]	[redacted]	£14,893	[redacted]	[redacted]
Scenario analysis A.5	Comparator efficacy informed by Northend et al. 3L+ RWE (epcoritamab population: DLBCL, no prior ASCT adjusted to Northend et al 3L+)	Epcoritamab extrapolations OS: Gompertz PFS: Gompertz TTD: exponential	Pola + BR extrapolations OS: generalised gamma PFS: loglogistic	[redacted]	[redacted]	£25,606	[redacted]	[redacted]
		Epcoritamab extrapolations OS: Gompertz PFS: Gompertz TTD: **gamma**		[redacted]	[redacted]	£25,522	[redacted]	[redacted]
		Epcoritamab extrapolations OS: Gompertz PFS: Gompertz TTD: exponential	Pola + BR extrapolations OS: **Gompertz** PFS: loglogistic	[redacted]	[redacted]	£24,597	[redacted]	[redacted]

The scenario analysis presented in the first row (Pola + BR based on Sehn *et al.* 3L+) represents AbbVie preferred scenario analysis for epcoritamab versus Pola + BR. These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: DLBCL: diffuse large B-Cell lymphoma; ICER: incremental cost-effectiveness ratio; LBCL: large B-Cell lymphoma; NHB: net health benefit; Pola +BR: polatuzumab vedotin, bendamustine and rituximab; QALY: quality adjusted life year; RWE: real world evidence.

Table 24: Results of scenario analyses for Pola + BR: ineligible for, or choose not to receive, intensive therapy (deterministic; with PAS)

Parameter	Scenario			Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis A.1	Comparator efficacy informed by Sehn et al. 3L+ (epcoritamab population: DLBCL, no prior CAR-T adjusted to Sehn et al. 3L+)	Epcoritamab extrapolations OS: generalised gamma PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations OS: loglogistic PFS: gamma	[redacted]	[redacted]	**£9,766**	[redacted]	[redacted]
		Epcoritamab extrapolations OS: **loglogistic** PFS: Generalised gamma TTD: exponential		[redacted]	[redacted]	£7,984	[redacted]	[redacted]
		Epcoritamab extrapolations OS: generalised gamma PFS: Generalised gamma TTD: **gamma**		[redacted]	[redacted]	£15,630	[redacted]	[redacted]
		Epcoritamab extrapolations OS: generalised gamma	Pola + BR extrapolations: OS: **lognormal** PFS: gamma	[redacted]	[redacted]	£10,157	[redacted]	[redacted]

Parameter	Scenario			Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations: OS: **generalised gamma** PFS: gamma	[redacted]	[redacted]	£6,298	[redacted]	[redacted]
			Pola + BR extrapolations: OS: loglogistic PFS: **lognormal**	[redacted]	[redacted]	£14,233	[redacted]	[redacted]
Scenario analysis A.2	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: DLBCL unadjusted)	Epcoritamab extrapolations OS: lognormal PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations OS: lognormal PFS: lognormal	[redacted]	[redacted]	£13,927	[redacted]	[redacted]
Scenario analysis A.3	Comparator efficacy informed by Liebers et al. RWE (epcoritamab population: LBCL unadjusted)	Epcoritamab extrapolations OS: lognormal PFS: Generalised gamma TTD: exponential	Pola + BR extrapolations OS: lognormal PFS: lognormal	[redacted]	[redacted]	£13,320	[redacted]	[redacted]

Parameter	Scenario			Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis A.5	Comparator efficacy informed by Northend et al. 3L+ RWE (epcoritamab population: DLBCL, no prior ASCT adjusted to Northend et al 3L+)	Epcoritamab extrapolations OS: Gompertz PFS: Gompertz TTD: exponential	Pola + BR extrapolations OS: generalised gamma PFS: loglogistic	[redacted]	[redacted]	£25,606	[redacted]	[redacted]
		Epcoritamab extrapolations OS: Gompertz PFS: Gompertz TTD: **gamma**		[redacted]	[redacted]	£23,818	[redacted]	[redacted]
		Epcoritamab extrapolations OS: Gompertz PFS: Gompertz TTD: exponential	Pola + BR extrapolations OS: **Gompertz** PFS: loglogistic	[redacted]	[redacted]	£23,468	[redacted]	[redacted]

The scenario analysis presented in the first row (Pola + BR based on Sehn *et al.* 3L+) represents AbbVie preferred scenario analysis for epcoritamab versus Pola + BR. These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: DLBCL: diffuse large B-Cell lymphoma; ICER: incremental cost-effectiveness ratio; LBCL: large B-Cell lymphoma; NHB: net health benefit; Pola +BR: polatuzumab vedotin, bendamustine and rituximab; QALY: quality adjusted life year; RWE: real world evidence.

References

1. AbbVie Advisory Board. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). 14 July 2022.
2. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone marrow transplantation 2016;51:51-57.
3. NICE. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. Available at: https://www.nice.org.uk/guidance/TA567 [Accessed: 18 November 2022].
4. Hamadani M, Liao L, Yang T, et al. Characteristics and Clinical Outcomes of Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma Who Received At Least 3 Lines of Therapies. Clinical Lymphoma Myeloma and Leukemia 2022;22:373-381.
5. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-165.
6. Parker C, Liu FF, Deger KA, et al. Cost-Effectiveness of Lisocabtagene Maraleucel Versus Axicabtagene Ciloleucel and Tisagenlecleucel in the Third-Line or Later Treatment Setting for Relapsed or Refractory Large B-cell Lymphoma in the United States. Adv Ther 2023;40:2355-2374.
7. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA872]. Available at: https://www.nice.org.uk/guidance/ta872 [Accessed: 31 March 2023].
8. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood advances 2021;5:4149-4155.
9. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808.
10. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. Final appraisal document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document [Accessed: 1 November 2022].
11. Alarcon Tomas A, Fein JA, Fried S, et al. Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma. Leukemia 2023;37:154-163.
12. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood Adv 2021;5:4149-4155.
13. Maloney DG, Kuruvilla J, Liu FF, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol 2021;14:140.
14. Avivi I, Perry C, Segman Y, et al. Polatuzumab-based regimen or CAR T cell for patients with refractory/relapsed DLBCL-a matched cohort analysis. Ann Hematol 2022;101:755-762.
15. NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. Report by the Decision Support Unit. Available at: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD19-Partitioned-Survival-Analysis-final-report.pdf [Accessed: 14 February 2023].
16. AbbVie Data on File. Epcoritamab in Large B-Cell Lymphoma: Clinical Validation Interviews. December 2022–May 2023.

17. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
18. AbbVie Data on File. EPCORE™ NHL-1 CSR. January 2022. .
19. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.
20. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
21. Kuhnl A, Roddie C, Kirkwood AA, et al. A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience. Br J Haematol 2022;198:492-502.
22. NHS. Chemotherapy Protocol (R-GemOx). Available at: https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Lymphoma/Rituximab-Gemcitabine-Oxaliplatin-R-GemOx.pdf [Accesed: 29 Aug 2023].
23. NHS Thames Valley Strategic Clinical Networl. Gem-Ox [+/-R]. Available at: https://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-chemo-protocols/L-100-r-gem-ox.pdf [Accessed: 19 Aug 2023].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments

[ID4045]

Technical Engagement Appendix

August 2023

File name	Version	Contains confidential information	Date
ID4045_Epcoritamab_ NICE TE Appendix [FULLY REDACTED]_Final_29 Aug23	Final	Yes	29 August 2023

Contents

Contents 2
Tables 4
Figures 9
Introduction 14
A.1 Overview of the clinical effectiveness results 14
A.2 Patient disposition 15
A.3 Primary endpoint 16
A.4 Secondary endpoints 17
A.5 Additional secondary endpoints 22
A.5.1. ORR by investigator assessment, Lugano Criteria (FAS) 22
A.5.2. PFS by investigator assessment, Lugano Criteria (FAS) 23
A.5.3. Time to response and time to complete response based on IRC assessment, Lugano Criteria (FAS) 23
A.5.4. MRD negativity 24
A.6 Patient reported outcomes 25
A.6.1. FACT-Lym 25
A.6.2. EQ-5D-3L 27
A.7 Adverse reactions 28
A.7.1. Summary of treatment-emergent adverse events 28
A.7.2. Treatment-emergent adverse events 29
A.7.3. Serious TEAEs 30
A.7.4. Treatment-emergent adverse events leading to discontinuation 31
A.7.5. Adverse events of special interest 31
A.7.6. Patient deaths 32
A.8 Subgroup analysis 33
A.8.1. ORR subgroup analysis 33
A.8.2. Prior vs no prior CAR-T therapy subgroup analysis 35
A.8.3. 2, 3 and 4+ prior anti-lymphoma treatments subgroup analysis 47
Appendix B Indirect treatment comparisons 66
B.1 MAICs informing the base case and scenario analyses 66
B.1.1. Adjusted baseline characteristics 68
B.1.2. Efficacy results 79
B.2 Additional supportive MAICs 91
B.2.1. Adjusted baseline characteristics 93
B.2.1. Efficacy results 110
Appendix C Time-to-event analyses 126
C.1 Overview 126
C.2 Epcoritamab 126
C.2.1. Updated base case analysis A: DLBCL, no prior CAR-T adjusted to the SCHOLAR-1 population (epcoritamab versus R-based CIT) 126
C.2.2. Scenario analysis A.1: DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+ (epcoritamab versus Pola + BR) 132
C.2.3. Scenario analysis A.2: DLBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR) 138
C.2.4. Scenario analysis A.3: LBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR) 144
C.2.5. Scenario analysis A.4: DLBCL, no prior CAR-T fully adjusted to SCHOLAR-1 (epcoritamab versus R-based CIT) 150
C.2.6. Scenario analysis A.5: DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+ RW data (epcoritamab versus Pola + BR) 156
C.2.7. Updated TE base case analysis B: DLBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel) 161

C.2.8. Scenario analysis B.1: LBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel) 167
C.3 Comparators (proportional hazards approach) 172
C.3.1. Updated base case analysis A: DLBCL, no prior CAR-T adjusted to the SCHOLAR-1 population (epcoritamab versus R-based CIT) 173
C.3.2. Scenario analysis A.1: DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+ (epcoritamab versus Pola + BR) 175
C.3.3. Scenario analysis A.2: DLBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR) 177
C.3.4. Scenario analysis A.3: LBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR) 180
C.3.5. Scenario analysis A.4: DLBCL, no prior CAR-T fully adjusted to SCHOLAR-1 (epcoritamab versus R-based CIT) 182
C.3.6. Scenario analysis A.5: DLBCL, no prior ASCT adjusted to Northend et al. 3L+ RW data (epcoritamab versus Pola + BR) 184
C.3.7. Updated base case analysis B: DLBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel) 186
C.3.8. Scenario analysis B.1: LBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel) 189
C.4 Comparators (independent modelling approach) 191
C.4.1. R-based CIT based on SCHOLAR-1 192
C.4.2. Pola + BR based on Sehn *et al.* 3L+ 195
C.4.3. Pola + BR based on Liebers et al. RW data 199
C.4.4. Pola + BR based on Northend et al. 3L+ RW data 203
C.4.5. Axi-cel based on ZUMA-1 207
Appendix D Additional responses related to Pola + BR 211
D.1 Key Issue 4 and Key Issue 9 211
D.2 Key Issue 7 212
D.3 Key Issues 11–14 213
References 214

Tables

Table 1: Overview of key clinical effectiveness results for both EPCORE™ NHL-1 data cuts (FAS; DLBCL; N=139) 14
Table 2: Disposition of patients (FAS; [redacted] data cut-off) 15
Table 3: ORR and BOR based on IRC Assessment, Lugano Criteria for both data-cuts (FAS; (FAS; DLBCL; N=139) 16
Table 4: DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 17
Table 5: PFS based on IRC assessment Lugano Criteria (FAS; [redacted] data cut-off) 19
Table 6: OS (FAS; [redacted] data cut-off) 21
Table 7: TTNT (FAS; [redacted] data cut-off) 22
Table 8: BOR based on INV, Lugano criteria (FAS; [redacted] data cut-off) 22
Table 9: PFS based on INV, Lugano Criteria (FAS; [redacted] data cut-off) 23
Table 10: TTR and TTCR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 24
Table 11: Duration of MRD Negativity per ctDNA Assay - aNHL Cohort, Expansion Part (MRD-Evaluable Set; [redacted] data cut-off) 24
Table 12: Mean scores for FACT-Lym total score and FACT-LymS while on treatment (FAS – [redacted] data cut-off) 26
Table 13: Mean scores for EQ-5D-3L health utility score while on treatment (FAS; [redacted] data cut-off) 27
Table 14: Summary of TEAEs (SAF; [redacted] data cut-off) 28
Table 15: Most common (at least 10% in any group) TEAEs by SOC and PT (SAF; [redacted] data cut-off) 29
Table 16: Most common (2% or more in any group) serious TEAEs by SOC and PT (SAF; [redacted] data cut-off) 31
Table 17: Summary of AESIs (SAF; [redacted] data cut-off) 32
Table 18: Summary of fatal TEAEs by PT (SAF; [redacted] data cut-off) 32
Table 19: Summary of TEAEs for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off) 40
Table 20: Most common (at least 10% in any group) TEAEs by SOC and PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off) 42
Table 21: Most common (2% or more in any group) serious TEAEs by SOC and PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off) 43
Table 22: Summary of AESIs for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off) 45
Table 23: Summary of fatal TEAEs by PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off) 46
Table 24: Summary of TEAEs by number of prior lines of therapy (SAF; [redacted] data cut-off) . 53
Table 25: Most common (at least 10% in any group) TEAEs by SOC and PT by number of prior lines of therapy (SAF; [redacted] data cut-off) 55
Table 26: Most common (2% or more in any group) serious TEAEs by SOC and PT by number of prior lines of therapy (SAF; [redacted] data cut-off) 59
Table 27: Summary of AESIs by number of prior lines of therapy (SAF; [redacted] data cut-off)... 64
Table 28: Summary of fatal TEAEs by PT by number of prior lines of therapy (SAF; [redacted] data cut-off) 65
Table 29: Summary of the MAICs conducted informing the updated base case analyses and scenario analyses 67
Table 30: Baseline characteristics for updated TE base case analysis A (epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) 68
Table 31: Baseline characteristics for the comparison of epcoritamab versus Pola + BR (epcoritamab DLBCL population adjusted to Sehn *et al.* 3L+) 69
Table 32: Baseline characteristics for the comparison of epcoritamab versus Pola + BR (epcoritamab DLBCL population adjusted to Liebers *et al.* RW data) 70

Table 33: Baseline characteristics for the comparison of epcoritamab versus Pola + BR (epcoritamab LBCL population adjusted to Liebers *et al.* RW data) 71
Table 34: Baseline characteristics for scenario analysis A.4 (nine reported variables matched, no truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) 73
Table 35: Baseline characteristics for scenario analysis A.5 (11 reported variables matched, with truncation; epcoritamab DLBCL, no prior ASCT population adjusted to Northend) 75
Table 36: Baseline characteristics for the comparison of epcoritamab versus axi-cel (epcoritamab DLBCL, CAR-T eligible population adjusted to ZUMA-1) 76
Table 37: Baseline characteristics for scenario analysis B.2 (epcoritamab LBCL, CAR-T eligible population adjusted to ZUMA-1) 77
Table 38: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 79
Table 39: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, no prior CAR-T) versus Pola + BR (Sehn *et al.* 3L+) 80
Table 40: Unadjusted and adjusted outcomes for epcoritamab (DLBCL) versus Pola + BR (Liebers *et al.* RW data) 82
Table 41: Unadjusted and adjusted outcomes for epcoritamab (LBCL) versus Pola + BR (Liebers *et al.* RW data) 84
Table 42: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (SCHOLAR-1; nine reported variables adjusted for) 86
Table 43: Unadjusted and adjusted outcomes for epcoritamab versus Pola + BR (Northend *et al.* 3L+; 11 reported variables adjusted for, with truncation) 87
Table 44: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, CAR-T eligible) versus axi-cel (ZUMA-1) 88
Table 45: Unadjusted and adjusted outcomes for epcoritamab (LBCL, CAR-T eligible) versus axi-cel (ZUMA-1) 90
Table 46: Summary of additional supportive MAICs conducted 91
Table 47: Baseline characteristics for fully adjusted MAIC versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) 93
Table 48: Baseline characteristics for fully adjusted MAIC versus Pola + BR (10 reported variables matched, with truncation; epcoritamab DLBCL population fully adjusted to Sehn et al. 3L+) 94
Table 49: Baseline characteristics for MAIC versus SCHOLAR-1 (base case variables matched; epcoritamab LBCL, no prior CAR-T population adjusted to SCHOLAR-1) 96
Table 50: Baseline characteristics for fully adjusted MAIC versus R-based CIT (5 reported variables matched; DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T) 97
Table 51: Baseline characteristics for fully adjusted MAIC versus R-based CIT (5 reported variables matched; LBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T) 98
Table 52: Baseline characteristics for fully adjusted MAIC versus R-based CIT (all variables matched; DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T) 100
Table 53: Baseline characteristics for fully adjusted MAIC versus R-based CIT (all variables matched; LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T) 101
Table 54: Baseline characteristics for MAIC versus Pola + BR (11 variables matched, without truncation; DLBCL, no prior ASCT) 102
Table 55: Baseline characteristics for MAIC versus Pola + BR (13 variables matched, without truncation; DLBCL, no prior ASCT) 104
Table 56: Baseline characteristics for MAIC versus Pola + BR (13 variables matched, without truncation; DLBCL, no prior ASCT) 105
Table 57: Baseline characteristics for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab DLBCL, CAR-T eligible population fully adjusted to match axi-cel) 107
Table 58: Baseline characteristics for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab LBCL, CAR-T eligible population fully adjusted to match axi-cel) 109
Table 59: Unadjusted and adjusted outcomes for fully adjusted MAIC versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) 111

Table 60: Unadjusted and adjusted outcomes for fully adjusted MAIC versus Pola + BR (10 reported variables matched, with truncation; DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+) 112
Table 61: Unadjusted and adjusted outcomes for MAIC versus SCHOLAR-1 (base case variables matched [n=7]; epcoritamab LBCL, no prior CAR-T population adjusted to SCHOLAR-1) 113
Table 62: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (DLBCL; prior CAR-T therapy, epcoritamab 1L post CAR-T) 114
Table 63: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (LBCL; prior CAR-T therapy, epcoritamab 1L post CAR-T) 115
Table 64: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (DLBCL; prior CAR-T therapy, epcoritamab any-line post CAR-T) 116
Table 65: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (LBCL; prior CAR-T therapy, epcoritamab any-line post CAR-T) 117
Table 66: Unadjusted and adjusted outcomes for MAIC versus Pola + BR based on Northend *et al.* 3L+ (11 reported variables matched, without truncation; DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+) 118
Table 67: Unadjusted and adjusted outcomes for MAIC versus Pola + BR based on Northend *et al.* 3L+ (13 reported variables matched, with truncation; DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+) 120
Table 68: Unadjusted and adjusted outcomes for MAIC versus Pola + BR based on Northend *et al.* 3L+ (13 reported variables matched, without truncation; DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+) 121
Table 69: Unadjusted and adjusted outcomes for fully adjusted MAIC versus axi-cel (all reported variables matched; DLBCL, CAR-T eligible adjusted to ZUMA-1) 123
Table 70: Unadjusted and adjusted outcomes for fully adjusted MAIC versus axi-cel (all reported variables matched; LBCL, CAR-T eligible adjusted to ZUMA-1) 125
Table 71: Goodness of fit statistics for OS (AIC and BIC; updated base case analysis A) 127
Table 72: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (updated base case analysis A) 128
Table 73: Goodness of fit statistics for PFS (AIC and BIC; updated base case A) 129
Table 74: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (updated base case analysis A) 130
Table 75: Goodness of fit statistics for TTD (AIC and BIC; updated base case analysis A) 131
Table 76: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (updated base case analysis A) 132
Table 77: Goodness of fit statistics for OS (AIC and BIC; scenario analysis A.1) 133
Table 78: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1) 134
Table 79: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.1) 135
Table 80: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1) 136
Table 81: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis A.1) 137
Table 82: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1) 138
Table 83: Goodness of fit statistics for OS (AIC and BIC; Scenario A.2) 139
Table 84: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.2) 140
Table 85: Goodness of fit statistics for PFS (AIC and BIC; Scenario analysis A.2) 141
Table 86: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.2) 142
Table 87: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.2) 143
Table 88: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.2) 144
Table 89: Goodness of fit statistics for OS (AIC and BIC; Scenario analysis A.3) 145

Table 90: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.3) 146
Table 91: Goodness of fit statistics for PFS (AIC and BIC; Scenario analysis A.3) 147
Table 92: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.3) 148
Table 93: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.3) 148
Table 94: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.3) 149
Table 95: Goodness of fit statistics for OS (AIC and BIC; Scenario analysis A.4) 151
Table 96: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.4) 152
Table 97: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.4) 152
Table 98: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.4) 153
Table 99: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.4) 154
Table 100: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.4) 155
Table 101: Goodness of fit statistics for OS (AIC and BIC; Scenario analysis A.5) 156
Table 102: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.5) 157
Table 103: Goodness of fit statistics for PFS (AIC and BIC; Scenario analysis A.5) 158
Table 104: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.5) 159
Table 105: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.5) 160
Table 106: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.5) 161
Table 107: Goodness of fit statistics for OS (AIC and BIC; updated base case analysis B) 162
Table 108: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (updated base case analysis B) 163
Table 109: Goodness of fit statistics for PFS (AIC and BIC; updated base case analysis B) 164
Table 110: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (updated base case analysis B) 165
Table 111: Goodness of fit statistics for TTD (AIC and BIC; updated base case analysis B) 166
Table 112: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (updated base case analysis B)) 167
Table 113: Goodness of fit statistics for OS (AIC and BIC; scenario analysis B.1) 168
Table 114: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1) 169
Table 115: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis B.1) 170
Table 116: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1) 171
Table 117: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis B.1) 171
Table 118: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (scenario analysis B.1) 172
Table 119: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (updated base case A) 174
Table 120: Unadjusted and adjusted outcomes for epcoritamab (DLBCL population adjusted to Sehn et al. 3L+) versus Pola + BR (Sehn *et al.* 3L+) 177
Table 121: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (Pola + BR) 179
Table 122: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (Pola + BR) 182
Table 123: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (R-based CIT) 183
Table 124: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (Pola + BR) 186

Table 125: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – updated base case analysis B 189
Table 126: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – scenario analysis B.1 191
Table 127: Goodness of fit statistics for OS (AIC and BIC; R-based CIT independent extrapolation) 192
Table 128: Predicted and observed OS for R-based CIT at several landmarks for each extrapolation 194
Table 129: Goodness of fit statistics for OS (AIC and BIC; Pola + BR independent extrapolation) 195
Table 130: Predicted and observed OS for Pola + BR at several landmarks for each extrapolation 197
Table 131: Goodness of fit statistics for PFS (AIC and BIC; Pola + BR independent extrapolation) 197
Table 132: Predicted and observed PFS for Pola + BR at several landmarks for each extrapolation 198
Table 133: Goodness of fit statistics for OS (AIC and BIC; Pola + BR independent extrapolation) 199
Table 134: Predicted and observed OS for Pola + BR at several landmarks for each extrapolation 200
Table 135: Goodness of fit statistics for PFS (AIC and BIC; Pola + BR independent extrapolation) 201
Table 136: Predicted and observed PFS for Pola + BR at several landmarks for each extrapolation 202
Table 137: Goodness of fit statistics for OS (AIC and BIC; Pola + BR independent extrapolation) 203
Table 138: Predicted and observed OS for Pola + BR at several landmarks for each extrapolation (Pola + BR independent extrapolation) 204
Table 139: Goodness of fit statistics for PFS (AIC and BIC; Pola + BR independent extrapolation) 205
Table 140: Predicted and observed PFS for Pola + BR at several landmarks for each extrapolation (Pola + BR independent extrapolation) 206
Table 141: Goodness of fit statistics for OS (AIC and BIC; axi-cel independent extrapolation) 207
Table 142: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (axi-cel independent extrapolation) 209
Table 143: Goodness of fit statistics for PFS (AIC and BIC; axi-cel independent extrapolation) 209
Table 144: Predicted and observed PFS for axi-cel at several landmarks for each extrapolation 210
Table 145: Comparison of MAIC results for epcoritamab versus Pola + BR, based on Sehn *et al.* 3L+ and Northend *et al.* 3L+ 211
Table 146: Comparison of MAIC results for epcoritamab versus Pola + BR, based on Sehn *et al.* 3L+ and Northend *et al.* 3L+ 212

Figures

Figure 1: Waterfall plot of best reduction in SPD based on IRC assessment per Lugano Criteria (FAS; DLBCL; [redacted] data cut-off) 17
Figure 2: KM plot of DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 18
Figure 3: KM plot of PFS based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off) 20
Figure 4: KM plot of PFS based on IRC assessment, Lugano Criteria, by BOR (FAS; [redacted] data cut-off) 20
Figure 5: KM plot of OS (FAS; [redacted] data cut-off) 21
Figure 6: Mean change from baseline in EQ-5D-3L Health Utility Score (PRO-evaluable Set; [redacted] data cut-off) 27
Figure 7: Forest plot of ORR in prespecified subgroups based on IRC assessment determined by Lugano Criteria - DLBCL patients (FAS; [redacted] data cut-off) 34
Figure 8: KM plot of OS by prior CAR-T – DLBCL patients (FAS; [redacted] data cut-off) 36
Figure 9: KM plot of OS by prior CAR-T – LBCL patients (FAS; [redacted] data cut-off) 37
Figure 10: KM plot of PFS by prior CAR-T – DLBCL patients (FAS; [redacted] data cut-off) 38
Figure 11: KM plot of PFS by prior CAR-T – LBCL patients (FAS; [redacted] data cut-off) 39
Figure 12: KM plot of OS by number of prior lines of therapy – DLBCL patients (FAS; [redacted] data cut-off) 48
Figure 13: KM plot of OS by number of prior lines of therapy – LBCL patients (FAS; [redacted] data cut-off) 49
Figure 14: KM plot of PFS by number of prior lines of therapy – DLBCL patients (FAS; [redacted] data cut-off) 50
Figure 15: KM plot of PFS by number of prior lines of therapy – LBCL patients (FAS; [redacted] data cut-off) 51
Figure 16: Adjustment weights distribution for updated base case analysis A (epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1) 69
Figure 17: Adjustment weights distribution for scenario analysis A.1 (epcoritamab DLBCL population adjusted to Sehn et al. 3L+; no truncation required) 70
Figure 18: Adjustment weights distribution for scenario analysis A.2 (epcoritamab DLBCL population adjusted to match Liebers *et al.* RW data; no truncation required) 71
Figure 19: Adjustment weights distribution for scenario analysis A.3 (epcoritamab LBCL population adjusted to Liebers et al. RW data; no truncation required) 72
Figure 20: Adjustment weights distribution for scenario analysis A.4 (epcoritamab LBCL population adjusted to SCHOLAR-1; nine reported variables adjusted for; no truncation required) 74
Figure 21: Adjustment weights distribution for fully adjusted MAIC versus Northend (11 reported variables matched) 76
Figure 22: Adjustment weights distribution for updated base case analysis B (epcoritamab DLBCL, CAR-T eligible population adjusted to match axi-cel) 77
Figure 23: Adjustment weights distribution for scenario analysis B.2 (epcoritamab LBCL, CAR-T eligible population adjusted to match axi-cel) 78
Figure 24: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 80
Figure 25: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population 81
Figure 26: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population 82
Figure 27: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – DLBCL, no prior CAR-T epcoritamab population 83
Figure 28: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – DLBCL, no prior CAR-T epcoritamab population 83

Figure 29: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – LBCL, no prior CAR-T epcoritamab population) 85
Figure 30: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – LBCL, no prior CAR-T epcoritamab population 85
Figure 31: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population fully adjusted to SCHOLAR-1 (9 reported variables, no truncation) 86
Figure 32: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no ASCT epcoritamab population adjusted to Northend *et al* 3L+ (11 reported variables, with truncation) 87
Figure 33: Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no ASCT epcoritamab population adjusted to Northend *et al.* 3L+ (11 reported variables, with truncation) 88
Figure 34: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population 89
Figure 35: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population..... 89
Figure 36: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population 91
Figure 37: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population 91
Figure 38: Adjustment weights distribution for fully adjusted MAIC versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)..... 94
Figure 39: Adjustment weights distribution for fully adjusted MAIC versus Pola + BR (10 reported variables matched, with truncation; epcoritamab DLBCL population fully adjusted to Sehn et al. 3L+) 95
Figure 40: Adjustment weights distribution for MAIC versus SCHOLAR-1 (base case variables matched; epcoritamab LBCL, no prior CAR-T population adjusted to SCHOLAR-1) 97
Figure 41: Adjustment weights distribution for MAIC versus Northend et al. 3L+ (11 reported variables matched, without truncation; epcoritamab DLBCL, no prior ASCT population) 103
Figure 42: Adjustment weights distribution for MAIC versus Northend et al. 3L+ (13 reported variables matched, with truncation; epcoritamab DLBCL, no prior ASCT population) 105
Figure 43: Adjustment weights distribution for MAIC versus Northend et al. 3L+ (13 reported variables matched, without truncation; epcoritamab DLBCL, no prior ASCT population) 107
Figure 44: Adjustment weights distribution for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab DLBCL, CAR-T eligible population fully adjusted to match axi-cel)..... 108
Figure 45: Adjustment weights distribution for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab LBCL, CAR-T eligible population fully adjusted to match axi-cel) 110
Figure 46: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 (all reported variables, with truncation)..... 111
Figure 47: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population (10 reported variables matched, with truncation) 112
Figure 48: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population (10 reported variables matched, with truncation) 113
Figure 49: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – LBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 (base case variables matched)..... 114
Figure 50: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T..... 115

Figure 51: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T 116
Figure 52: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T ... 117
Figure 53: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T 118
Figure 54: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (11 reported variables matched, without truncation) 119
Figure 55: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (11 reported variables matched, without truncation) 119
Figure 56: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, with truncation) 120
Figure 57: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, with truncation) 121
Figure 58: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, without truncation) 122
Figure 59: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, without truncation) 122
Figure 60: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched) 124
Figure 61: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched) 124
Figure 62: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched) 125
Figure 63: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched) 126
Figure 64: KM plot of PFS, OS and TTD used in updated base case analysis A ([redacted]* data cut-off) 127
Figure 65: Long-term OS extrapolations for epcoritamab (updated base case analysis A) 128
Figure 66: Long-term PFS extrapolations for epcoritamab (updated base case analysis A) 130
Figure 67: Long-term TTD extrapolations for epcoritamab (updated base case analysis A) 131
Figure 68: KM plot of PFS, OS and TTD used in scenario analysis A.1 ([redacted] data cut-off) 133
Figure 69: Long-term OS extrapolations for epcoritamab (scenario analysis A.1) 134
Figure 70: Long-term PFS extrapolations for epcoritamab (scenario analysis A.1) 136
Figure 71: Long-term TTD extrapolations for epcoritamab (scenario analysis A.1) 137
Figure 72: KM plot of PFS, OS and TTD in the DLBCL population (N=139) from EPCORE™ NHL-1 adjusted to Liebers et al. RW data, used in scenario analysis A.2 ([redacted]* data cut-off) 139
Figure 73: Long-term OS extrapolations for epcoritamab (Scenario analysis A.2) 140
Figure 74: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.2) 142
Figure 75: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.2) 143
Figure 76: KM plot of PFS, OS and TTD in the LBCL population (N=157) from EPCORE™ NHL-1 adjusted to match Liebers *et al.* RW data, used in scenario analysis A.3 ([redacted]* data cut-off) 145
Figure 77: Long-term OS extrapolations for epcoritamab (Scenario analysis A.3) 146
Figure 78: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.3) 147

Figure 79: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.3) 149
Figure 80: KM plot of PFS, OS and TTD in the DLBCL population (N=[redacted] from EPCORE™ NHL-1 fully adjusted to match SCHOLAR-1, used in scenario analysis A.4 ([redacted] data cut-off) 150
Figure 81: Long-term OS extrapolations for epcoritamab (Scenario analysis A.4) 151
Figure 82: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.4) 153
Figure 83: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.4) 155
Figure 84: KM plot of PFS and OS in the DLBCL, no prior ASCT population from EPCORE™ NHL-1 adjusted to Northend *et al*. 3L+ RW data (N=[redacted]), used in scenario analysis A.5 ([redacted] data cut-off) 156
Figure 85: Long-term OS extrapolations for epcoritamab (Scenario analysis A.5) 157
Figure 86: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.5) 159
Figure 87: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.5) 160
Figure 88: KM plot of PFS, OS and TTD used in the updated base case analysis B ([redacted] data cut-off) 162
Figure 89: Long-term OS extrapolations for epcoritamab (updated base case analysis B) 163
Figure 90: Long-term PFS extrapolations for epcoritamab (updated base case analysis B) 165
Figure 91: Long-term TTD extrapolations for epcoritamab (updated base case analysis B) 166
Figure 92: KM plot of PFS, OS and TTD used in scenario analysis B.1 ([redacted] data cut-off) 168
Figure 93: Long-term OS extrapolations for epcoritamab (scenario analysis B.1) 169
The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in In line with the reasoning outlined in Appendix C.2.7, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.Figure 94. The corresponding survival estimates at several landmarks are presented in Table 116. In line with the reasoning outlined in Appendix C.2.7, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.Figure 94: Long-term PFS extrapolations for epcoritamab (scenario analysis B.1) 170
Figure 95: Long-term TTD extrapolations for epcoritamab (scenario analysis B.1) 172
Figure 96: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT) 173
Figure 97: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT) 174
Figure 98: Log-cumulative hazard curve – Epcoritamab versus Pola + BR 175
Figure 99. Schoenfeld residual curve – Epcoritamab versus Pola + BR 175
Figure 100: Log-cumulative hazard curve – Epcoritamab versus Pola + BR 176
Figure 101: Schoenfeld residual curve – Epcoritamab versus Pola + BR 176
Figure 102: Log-cumulative hazard curve – OS (epcoritamab versus Pola +BR) 178
Figure 103: Schoenfeld residual curve – OS (epcoritamab versus Pola +BR) 178
Figure 104: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR) 179
Figure 105: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR) 179
Figure 106: Log-cumulative hazard curve – OS (epcoritamab versus Pola +BR) 180
Figure 107: Schoenfeld residual curve – OS (epcoritamab versus Pola +BR) 181
Figure 108: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR) 181
Figure 109: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR) 182
Figure 110: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT) 183
Figure 111: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT) 183
Figure 112: Log-cumulative hazard curve – OS (epcoritamab versus Pola + BR) 184
Figure 113: Schoenfeld residual curve – OS (epcoritamab versus Pola + BR) 185
Figure 114: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR) 185
Figure 115: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR) 186
Figure 116: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel) 187
Figure 117: Schoenfeld residual curve – OS (epcoritamab versus axi-cel) 187
Figure 118: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel) 188
Figure 119: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel) 188
Figure 120: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel) 189
Figure 121: Schoenfeld residual curve – OS (epcoritamab versus axi-cel) 190
Figure 122: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel) 190
Figure 123: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel) 191
Figure 124: KM plot of OS for R-based CIT based on SCHOLAR-1 192

Figure 125: Long-term OS extrapolations for R-based CIT 193
Figure 126: KM plot of PFS and OS for Pola + BR based on Sehn *et al.* 3L+ 195
Figure 127: Long-term OS extrapolations for Pola + BR 196
Figure 128: Long-term PFS extrapolations for Pola + BR 198
Figure 129: KM plot of PFS and OS for Pola + BR based on Liebers *et al.* RW data 199
Figure 130: Long-term OS extrapolations for Pola + BR 200
Figure 131: Long-term PFS extrapolations for Pola + BR 202
Figure 132: KM plot of PFS and OS for Pola + BR, based on Northend et al 3L+ 203
Figure 133: Long-term OS extrapolations for Pola + BR (Pola + BR independent extrapolation) 204
Figure 134: KM plot of PFS and OS for axi-cel, based on ZUMA-1 207
Figure 135: Long-term OS extrapolations for axi-cel (axi-cel independent extrapolation) 208
Figure 136: Long-term PFS extrapolations for axi-cel 210
Figure 137: PFS and OS KM curves for Pola + BR, split by treatment line (2L versus 3L+), based on UK RWE 213

Introduction

As highlighted in response to Key Issue 8, the original submission presented data from the [redacted] data cut of EPCORE™ NHL-1, but since the original submission further data has become available from an [redacted] data cut (median follow-up [redacted]). As such, clinical data previously presented in both the CS and in response to the CQs are presented for the [redacted] data cut in the following sections, with the aim of addressing some of the uncertainties and issues raised by the EAG.

Furthermore, all ITCs and economic analyses provided as part of the technical engagement response are based on this new data cut; this includes relevant analyses previously presented in response to the EAG CQs that have been re-run using the [redacted] data cut. Clinical Data

A.1 Overview of the clinical effectiveness results

A summary of the key clinical outcomes from the EPCORE™ NHL-1 trial for the DLBCL cohort of the FAS aNHL population for both the [redacted] and [redacted] data cuts of EPCORE™ NHL-1 are shown in Table 1.

Table 1: Overview of key clinical effectiveness results for both EPCORE™ NHL-1 data cuts (FAS; DLBCL; N=139)

Outcome	[redacted]	[redacted]
ORR (IRC, Lugano criteria)	[redacted]	[redacted]
(95% CI)[a]	[redacted]	[redacted]
BOR (IRC, Lugano criteria)		
CR (IRC, Lugano criteria)	[redacted]	[redacted]
(95% CI)a	[redacted]	[redacted]
PR (IRC, Lugano criteria)	[redacted]	[redacted]
(95% CI)a	[redacted]	[redacted]
DOR (months) all responders (IRC, Lugano criteria)		
Number of responders	[redacted]	[redacted]
Min, max[b]	[redacted]	[redacted]
Median (95% CI)[c]	[redacted]	[redacted]
PFS (months) (IRC, Lugano criteria)		
Number of events	[redacted]	[redacted]
Min, Max[b]	[redacted]	[redacted]
Median (95% CI)[c]	[redacted]	[redacted]
OS (months)		
Number of events	[redacted]	[redacted]
Number of censored	[redacted]	[redacted]
Min, max[b]	[redacted]	[redacted]
Median (95% CI)[c]	[redacted]	[redacted]
TTNT (months)		
Number of events[d]	[redacted]	[redacted]
Number of censored	[redacted]	[redacted]

Min, Max[b]	[redacted]	[redacted]
Median (95% CI)[b,c]	[redacted]	[redacted]

[a] Based on the Clopper and Pearson method; [b] Symbol '+' indicates a censored value; [c] Based on Kaplan–Meier estimate; [d] Event is defined as administration of subsequent anti-lymphoma therapy with curative intent or death due to disease progression.
Abbreviations: CI: confidence interval; CR: complete response rate; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; IRC: independent review committee; LBCL: large B-cell lymphoma; Max: maximum; Min: minimum; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; PR: partial response; TTNT: time to next treatment.
Source: Table 14.2.1.1.1; Table 14.2.1.7.1; Table 14.2.1.12.1, Table 14.2.1.17, and Table 14.2.1.18 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.2 Patient disposition

As of the [redacted] data cut-off, [redacted] with DLBCL remained on epcoritamab treatment and [redacted] patients remain on trial. A total of [redacted] with DLBCL had discontinued epcoritamab treatment at the time of the data cut-off. The most frequent primary reasons for treatment discontinuation were disease progression ([redacted]), AEs ([redacted]), and the decision to proceed with transplant ([redacted]). A total of [redacted] with DLBCL permanently discontinued the trial; the most common reason for permanent discontinuation from the trial was death ([redacted]).

An overview of the disposition of patients in the LBCL and DLBCL cohorts of the EPCORE™ NHL-1 trial at the time of the [redacted] data cut is presented in Table 2.

Table 2: Disposition of patients (FAS; [redacted] data cut-off)

Number of Treated Patients, n (%)	aNHL Cohort	
	DLBCL (N=139)	LBCL (N=157)
Ongoing study treatment	[redacted]	[redacted]
Discontinued study treatment	[redacted]	[redacted]
Primary reason for treatment discontinuation		
Progressive disease[a]	[redacted]	[redacted]
Clinical progression	[redacted]	[redacted]
Disease progression according to response criteria	[redacted]	[redacted]
AE	[redacted]	[redacted]
Death	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]
Decision to proceed with transplant	[redacted]	[redacted]
Other	[redacted]	[redacted]
Patients remain on trial	[redacted]	[redacted]
Discontinued trial	[redacted]	[redacted]
Death	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]
Patient withdrew consent from trial	[redacted]	[redacted]

[a] Progressive disease includes both clinical progression and documented radiographic disease progression.

Abbreviations: AE: adverse event; aNHL: aggressive B-cell non-Hodgkin lymphoma; CAR-T: chimeric antigen receptor T-cells; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; LBCL: large B-cell lymphoma.
Source: Table 14.1.1.1.1 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.3 Primary endpoint

ORR based on IRC assessment, Lugano Criteria (FAS)

For the [redacted] data-cut the ORR in patients with DLBCL (N=139) was [redacted] ([redacted]; 95% CI: [redacted]) with [redacted] and [redacted] achieving best response of CR and PR, respectively, as shown in Table 3. Notably, there were [redacted] between the [redacted] and [redacted] data-cuts.

A waterfall plot of best reduction in sum of the product of the diameters by IRC assessment determined by Lugano criteria is provided for patients with DLBCL in Figure 1.

Table 3: ORR and BOR based on IRC Assessment, Lugano Criteria for both data-cuts (FAS; (FAS; DLBCL; N=139)

	[redacted]	[redacted]
ORR[a]	[redacted]	[redacted]
(95% CI)[b]	[redacted]	[redacted]
CR rate	[redacted]	[redacted]
(95% CI)[b]	[redacted]	[redacted]
BOR		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE	[redacted]	[redacted]

[a] CR+PR. Includes [redacted] who had a PR or CR after an assessment of PD or indeterminate response (i.e., pseudo progression); [b] Based on the Clopper and Pearson method.
Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; ORR: overall response rate; PD: partial disease; PR: partial response; SD: stable disease.
Source: Table 14.2.1.1.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Figure 1: Waterfall plot of best reduction in SPD based on IRC assessment per Lugano Criteria (FAS; DLBCL; [redacted] data cut-off)

Stars indicate that there is an increase of more than 100% in sum of product perpendicular diameters.
Abbreviations: FAS: full analysis set; IRC: Independent Review Committee; SPD: Sum of Product Perpendicular Diameter.
Source: Figure 14.2.1.8.1 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.4 Secondary endpoints

DOR based on IRC assessment, Lugano Criteria (FAS)

In patients with DLBCL who had achieved PR or CR ([redacted]), the median DOR was [redacted] (95% CI: [redacted]). The estimated percentage of patients remaining in PR or CR at three, six, and nine months was [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively. In patients with DLBCL who had achieved CR ([redacted], based on the median duration of follow-up of [redacted] the median DOR was [redacted]. The estimated percentage of patients remaining in CR at three, six, and nine months was [redacted] (95% CI: [redacted], [redacted](95% CI: [redacted], and [redacted] (95% CI: [redacted]), respectively. These results are shown in Table 4 and a Kaplan–Meier (KM) plot of DOR for DLBCL, LBCL and other subtypes is shown in Figure 2.

DOR among patients with LBCL and other subtypes of LBCL were consistent with that of patients with DLBCL.

Table 4: DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
All responders (PR or CR)	
Number of responders	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
DOR (months)	
Min, max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]

	DLBCL (N=139)
Estimate percentage of patients remaining in response (95% CI)[b]	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]
CR	
Number of patients with CR	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
DOR (months)	
Min, max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimate percentage of patients remaining in response (95% CI)[b]	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on KM estimate.
Abbreviations: CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; FAS: full analysis set; IRC: independent review committee; max: maximum; min: minimum; NR: not reached; PR: partial response.
Source: Table 14.2.1.7.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Figure 2: KM plot of DOR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; NR: not reached; PMBCL: primary mediastinal B-cell lymphoma.
Source: Figure 14.2.1.9.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

PFS based on IRC assessment, Lugano Criteria (FAS)

Among patients with DLBCL, [redacted] patients experienced a PFS event (disease progression or death) as assessed by IRC. The median PFS was [redacted]). The estimated percentage of patients remaining progression-free at six, nine, 12 and 24 months was [redacted], [redacted], [redacted] and [redacted] respectively.

Based on the [redacted] data cut-off, with a median follow-up was [redacted], for patients with DLBCL, median PFS was [redacted]. Among patients in PR, median PFS was [redacted] when compared with non-responders ([redacted] versus [redacted]).

The PFS based on IRC assessment (Lugano criteria) are presented in Table 5 and a KM plot of PFS based on IRC assessment is presented in Figure 3 and by BOR in Figure 4.

Table 5: PFS based on IRC assessment Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events	[redacted]
Number of censored	[redacted]
PFS (months)	
Min, Max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimated percentage of patients remaining progression-free (95% CI)[b]	
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]
15-month	[redacted]
18-month	[redacted]
21-month	[redacted]
24-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; LBCL: large B-cell lymphoma; Max: maximum; Min: minimum; NR: not reached; PFS: progression-free survival.
Source: Table 14.2.1.12.1 EPCORE™ NHL-1 Data Tables, [redacted].[1]

Figure 3: KM plot of PFS based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma.
Source: Figure 14.2.1.12.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Figure 4: KM plot of PFS based on IRC assessment, Lugano Criteria, by BOR (FAS; [redacted] data cut-off)

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PR: partial response.
Source: Figure 14.2.1.12.11 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

OS (FAS)

Among patients with DLBCL, [redacted] patients had died and [redacted] patients were still alive. After a median follow up of [redacted], median OS was [redacted] (95% CI: [redacted]). The estimated percentage of patients with DLBCL who remained alive at 6, 9, 12 and 24 months was

[redacted], [redacted], [redacted] and [redacted] respectively. This is shown below in Table 6 and a KM plot of OS in Figure 5.

Table 6: OS (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events	[redacted]
Number of censored	[redacted]
OS (months)	
Min, max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimated percentage of patients remaining alive (95% CI)[b]	
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]
15-month	[redacted]
18-month	[redacted]
21-month	[redacted]
24-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; Max: maximum; Min: minimum; NR: not reached; OS: overall survival.
Source: Table 14.2.1.17 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Figure 5: KM plot of OS (FAS; [redacted] data cut-off)

[redacted]

Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; PMBCL: primary mediastinal B-cell lymphoma; NR: not reached.
Source: Figure 14.2.1.13.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

TTNT (FAS)

Among patients with DLBCL (N=139), [redacted] patients experienced a TTNT event (of which [redacted] events were due to receiving subsequent anti-lymphoma therapy and [redacted] events were due to death) and [redacted] were censored. Median TTNT was [redacted] (95% CI: [redacted]). The estimated percentage of patients not initiating subsequent therapy at three, six, nine, and 12 months was [redacted], [redacted], [redacted], and [redacted], respectively. This is shown below in Table 7.

Table 7: TTNT (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events[a]	[redacted]
Number of censored	[redacted]
TTNT (months)	
Min, Max[b]	[redacted]
25% quartile (95% CI)[c]	[redacted]
Median (95% CI)[c]	[redacted]
75% quartile (95% CI)[c]	[redacted]
Estimated percentage of patients not initiating next line of therapy (95% CI)[b]	
3-month	[redacted]
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]
15-month	[redacted]

[a] Event is defined as administration of subsequent anti-lymphoma therapy with curative intent or death due to disease progression; [b] Symbol '+' indicates a censored value; [c] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; Max: maximum; Min: minimum; NR: not reached; TTNT: time to next anti-lymphoma therapy.
Source: Table 14.2.1.18 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.5 Additional secondary endpoints

A.5.1. ORR by investigator assessment, Lugano Criteria (FAS)

A summary of ORR by Investigator Assessment (INV) determined by Lugano criteria for patients in the aNHL expansion cohort is presented in Table 8.

The ORR in patients with DLBCL (N=139) was [redacted] (95% CI: [redacted]) with [redacted] and [redacted] patients achieving best response of CR and PR, respectively. An overview of the ORR and BOR results (INV, Lugano Criteria) for the DLBCL patient population is included in Table 8.

Concordance in responder states between the IRC and investigator assessments (Lugano criteria) was high. For patients with DLBCL, the concordance rate was [redacted]([redacted]).

Table 8: BOR based on INV, Lugano criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
ORR[a]	[redacted]
(95% CI)b	[redacted]

	DLBCL (N=139)
CR rate	[redacted]
(95% CI)b	[redacted]
BOR	
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
NE	[redacted]

[a] CR+PR. [b] Based on the Clopper and Pearson method.
Abbreviations: BOR: best overall response; CR: complete response; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; NE: not evaluable; PD: progressed disease; PR: partial response; SD: stable disease.
Source: Table 14.2.1.2.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.5.2. PFS by investigator assessment, Lugano Criteria (FAS)

A summary of PFS based on INV (Lugano Criteria) for patients in the aNHL expansion cohort is presented in Table 9.

Among all patients with DLBCL, [redacted] ([redacted]) patients experienced a PFS event (disease progression or death) as assessed by INV The median PFS was [redacted] ([redacted]). An overview of the PFS results are presented in Table 9.

Table 9: PFS based on INV, Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Number of events	[redacted]
Number of censored	[redacted]
PFS (months)	
Min, Max[a]	[redacted]
25% quartile (95% CI)[b]	[redacted]
Median (95% CI)[b]	[redacted]
75% quartile (95% CI)[b]	[redacted]
Estimated percentage of patients remaining progression-free (95% CI)[b]	
6-month	[redacted]
9-month	[redacted]
12-month	[redacted]

[a] Symbol '+' indicates a censored value; [b] Based on Kaplan–Meier estimate.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; Max: maximum; Min: minimum; NR: not reached; PFS: progression-free survival.
Source: Table 14.2.1.13.1 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.5.3. Time to response and time to complete response based on IRC assessment, Lugano Criteria (FAS)

A summary of TTR and TTCR results for patients with DLBCL from EPCORE™ NHL-1 is presented in Table 10. Among patients with DLBCL, median time to response (TTR) was [redacted]

[redacted] (which is in line with the first response assessment at 6 weeks) and median time to complete response (TTCR) was [redacted], although this value will be skewed by later conversions from PR to CR.

Table 10: TTR and TTCR based on IRC assessment, Lugano Criteria (FAS; [redacted] data cut-off)

	DLBCL (N=139)
Time to response (months)[a]	
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Q1, Q3	[redacted]
Time to complete response (months)[b]	
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Q1, Q3	[redacted]

[a] Only patients with BOR of PR or CR are included in the analysis. [b] Only patients with BOR of CR are included in the analysis.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; IRC: independent review committee; Max: maximum; Min: minimum; NR: not reached; SD: standard deviation; TTR: time to response; TTCR: time to complete response.
Source: Table 14.2.1.21.1 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.5.4. MRD negativity

Minimal residual disease (MRD) was assessed at protocol-specified time points and were initially performed using peripheral blood mononuclear cells (from whole blood samples). All exploratory MRD analyses were performed using the MRD-evaluable subset, which included patients who had at least one baseline or on-treatment MRD sample and were either MRD positive or not evaluated at baseline.

An overview of the duration of MRD negativity per ctDNA assay for the DLBCL population is provided in Table 11.

Table 11: Duration of MRD Negativity per ctDNA Assay - aNHL Cohort, Expansion Part (MRD-Evaluable Set; [redacted] data cut-off)

	DLBCL (N=[redacted])
Number of patients with MRD negativity[a]	[redacted]
Number of events	[redacted]
Number of censored	[redacted]
Duration of MRD negativity (months)[b]	
Min, Max[c]	[redacted]
25% quartile (95% CI)	[redacted]
Median (95% CI)	[redacted]

	DLBCL (N=[redacted])
75% quartile (95% CI)	[redacted]
Estimate percentage of patients remaining MRD negative (95% CI)[c]	
6-month	[redacted]

[a] Patients were considered MRD negative if there was at least 1 on-treatment MRD-negative sample; all remaining patients in the MRD-evaluable subset were considered MRD positive. [b] Duration of MRD-negativity was defined as the number of days from the first documentation of MRD-negativity to the date of MRD status change (not MRD-negative). The primary MRD-negativity threshold was selected as 10^{-5}. [c] Symbol '+' indicates a censored value.
Abbreviations: aNHL: aggressive B-cell non-Hodgkin lymphoma; CI: confidence interval; ctDNA: circulating tumour deoxyribonucleic acid; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; Max: maximum; Min: minimum; MRD: minimal residual disease; NR: not reached.
Source: Table 14.2.3.2.4. EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.6 Patient reported outcomes

A.6.1. FACT-Lym

An overview of the results of the FACT-Lym total score and the FACT-LymS are provided in Table 12.

While on treatment, there were marked improvements in the patient reported symptoms across all six symptoms of the FACT-Lym (body pain, fever, night sweats, lack of energy, tires easily, and weight loss) from Cycle 2 to Cycle 13.

Table 12: Mean scores for FACT-Lym total score and FACT-LymS while on treatment (FAS – [redacted] data cut-off)

Time point	DLBCL (N=139)		
	Sample size	FACT-Lym total score, mean (Sd)	FACT-LymS, mean (SD)
C1D1	[redacted]	[redacted]	[redacted]
C3D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C5D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]

Abbreviations: CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma55; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; FAS: full analysis set; SD:48 standard deviation.
Source: Table 14.2.3.5.5 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.6.2. EQ-5D-3L

Based on the [redacted] data cut-off, for patients with DLBCL, consistent and steady improvements in patient-reported quality of life were observed as reflected by improvements in mean (standard deviation) EQ-5D-3L health utility scores from [redacted] ([redacted]; N=[redacted]) at baseline to [redacted] ([redacted]; N=[redacted]) at C9D1. The mean changes are presented below in Table 13 and graphically in Figure 6. Similar improvements were observed in the LBCL cohort.

Table 13: Mean scores for EQ-5D-3L health utility score while on treatment (FAS; [redacted] data cut-off)

Time point	DLBCL (N=139)	
	Sample size	Health utility score, mean (SD)
C1D1	[redacted]	[redacted]
C3D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
C5D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
C7D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
C9D1	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]

Abbreviations: CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma; EQ-5D-3L: EuroQoL-5 diminesions-3 levels; FAS: full analysis set; SD: standard deviation.
Source: Table 14.2.3.5.6 EPCORE™ NHL-1 Data Tables, [redacted].[1]

Figure 6: Mean change from baseline in EQ-5D-3L Health Utility Score (PRO-evaluable Set; [redacted] data cut-off)

Horizontal reference line indicates [redacted]; Other includes nine patients with HGBCL, five patients with FL Gr 3B and four patients with PMBCL.
Abbreviations: CXDX: Cycle X Day X; DLBCL: diffuse large B-cell lymphoma; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; FL Gr 3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; MID: minimum important difference; PMBCL: primary mediastinal B-cell lymphoma; PRO: patient-reported outcome.
Source: Figure 14.2.3.5.5 EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.7 Adverse reactions

A.7.1. Summary of treatment-emergent adverse events

A summary of treatment-emergent adverse events (TEAEs) is reported in the EPCORE™ NHL-1 trials for patients with LBCL and patients with DLBCL is provided in Table 14. Further details on AEs are provided in subsequent sections. AEs among patients with LBCL and other subtypes were consistent with that of patients with DLBCL.

As of the [redacted] data cut off, [redacted] with LBCL had experienced at least one TEAE. Of these, [redacted] experienced TEAEs considered related to epcoritamab by the investigator. A total of [redacted] experienced grade 3 or higher TEAEs and [redacted] had [redacted] or higher TEAEs considered related to epcoritamab by the investigator.

Serious TEAEs were reported in [redacted] with LBCL and were considered related to epcoritamab by the investigator in [redacted]. A total of [redacted] patients with LBCL experienced a TEAE leading to treatment discontinuation and [redacted] had a TEAE leading to dose delay/interruption.

Fatal TEAEs were reported in [redacted] with LBCL only [redacted] of which were considered related to epcoritamab by the investigator.

Adverse events of special interest (AESIs) included cytokine release syndrome (CRS), immune effector cell-associated (ICANS), and clinical tumour lysis syndrome (CTLS). Approximately [redacted] of the trial patients ([redacted] patients) in the aNHL expansion cohort had an AESI of CRS; the AESI of ICANS occurred in [redacted] patients with LBCL. Events of CTLS were reported in [redacted] patients with LBCL.

Table 14: Summary of TEAEs (SAF; [redacted] data cut-off)

Number of patients (%)	LBCL (N=157)	DLBCL (N=139)
Number of patients with ≥1		
TEAE	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]
Grade 3 and higher TEAE	[redacted]	[redacted]
Grade 3 and higher related TEAE	[redacted]	[redacted]
TEAE by worst toxicity grade		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Serious related TEAE	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]

Number of patients (%)	LBCL (N=157)	DLBCL (N=139)
TEAE leading to dose delay	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]
Fatal related TEAE	[redacted]	[redacted]
AESI; Number of patients with ≥1		
CRS	[redacted]	[redacted]
ICANS	[redacted]	[redacted]
CTLS	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 14.3.1.1.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[2]

A.7.2. Treatment-emergent adverse events

A summary of TEAEs in the DLBCL population in EPCORE™ NHL-1 is presented in Table 15.

Among patients with LBCL (N=157), the most frequent (≥20%) TEAEs by preferred term (PT) were CRS ([redacted]), pyrexia (not associated with CRS; ([redacted]), fatigue ([redacted]), neutropenia ([redacted]), diarrhoea ([redacted]), nausea ([redacted]), and anaemia ([redacted].

A total of [redacted] with LBCL had TEAEs considered related to epcoritamab by the investigator. The most frequent treatment-related TEAEs (≥10%) were CRS ([redacted]), injection site reaction ([redacted]), neutropenia ([redacted]), fatigue ([redacted]), and pyrexia ([redacted]).

Table 15: Most common (at least 10% in any group) TEAEs by SOC and PT (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
Patients with ≥1 TEAE	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]

Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRS: cytokine release syndrome' DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 14.3.1.2.2 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[2]

A.7.3. Serious TEAEs

A summary of serious TEAEs in the LBCL population of EPCORE™ NHL-1 are presented in Table 16. Serious TEAEs were reported in [redacted] with LBCL. The most frequent serious TEAEs by PT in these patients were CRS ([redacted]), COVID-19 [redacted], COVID-19 pneumonia ([redacted] and pleural effusion ([redacted]).

Treatment-related, serious TEAEs were reported in [redacted] with LBCL. The most frequent treatment-related, serious TEAEs by PT in these patients were CRS ([redacted]) and ICANS ([redacted]).

Table 16: Most common (2% or more in any group) serious TEAEs by SOC and PT (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
Patients with ≥1 serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
CRS	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
ICANs	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 14.3.2.3.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[2]

A.7.4. Treatment-emergent adverse events leading to discontinuation

Among patients with LBCL (N=157), [redacted] experienced at least one TEAE that led to treatment discontinuation. The most common of these events were COVID-19 pneumonia, COVID-19 infection and myelodysplastic syndrome, each of which occurred in [redacted], [redacted] and [redacted], respectively.

A.7.5. Adverse events of special interest

AESIs were specified as ICANS, CRS and CTLS, of which the incidence of each are presented in Table 17.

Events of ICANS were reported in [redacted]; [redacted] had [redacted] ICANS, [redacted] had [redacted] ICANS, and [redacted] had [redacted] ICANS. The fatal episode of ICANS, was in [redacted], was an on-treatment event with onset on [redacted]

[redacted], [redacted] after the patient's most recent dose of study drug and was considered related to study drug.

In patients with LBCL, [redacted] had at least one CRS event. The majority of these were [redacted] ([redacted]) or [redacted] ([redacted]) events.

[redacted] with LBCL experienced events of CTLS, both of which were considered treatment-related within the setting of disease progression and were [redacted] in severity.

Table 17: Summary of AESIs (SAF; [redacted] data cut-off)

Number of patients (%)	LBCL (N=139)	DLBCL (N=157)
Patients with ≥1 ICANS event	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Patients with ≥1 CRS event	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Patients ≥1 CTLS event	[redacted]	[redacted]

CRS events are graded according to Lee et al, 2019.[3]
Abbreviations: AESI: adverse events of special interest; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set.
Source: Table 14.3.1.1.1. AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[2]

A.7.6. Patient deaths

Overall, [redacted] with LBCL died during the trial, including [redacted] who died within 60 days of last dose of study treatment. Most deaths were observed after disease progression ([redacted]).

Fatal TEAEs occurred in [redacted] with LBCL. COVID-19 pneumonia and COVID-19, which occurred in [redacted] and [redacted] with LBCL respectively, were the only fatal TEAEs reported in more than [redacted]. This is shown below in Table 18.

[redacted] fatal TEAEs were reported that were considered related to epcoritamab by the investigator and included [redacted].

Table 18: Summary of fatal TEAEs by PT (SAF; [redacted] data cut-off)

Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term	LBCL (N=157)		DLBCL (N=139)	
	All	Related	All	Related
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Bacterial pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Progressive multifocal leukoencephalopathy	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]

[a] Adverse events are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 14.3.2.1 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[2]

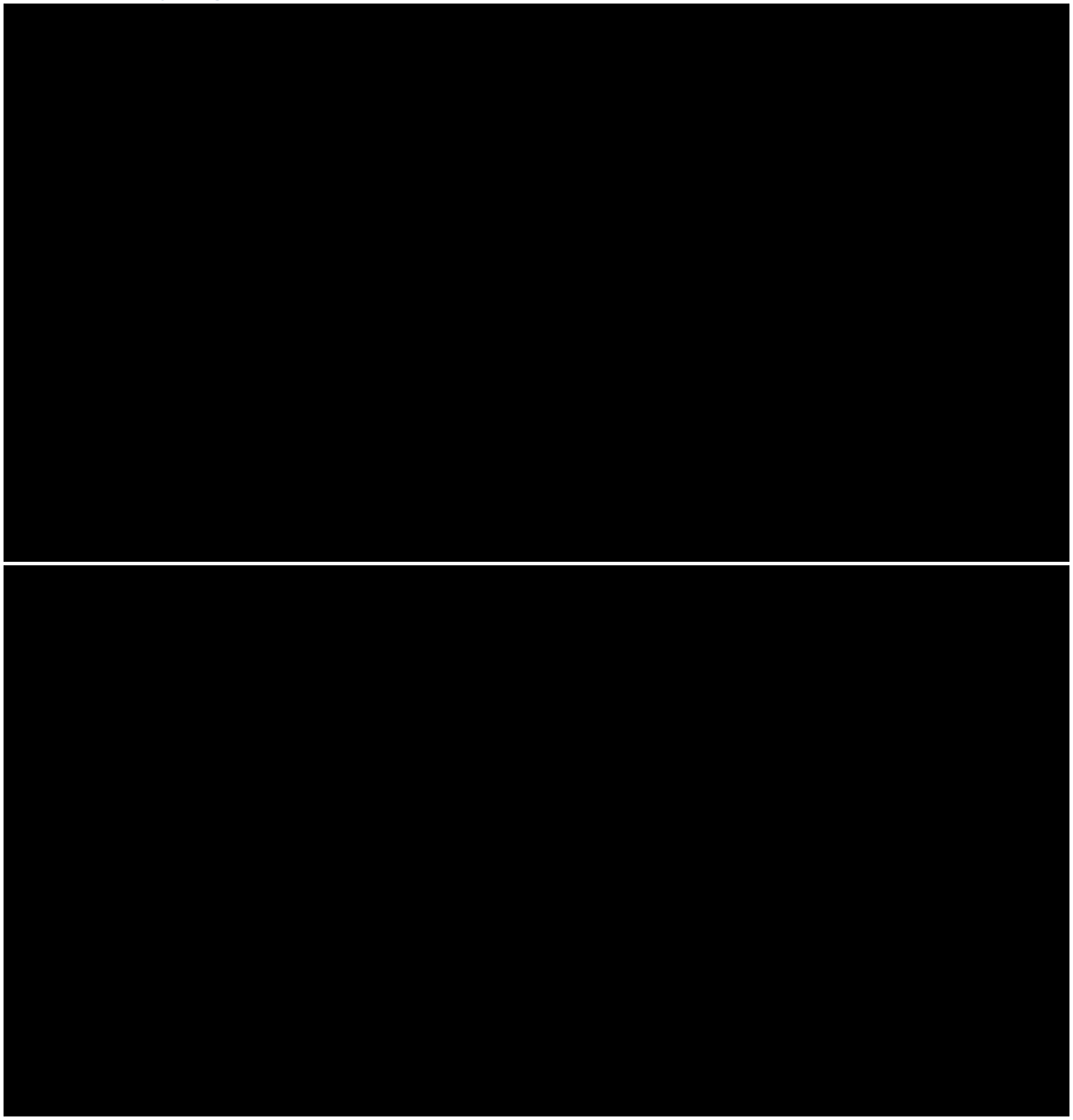
A.8 Subgroup analysis

A.8.1. ORR subgroup analysis

For most pre-specified subgroups, the ORRs were generally consistent with the ORR of the overall DLBCL population ([redacted]; 95% CI: [redacted]) (Figure 7). Furthermore, for most subgroups, the ORRs were generally consistent with the ORR of the overall LBCL population.

In the DLBCL population, ORR was [redacted] in the no prior CAR-T subgroup (N=[redacted]) versus the prior CAR-T subgroup (N=[redacted]) ([redacted] versus [redacted]). Although a numerical difference was observed, the 95% confidence intervals overlapped and there was [redacted] difference. Relatedly, in the subgroup of patients refractory to prior CAR-T (N=[redacted]), although a numerical difference was observed, there was [redacted] difference.

Figure 7: Forest plot of ORR in prespecified subgroups based on IRC assessment determined by Lugano Criteria - DLBCL patients (FAS; [redacted] data cut-off)



Abbreviations: ABC: activated B-cell; ADA: anti-drug antibody; ASCT: autologous stem cell transplantation; CAR-T: Chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; GCB: germinal centre B-cell; IPI: International Prognostic Index; IRC: independent review committee; ORR; overall response rate.
Source: Figure 14.2.1.1.1 AbbVie, EPCORE™ NHL-1 Data Tables, April 2023.[1]

A.8.2. Prior vs no prior CAR-T therapy subgroup analysis

Efficacy endpoints

The Kaplan–Meier (KM) plots of overall survival (OS) and progression-free survival (PFS) by prior chimeric antigen receptor T-cell (CAR-T) therapy from the [redacted] data cut of EPCORE™ NHL-1, for the diffuse large B-cell lymphoma (DLBCL) and large B-cell lymphoma (LBCL) populations are presented in Figure 8–Figure 11. Overall, the OS and PFS KM plots by prior CAR-T therapy demonstrate that epcoritamab has the potential to provide benefits in OS and PFS, regardless of prior CAR-T therapy status.

Figure 8: KM plot of OS by prior CAR-T – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; OS: overall survival.
Source: Figure 901.3_04.01.07 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[2]

Figure 9: KM plot of OS by prior CAR-T – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival.
Source: Figure 901.3_04.01.07 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[2]

Figure 10: KM plot of PFS by prior CAR-T – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; PFS: progression-free survival.
Source: Figure 901.3_03.01.07 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[2]

Figure 11: KM plot of PFS by prior CAR-T – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival.
Source: Figure 901.3_03.01.07 AbbVie, EPCORE™ NHL-1 Figures, [redacted].[2]

Adverse events

The summary of AEs split by prior CAR-T therapy and no prior CAR-T therapy are provided in Table 19–Table 23. Overall, the AEs for patients with prior and no prior CAR-T therapy are consistent across the majority of AEs.

Considering individual TEAEs, no differences in frequency of 10% or more occurred between the subgroups, except for CRS; patients who had received prior CAR-T were less likely to experience a CRS event compared with those who had not received prior CAR-T therapy. However, in both subgroups, the majority of CRS events were grade 1 or 2, with [redacted] and [redacted] experiencing grade 3 CRS events in the prior CAR-T and no prior CAR-T subgroups of the LBCL population.

For grade 3 or higher TEAEs, no differences in frequency of 10% or higher occurred between the subgroups.

Table 19: Summary of TEAEs for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

Number of patients (%)	Prior CAR-T		No prior CAR-T	
	LBCL (N=[redacted])	DLBCL (N=[redacted])	LBCL (N=[redacted])	DLBCL (N=[redacted])
Number of patients with ≥1				
TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by worst toxicity grade				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to dose delay/interruption	[redacted]	[redacted]	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Fatal related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
AESI; Number of patients with ≥1				

Number of patients (%)	Prior CAR-T		No prior CAR-T	
	LBCL (N=[redacted])	DLBCL (N=[redacted])	LBCL (N=[redacted])	DLBCL (N=[redacted])
CRS	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]
CTLS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 901.4_01.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 20: Most common (at least 10% in any group) TEAEs by SOC and PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	Prior CAR-T				No prior CAR-T			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 TEAE	[redacted]							
General disorders and administration site conditions	[redacted]							
Pyrexia	[redacted]							
Fatigue	[redacted]							
Injection site reaction	[redacted]							
Oedema peripheral	[redacted]							
Asthenia	[redacted]							
Gastrointestinal disorders	[redacted]							
Diarrhoea	[redacted]							
Nausea	[redacted]							
Abdominal pain	[redacted]							
Constipation	[redacted]							
Vomiting	[redacted]							
Immune system disorders	[redacted]							
CRS	[redacted]							
Infections and infestations	[redacted]							
COVID-19	[redacted]							
Blood and lymphatic system disorders	[redacted]							
Neutropenia	[redacted]							

Anaemia								
Thrombocytopenia								
Musculoskeletal and connective tissue disorders								
Back pain								
Metabolism and nutrition disorders								
Decreased appetite								
Hypokalaemia								
Nervous system disorders								
Headache								
Psychiatric disorders								
Insomnia								

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 901.4_02.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 21: Most common (2% or more in any group) serious TEAEs by SOC and PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	Prior CAR-T				No prior CAR-T			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 serious TEAE								
Immune system disorders								
CRS								
Infections and infestations								
Sepsis								
COVID-19								

Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 901.4_04.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 22: Summary of AESIs for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

Number of patients (%)	Prior CAR-T		No prior CAR-T	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Patients with ≥1 ICANS event	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 CRS event[a]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]

[a] CRS events are graded according to Lee et al, 2019.[3]
Abbreviations: AESI: adverse events of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndroms; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set.
Source: Tables 901.4_10.01.03, 901.4_11.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 23: Summary of fatal TEAEs by PT for prior CAR-T and no prior CAR-T subgroups (SAF; [redacted] data cut-off)

Preferred Term	Prior CAR-T				No prior CAR-T			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive multifocal leukoencephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] AEs are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 901.4_09.01.03 AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

A.8.3. 2, 3 and 4+ prior anti-lymphoma treatments subgroup analysis

The KM plots of OS and PFS by prior anti-lymphoma treatments from the [redacted] data cut of EPCORE™ NHL-1, for the DLBCL and LBCL population are presented in Figure 12–Figure 15.

In line with the data based on the [redacted] data cut, the OS and PFS KM plots by prior anti-lymphoma treatments demonstrate that epcoritamab has the potential to provide benefits in OS and PFS, regardless of the number of prior lines of anti-lymphoma treatments received. The PFS data show similar long-term outcomes regardless of number of prior lines of therapy, which supports extended responses in patients.

Figure 12: KM plot of OS by number of prior lines of therapy – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; OS: overall survival; NR: not reached; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_04.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 13: KM plot of OS by number of prior lines of therapy – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; NR: not reached; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_04.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 14: KM plot of PFS by number of prior lines of therapy – DLBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; FAS: full analysis set; KM: Kaplan–Meier; PFS: progression-free survival; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_03.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Figure 15: KM plot of PFS by number of prior lines of therapy – LBCL patients (FAS; [redacted] data cut-off)

Abbreviations: CI: confidence interval; FAS: full analysis set; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival; 2L: two lines; 3L: three lines: 4L+: four lines and beyond.
Source: Figure 901.3_03.01.02a AbbVie, EPCORE™ NHL-1 Figures, [redacted].[1]

Adverse events

The summary of AEs split by number of prior lines of treatment are presented in Table 24–Table 28. In line with data from the [redacted] data cut, the AEs split by number of prior lines of treatment are highly consistent across the subgroups.

Table 24: Summary of TEAEs by number of prior lines of therapy (SAF; [redacted] data cut-off)

Number of patients (%)	2 prior lines		3 prior lines		4+ prior lines	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Number of patients with ≥1						
TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 and higher related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE by worst toxicity grade						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to dose delay/interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

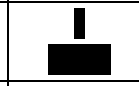
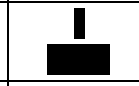
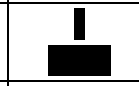
Number of patients (%)	2 prior lines		3 prior lines		4+ prior lines	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
AESI; Number of patients with ≥1						
CRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 901.4_01.01.02a, 901.4_10.01.02a, and 901.4_11.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 25: Most common (at least 10% in any group) TEAEs by SOC and PT by number of prior lines of therapy (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	2 prior lines				3 prior lines				4+ prior lines			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 TEAE	[redacted]											
General disorders and administration site conditions	[redacted]											
Pyrexia	[redacted]											
Fatigue	[redacted]											
Injection site reaction	[redacted]											
Injection site erythema	[redacted]											
Oedema peripheral	[redacted]											
Asthenia	[redacted]											
Gastrointestinal disorders	[redacted]											
Diarrhoea	[redacted]											
Nausea	[redacted]											
Abdominal pain	[redacted]											
Constipation	[redacted]											
Vomiting	[redacted]											

Immune system disorders												
CRS												
Infections and infestations												
COVID-19												
Pneumonia												
Urinary tract infection												
Blood and lymphatic system disorders												
Neutropenia												
Anaemia												
Thrombocytopenia												
Musculoskeletal and connective tissue disorders												
Arthralgia												
Back pain												
Muscle spasms												
Pain in extremity												

Metabolism and nutrition disorders												
Decreased appetite												
Hypokalaemia												
Hypomagnesaemia												
Nervous system disorders												
Headache												
Skin and subcutaneous tissue disorders												
Pruritus												
Investigations												
C-reactive protein increased												
Weight decreased												
Respiratory, thoracic and mediastinal disorders												
Dyspnoea												
Cough												

Pleural effusion	[redacted]											
Vascular disorders	[redacted]											
Hypotension	[redacted]											
Psychiatric disorders	[redacted]											
Insomnia	[redacted]											

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 901.4_12.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 26: Most common (2% or more in any group) serious TEAEs by SOC and PT by number of prior lines of therapy (SAF; [redacted] data cut-off)

System Organ Class/Preferred Term	2 prior lines				3 prior lines				4+ prior lines			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 most common (≥2%) serious TEAE	[redacted]											
Immune system disorders	[redacted]											
CRS	[redacted]											
Infections and infestations	[redacted]											
COVID-19	[redacted]											
Bacteraemia	[redacted]											
COVID-19 pneumonia	[redacted]											
Device related infection	[redacted]											
Influenza	[redacted]											
Lower respiratory tract infection	[redacted]											
Pneumonia	[redacted]											
Pneumonia bacterial	[redacted]											
Respiratory tract infection	[redacted]											
Sepsis	[redacted]											
Staphylococcal bacteraemia	[redacted]											

Viral infection												
Cellulitis												
Pneumonia haemophilus												
Progressive multifocal leukoencephalopathy												
Pyelonephritis												
Septic shock												
Sialadenitis												
Upper respiratory tract infection												
Neoplasms benign, malignant and unspecified[a]												
Infected neoplasm												
Tumour pain												
Basal cell carcinoma												
Myelodysplastic syndrome												
Lung neoplasm malignant												
Prostate cancer stage II												
Nervous system disorders												
ICANS												
Cerebral ischaemia												
Hydrocephalus												

Acute polyneuropathy												
Chronic lymphocytic inflammation[b]												
Headache												
Post herpetic neuralgia												
Vascular disorders												
Haematoma												
Hypotension												
Thrombophlebitis												
Blood and lymphatic system disorders												
Febrile neutropenia												
Lymphadenopathy												
Lymphopenia												
Neutropenia												
Investigations												
Blood creatinine increased												
C-reactive protein increased												
Weight decreased												
Respiratory, thoracic, and mediastinal disorders												
Pleural effusion												
Dyspnoea												

Hypoxia	[redacted]											
Pulmonary embolism	[redacted]											
Respiratory failure	[redacted]											
Cardiac disorders	[redacted]											
Myocarditis	[redacted]											
Tachycardia	[redacted]											
Gastrointestinal disorders	[redacted]											
Pancreatitis	[redacted]											
Abdominal pain upper	[redacted]											
Duodenal perforation	[redacted]											
Nausea	[redacted]											
Vomiting	[redacted]											
Hepatobiliary disorders	[redacted]											
Hepatotoxicity	[redacted]											
Musculoskeletal and connective tissue disorders	[redacted]											
Fistula	[redacted]											
Blood and lymphatic system disorders	[redacted]											
Anaemia	[redacted]											
Febrile neutropenia	[redacted]											
General disorders and administration site conditions	[redacted]											

Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mental state changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malnutrition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Including cysts and polyps. [b] With pontine perivascular enhancement responsive to steroids
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
Source: Table 901.4_13.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 27: Summary of AESIs by number of prior lines of therapy (SAF; [redacted] data cut-off)

Number of patients (%)	2 prior lines		3 prior lines		4+ prior lines	
	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])	LBCL ([redacted])	DLBCL ([redacted])
Patients with ≥1 ICANS event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥1 CRS event[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] CRS events are graded according to Lee et al, 2019.[3]

Abbreviations: AESI: adverse events of special interest; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; CTLS: clinical tumour lysis syndrome; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; SAF: safety analysis set.

Source: Tables 901.4_10.01.02a and 901.4_11.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Table 28: Summary of fatal TEAEs by PT by number of prior lines of therapy (SAF; [redacted] data cut-off)

Preferred Term	2 prior lines				3 prior lines				4+ prior lines			
	LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])		LBCL ([redacted])		DLBCL ([redacted])	
	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Patients with ≥1 fatal TEAE[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive multifocal leukoencephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICANS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] AEs are classified using Medical Dictionary for Regulatory Activities v24.1 and are counted only once per PT.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; LBCL: large B-cell lymphoma; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Table 901.4_09.01.02a AbbVie, EPCORE™ NHL-1 Data Tables, [redacted].[1]

Appendix B Indirect treatment comparisons

B.1 MAICs informing the base case and scenario analyses

A summary of the MAICs included in the cost-effectiveness model informing the updated base case analyses and scenario analyses are presented in Table 29, including the epcoritamab populations used in the analyses. For all MAICs conducted and presented as part of Technical Engagement, the epcoritamab efficacy data are based on the [redacted] data cut.

As mentioned in response to Key Issue 7, AbbVie maintain that the MAICs included in the updated base case, in which all clinically important baseline characteristics are adjusted for, provide the most robust estimates of comparative efficacy. However, in response to the EAG's request, AbbVie have conducted MAICs versus R-based CIT, Pola + BR and axi-cel in which all reported variables are adjusted for. Results from these supportive analyses, alongside other supportive MAICs, are presented in Appendix B.2.

Results from all MAICs informing the base case analyses and scenario analyses are presented in the following section.

Table 29: Summary of the MAICs conducted informing the updated base case analyses and scenario analyses

	Epcoritamab population	Comparator	Comparator population adjusted to
Ineligible for, or choose not to receive, intensive therapy			
Updated TE base case analysis A therapy	DLBCL, no prior CAR-T therapy (N=[redacted])	R-based CIT (SCHOLAR-1)	Adjusted to match SCHOLAR-1
Scenario analysis A.1	DLBCL, no prior CAR-T therapy (N=[redacted])	Pola + BR (Sehn *et al.* 3L+)	Adjusted to match Sehn *et al.* 3L+
Scenario analysis A.2[a]	DLBCL (n=139)	Pola + BR (Liebers *et al.* RW data)	Adjusted to match Liebers *et al.* RW data
Scenario analysis A.3[a]	LBCL (n=157)	Pola + BR (Liebers *et al.* RW data)	Adjusted to match Liebers *et al.* RW data
Scenario analysis A.4	DLBCL, no prior CAR-T therapy (N=[redacted])	R-based CIT (SCHOLAR-1)	Fully adjusted to match SCHOLAR-1 (9 reported variables matched, no truncation)
Scenario analysis A.5	DLBLC, no prior ASCT (n=[redacted])	Pola + BR (Northend *et al.* RW data)	Adjusted to match Northend *et al.* RW data
Eligible for intensive therapy			
Updated TE base case analysis B	DLBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Adjusted to match ZUMA-1
Scenario analysis B.1[a]	LBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Adjusted to match ZUMA-1

[a] In contrast with the original CS, scenario analyses A.2, A.3 and B.1 now use the adjusted results of the MAICs, rather than the unadjusted results.
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; MAIC: matching adjusted indirect comparisons; Pola + BR; polatuzumab vedotin with bendamustine plus rituximab: Pola + BR/R: polatuzumab vedotin with rituximab, with or without bendamustine; R: rituximab.

B.1.1. Adjusted baseline characteristics

B.1.1.1 Updated TE base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy population). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the SCHOLAR-1 population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 30. The distribution of weights for this MAIC are presented in Figure 16.

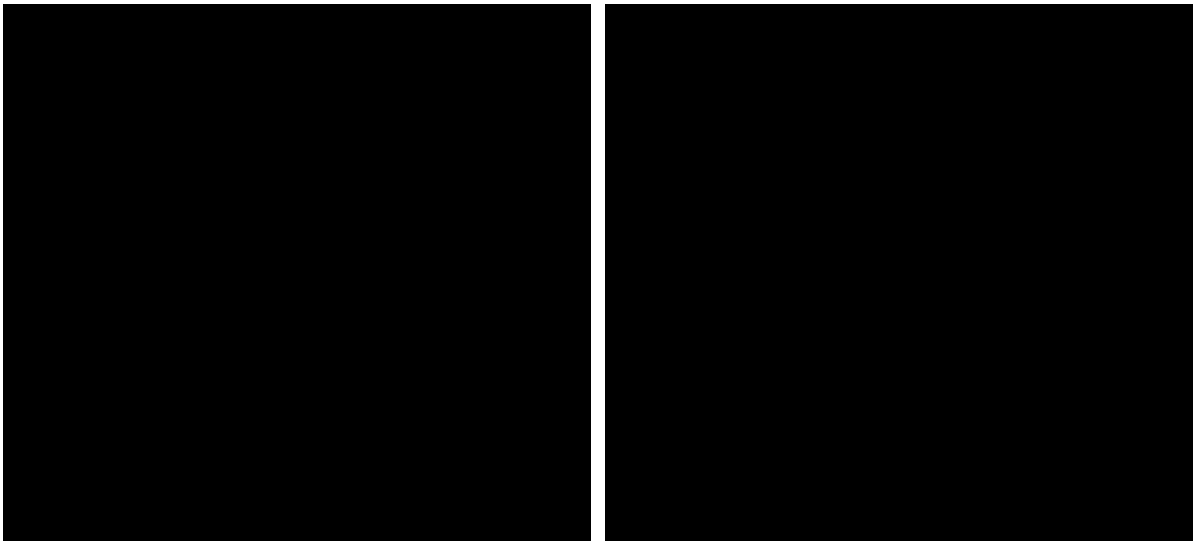
Table 30: Baseline characteristics for updated TE base case analysis A (epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Unadjusted epcoritamab DLBCL, no CAR-T ([redacted])	Adjusted epcoritamab DLBCL, no CAR-T ([redacted])*	SCHOLAR-1 CIT (N=340)
Age			
Median (years)	[redacted]	[redacted]	55.0
≥ 65 years	[redacted]	[redacted]*	**16.5%***
Male	[redacted]	[redacted]*	**67.9%***
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III-IV	[redacted]	[redacted]*	**64.5%**
IPI score ≥3	[redacted]	[redacted]	27.7%
Number of prior lines			
≥3 lines of chemo and ASCT	[redacted]	[redacted]	28.8%
Primary refractory	[redacted]	[redacted]*	**37.1%***
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]*	**50.0%***
Relapse within 12 months of ASCT	[redacted]	[redacted]*	**21.8%***
SCT any time after refractory disease	[redacted]	[redacted]	37.1%

*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, primary refractory, refractory to ≥2 consecutive lines of therapy, and relapse within 12 months of ASCT; weights truncated at 1% and 99%
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; SCT: stem cell transplant.

Figure 16: Adjustment weights distribution for updated base case analysis A (epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

A) Without truncation B) With truncation at 1% & 99%



Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-Cell lymphoma.

B.1.1.2 Scenario analyses: Patients ineligible for, or choose not to receive, intensive therapies

Scenario analysis A.1

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy population). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the decision problem and Sehn *et al.* 3L+ (based on synthetic survival data). An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 31, with the adjusted weight distributions presented in Figure 17.

Table 31: Baseline characteristics for the comparison of epcoritamab versus Pola + BR (epcoritamab DLBCL population adjusted to Sehn *et al.* 3L+)

	Unadjusted epcoritamab (N=[redacted])	Epcoritamab adjusted to Sehn *et al.* 3L+ (N_{eff}=[redacted])	Sehn *et al.* 3L+ (N=29)[b, 4, 5]
Age			
Median (years)	[redacted]	[redacted]	65.0
≥65 years	[redacted]	[redacted]*	**51.7%***
Male	[redacted]	[redacted]*	**72.4%***
ECOG PS 0–1 (vs 2)	[redacted]	[redacted]*	**89.3%***
Disease stage III–IV	[redacted]	[redacted]*	**86.2%***
IPI score ≥3	[redacted]	[redacted]	55.2%
Number of prior lines			
2 lines of prior therapy	[redacted]	[redacted]	37.9%
≥3 lines of chemo and ASCT	[redacted]	[redacted]	62.1%

Refractory to last prior anti-CD20 agents[c]	[redacted]	[redacted]*	**51.7%***
Refractory to last prior anti-lymphoma therapy[d]	[redacted]	[redacted]	93.1%
Prior ASCT	[redacted]	[redacted]*	**34.5%***

*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, refractory to last prior anti-CD20 agents, and prior ASCT; [b] Data from the EUnetHTA submission for Pola + BR were used to inform baseline characteristics of the 3L+ population. Data from Sehn *et al.* (2019) and Sehn *et al.* (2022) were used to estimate 3L+ survival curves and inform best response outcomes. [c] Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date in patients whose last prior regimen contained anti-CD20; [d] Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab; TFL: transformed follicular lymphoma; 3L+: third-line and beyond.

Figure 17: Adjustment weights distribution for scenario analysis A.1 (epcoritamab DLBCL population adjusted to Sehn et al. 3L+; no truncation required)

Abbreviations: 3L+: third line and beyond; DLBCL: diffuse large-B-Cell lymphoma.

Scenario analysis A.2

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL). The unadjusted and adjusted baseline characteristics for the comparison of epcoritamab versus Pola + BR are presented in Table 32, with the adjusted weight distributions presented in Figure 18.

Table 32: Baseline characteristics for the comparison of epcoritamab versus Pola + BR (epcoritamab DLBCL population adjusted to Liebers *et al.* RW data)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Pola + BR, Liebers et al. (N=54)
Age			
Median, years	[redacted]	[redacted]	73.5
≥73.5 years	[redacted]	[redacted]*	**50%***
Male	[redacted]	[redacted]*	**68.5%***
DLBCL	[redacted]	[redacted]	90.7%

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Pola + BR, Liebers et al. (N=54)
Time from diagnosis, years (median)	[redacted]	[redacted]	1.55
Number of prior treatment lines (median)	[redacted]	[redacted]	3
Failed ASCT[b]	[redacted]	[redacted]*	**9.3%***
Prior CAR-T therapy	[redacted]	[redacted]*	**9.3%***
Refractory to last treatment	[redacted]	[redacted]*	**87.0%***

*Values adjusted for: age (≥73.5 years), male, failed ASCT, prior CAR-T therapy and refractory to last treatment.
[b] Failed ASCT was determined as relapse within 12 months of receiving ASCT.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; Pola + BR: polatuzumab vedotin plus rituximab with bendamustine.

Figure 18: Adjustment weights distribution for scenario analysis A.2 (epcoritamab DLBCL population adjusted to match Liebers *et al.* RW data; no truncation required)

Abbreviations: DLBCL: diffuse large-B-Cell lymphoma; RW: real world.

Scenario analysis A.3

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL). The unadjusted and adjusted baseline characteristics for the pairwise comparison of epcoritamab versus Pola + BR are presented in Table 33, with the adjusted weight distributions presented in Figure 19.

Table 33: Baseline characteristics for the comparison of epcoritamab versus Pola + BR (epcoritamab LBCL population adjusted to Liebers *et al.* RW data)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Pola + BR, Liebers et al. (N=54)
Age			
Median, years	[redacted]	[redacted]	73.5
≥73.5 years	[redacted]	[redacted]*	**50.0%***
Male	[redacted]	[redacted]*	**68.5%***
DLBCL	[redacted]	[redacted]*	**90.7%***
Time from diagnosis, years (median)	[redacted]	[redacted]	1.55

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Pola + BR, Liebers et al. (N=54)
Number of prior treatment lines (median)	[redacted]	[redacted]	3
Failed AHCT[a]	[redacted]	[redacted]*	**9.3%***
Prior CAR-T therapy	[redacted]	[redacted]*	**9.3%***
Refractory to last treatment	[redacted]	[redacted]*	**87.0%***

*Values adjusted for: age (≥73.5 years), male, DLBCL, failed AHCT, prior CAR-T therapy and refractory to last treatment. [a] Failed AHCT was determined as relapse within 12 months of receiving AHCT.
Abbreviations: AHCT: autologous hematopoietic cell transplant; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; Pola + BR: polatuzumab vedotin plus rituximab with bendamustine.

Figure 19: Adjustment weights distribution for scenario analysis A.3 (epcoritamab LBCL population adjusted to Liebers et al. RW data; no truncation required)

Abbreviations: LBCL: large-B-Cell lymphoma; RW: real world.

Scenario analysis A.4

In response to the EAG's request, AbbVie have conducted an additional MAIC versus R-based CIT in which nine reported variables (all reported variables excluding SCT after refractory disease due to the model not converging) are adjusted for; the additional baseline characteristics adjusted for compared with the updated base case analysis A are IPI score ≥3 and ≥3 lines of chemotherapy and ASCT.

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy population) and adjusted to match the SCHOLAR-1 population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 34.

Table 34: Baseline characteristics for scenario analysis A.4 (nine reported variables matched, no truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Unadjusted epcoritamab DLBCL, no CAR-T ([redacted])	Adjusted epcoritamab DLBCL, no CAR-T ([redacted])	SCHOLAR-1 CIT (N=340)
Age			
Median (years)	[redacted]	[redacted]	55.0
≥ 65 years	[redacted]	[redacted]*	**16.5%***
Male	[redacted]	[redacted]*	**67.9%***
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III-IV	[redacted]	[redacted]*	**64.5%***
IPI score ≥3	[redacted]	[redacted]*	**27.7%***
Number of prior lines			
≥3 lines of chemo and ASCT	[redacted]	[redacted]*	**28.8%***
Primary refractory	[redacted]	[redacted]*	**37.1%***
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]*	**50.0%***
Relapse within 12 months of ASCT	[redacted]	[redacted]*	**21.8%***
SCT any time after refractory disease[a]	[redacted]	[redacted]	37.1%

*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, IPI score ≥3, ≥3 lines of chemo and ASCT, primary refractory, refractory to ≥2 consecutive lines of therapy, and relapse within 12 months of ASCT; weights truncated at 1% and 99%. [a] Model does not converge if SCT any time after refractory disease is also adjusted for (without truncation of weights).
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; SCT: stem cell transplant

Figure 20: Adjustment weights distribution for scenario analysis A.4 (epcoritamab LBCL population adjusted to SCHOLAR-1; nine reported variables adjusted for; no truncation required)

Abbreviations: LBCL: large-B-Cell lymphoma.

Scenario analysis A.5

AbbVie have conducted an additional MAIC in which the epcoritamab population is adjusted to match the Pola + BR population from Northend *et al.* 3L+ RW data. UK clinical experts stated that data from Northend *et al.* are more representative of outcomes associated with Pola + BR in UK clinical practice following two prior systemic therapies.

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior ASCT population) and adjusted to match the Northend *et al.* 3L+ population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 37.

In this MAIC, 11 reported variables were adjusted for, with distribution weights truncated at 2.5% and 97.5%. It was not feasible to adjust for ECOG performance score due to the difference between the populations. In order to address this, IPI score was adjusted for in order to indirectly address the imbalance in ECOG. Whilst a greater proportion of patients in the Northend *et al.* 3L+ population have a worse ECOG performance score, IPI score is well-balanced between the populations. This indicates that the balance between the populations for the other components of IPI score (such as disease stage, age or normal/high LDH) are likely to bias against epcoritamab. UK clinical experts confirmed that whilst the Northend *et al.* 3L+ population shows worse ECOG performance status, the approach adopted should address the bias introduced by this, and the epcoritamab population has an increased proportion of refractory patients which is also associated with more challenging to treat cohort.

Additional exploratory analyses were conducted in which number of prior lines of treatment was also matched and no truncation was included (Appendix B.2).

Table 35: Baseline characteristics for scenario analysis A.5 (11 reported variables matched, with truncation; epcoritamab DLBCL, no prior ASCT population adjusted to Northend)

	Unadjusted epcoritamab DLBCL, no ASCT ([redacted])	Adjusted epcoritamab DLBCL, no ASCT ([redacted])	Pola + BR, based on Northend *et al.* 3L+ (N=[redacted])
Age			
Median Age	[redacted]	[redacted]	[redacted]
Age ≥ 73	[redacted]	[redacted]*	[redacted]*
Male	[redacted]	[redacted]*	[redacted]*
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
Stage 3	[redacted]	[redacted]*	[redacted]*
Stage 4	[redacted]	[redacted]*	[redacted]*
IPI=3	[redacted]	[redacted]*	[redacted]*
IPI >3	[redacted]	[redacted]*	[redacted]*
Normal LDH at baseline	[redacted]	[redacted]	[redacted]
High LDH at baseline	[redacted]	[redacted]	[redacted]
Extranodal involvement at baseline	[redacted]	[redacted]	[redacted]
Bulky disease[a]	[redacted]	[redacted]*	[redacted]*
2 Prior treatment lines	[redacted]	[redacted]	[redacted]
3 Prior treatment lines	[redacted]	[redacted]	[redacted]
>3 Prior treatment lines	[redacted]	[redacted]	[redacted]
Prior CAR-T	[redacted]	[redacted]*	[redacted]*
Refractory to R-CHOP / Primary refractory	[redacted]	[redacted]*	[redacted]*
Refractoriness to any prior treatment	[redacted]	[redacted]*	[redacted]*
Refractoriness to last treatment	[redacted]	[redacted]*	[redacted]*

*Values adjusted for: age (≥73 years), male, disease stage, IPI score (3), IPI Score (>3) Bulky disease, prior CAR-T, refractory to R-CHOP (Northend Pola-BR) / Primary refractory (EPCORE), refractory to any prior treatment, refractory to last treatment; [a]Due to differences in experimental design, bulky disease is defined as a tumour load >7 cm in EPCORE and >=7.5 cm in Northend 3L+.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor therapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; R-CHOP; Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.

Figure 21: Adjustment weights distribution for fully adjusted MAIC versus Northend (11 reported variables matched)

Without truncation

With truncation at 2.5% & 97.5%

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large-B-Cell lymphoma.

B.1.1.3 Updated TE base case analysis B: patients eligible for intensive therapies

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T, eligible for CAR-T). The unadjusted and adjusted baseline characteristics for the comparison of epcoritamab versus axi-cel are presented in Table 36, with the adjusted weight distributions presented in Figure 22.

Table 36: Baseline characteristics for the comparison of epcoritamab versus axi-cel (epcoritamab DLBCL, CAR-T eligible population adjusted to ZUMA-1)

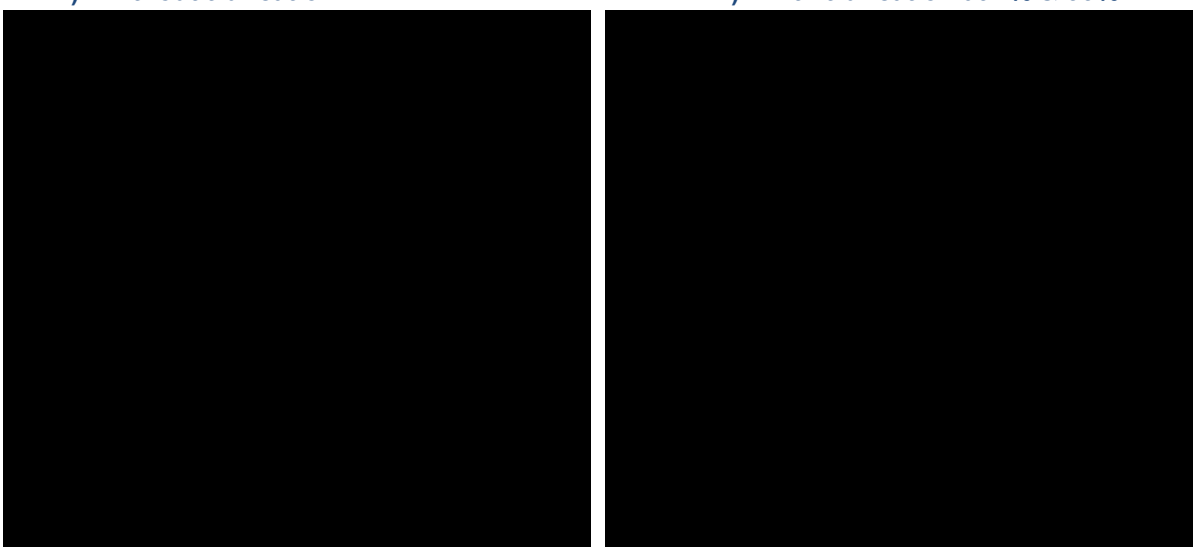
	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Axi-cel, ZUMA-1 (N=101)
Age			
Median, years	[redacted]	[redacted]	58.0
≥65 years	[redacted]	[redacted]	**23.8%***
Male	[redacted]	[redacted]	**67.3%***
DLBCL (including TFL)	[redacted]	[redacted]	92.1%
ECOG PS 0 or 1 (versus 2)	[redacted]	[redacted]	**100.0%***
Disease stage III–IV	[redacted]	[redacted]	**85.1%***
IPI score ≥3	[redacted]	[redacted]	45.5%
Number of prior lines of treatment			
≥3 prior lines of treatment	[redacted]	[redacted]	69.3%
History of primary refractory disease	[redacted]	[redacted]	**25.7%***
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]	**53.5%***

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Axi-cel, ZUMA-1 (N=101)
Refractory to second-line or subsequent therapy	[redacted]	[redacted]	76.2%
Relapse after ASCT within 12 months	[redacted]	[redacted]	**20.8%***

*Values adjusted for: age (≥65 years), male, DLBCL, ECOG PS (0 or 1), disease stage III–IV, history of primary refractory disease, history of resistance to two consecutive lines of therapy and relapse after autoSCT within 12 months.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; TFL: transformed follicular lymphoma.

Figure 22: Adjustment weights distribution for updated base case analysis B (epcoritamab DLBCL, CAR-T eligible population adjusted to match axi-cel)

A) Without truncation **B) With truncation at 1% & 99%**



Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large-B-Cell lymphoma.

B.1.1.4 Scenario analyses: Patients eligible for intensive therapies

Scenario analysis B.1

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, no prior CAR-T therapy, eligible for CAR-T therapy population). An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the axi-cel population included in the analysis is presented in Table 37, with the adjustment weights distributions presented in Figure 23.

Table 37: Baseline characteristics for scenario analysis B.2 (epcoritamab LBCL, CAR-T eligible population adjusted to ZUMA-1)

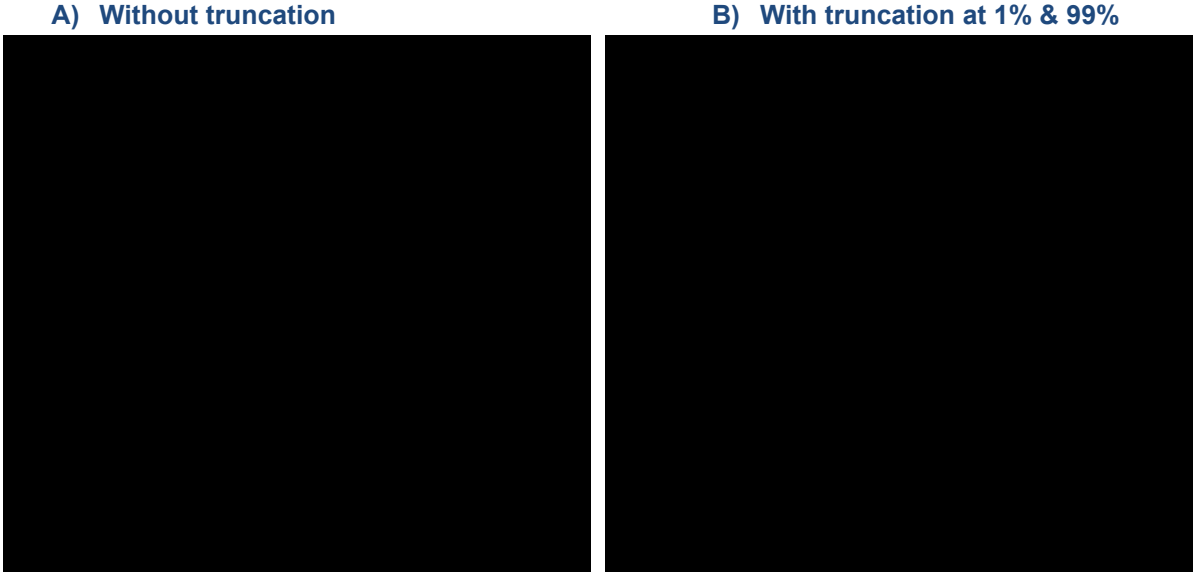
	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])*	Axi-cel, ZUMA-1 (N=101)
Age			
Median, years	[redacted]	[redacted]	58.0

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])*	Axi-cel, ZUMA-1 (N=101)
≥65 years	[redacted]	[redacted]*	**23.8%***
Male	[redacted]	[redacted]*	**67.3%***
DLBCL (including TFL)	[redacted]	[redacted]*	**92.1%***
ECOG PS 0 or 1 (versus 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III–IV	[redacted]	[redacted]*	**85.1%***
IPI score ≥3	[redacted]	[redacted]	45.5%
Number of prior lines of treatment			
≥3 prior lines of treatment	[redacted]	[redacted]	69.3%
History of primary refractory disease	[redacted]	[redacted]*	**25.7%***
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]*	**53.5%***
Refractory to second-line or subsequent therapy	[redacted]	[redacted]	76.2%
Relapse after ASCT within 12 months	[redacted]	[redacted]*	**20.8%***

*Values adjusted for: age (≥65 years), male, DLBCL (including TFL), ECOG PS, disease stage, history of primary refractory disease, history of resistance to two consecutive lines of therapy and relapse after autoSCT within 12 months.

Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; TFL: transformed follicular lymphoma.

Figure 23: Adjustment weights distribution for scenario analysis B.2 (epcoritamab LBCL, CAR-T eligible population adjusted to match axi-cel)



Abbreviations: LBCL: large-B-Cell lymphoma.

B.1.2. Efficacy results

B.1.2.1 Updated TE base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

Updated TE base case analysis A (epcoritamab versus R-based CIT): Patients ineligible for, or choose not to receive, intensive therapy

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 38. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from SCHOLAR-1 are presented in Figure 24. No PFS KM data were available from SCHOLAR-1.

As presented in Table 38, the unadjusted OS HR for epcoritamab versus R-based CIT is [redacted]. Following adjustment, the adjusted OS HR for epcoritamab versus R-based CIT is [redacted], demonstrating that epcoritamab provides a [redacted] treatment benefit versus R-based CIT.

Table 38: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; DLBCL: diffuse large B-Cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival; R: rituximab.

Figure 24: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1

Abbreviations: KM: Kaplan–Meier; OS: overall survival; R: rituximab.

B.1.2.2 Scenario analyses: Patients ineligible for, or choose not to receive, intensive therapies

Scenario analysis A.1

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 39, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 25 and Figure 26, for OS and PFS respectively.

The adjusted OS and PFS HRs for epcoritamab versus Pola + BR up to [redacted] are [redacted] and [redacted], respectively. After [redacted] the adjusted OS and PFS HRs are [redacted] and [redacted] This demonstrates that prior to [redacted], Pola + BR is associated with [redacted] in terms of OS and PFS versus epcoritamab (but this is [redacted]); after 7.5, there is [redacted] in favour of epcoritamab versus Pola + BR (but this difference is [redacted]).

There was [redacted] in CR rate and ORR between epcoritamab and Pola + BR. However, as discussed, it is clear from clinical expert feedback that the Sehn *et al.* trial overestimates efficacy for the cohort with two prior systemic therapies.

Table 39: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, no prior CAR-T) versus Pola + BR (Sehn *et al.* 3L+)

	Epcoritamab DLBCL, no prior CAR-T unadjusted (N=[redacted])	Epcoritamab DLBCL, no prior CAR-T adjusted (N_{eff}=[redacted])	
		Up to[redacted]	After [redacted]
Survival, HR (95% CI)[a]			
OS	NA	[redacted]	[redacted]
PFS	NA	[redacted]	[redacted]

	Epcoritamab DLBCL, no prior CAR-T unadjusted (N=[redacted])	Epcoritamab DLBCL, no prior CAR-T adjusted (N_{eff}=[redacted])	
		Up to[redacted]	After [redacted]
Response rates, %			
CR (epcoritamab vs Pola + BR)	[redacted]	[redacted]	
Difference, % (95% CI)	[redacted]	[redacted]	
ORR (epcoritamab vs Pola + BR)	[redacted]	[redacted]	
Difference, % (95% CI)	[redacted]	[redacted]	

[a] Unadjusted piecewise HRs for OS and PFS were not generated.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 25: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 26: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Scenario analysis A.2

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 40, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 27 and Figure 28, for OS and PFS respectively.

Importantly, following adjustment, the results demonstrate that there is a [redacted] of epcoritamab versus Pola + BR, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted] and PFS (unadjusted HR [redacted] adjusted HR: [redacted])

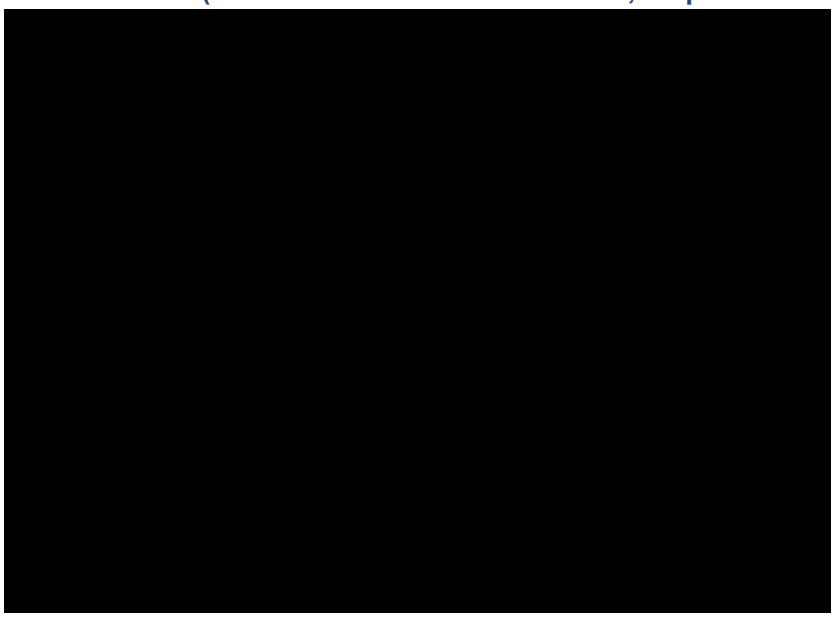
Notably, there was also a [redacted] in CR rate and ORR between epcoritamab and Pola + BR.

Table 40: Unadjusted and adjusted outcomes for epcoritamab (DLBCL) versus Pola + BR (Liebers *et al.* RW data)

	Epcoritamab DLBCL unadjusted (N=[redacted])	Epcoritamab DLBCL adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs Pola + BR)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs Pola + BR)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 27: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – DLBCL, no prior CAR-T epcoritamab population



Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; epco: epcoritamab; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; RW: real-world.

Figure 28: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – DLBCL, no prior CAR-T epcoritamab population

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; epco: epcoritamab; KM: Kaplan–Meier; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; RW: real-world.

Scenario analysis A.3

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 41, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 29 and Figure 30, for OS and PFS respectively.

Importantly, following adjustment, the results demonstrate that there is a [redacted] of epcoritamab versus Pola + BR, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted]; adjusted HR: [redacted]).

Notably, there was [redacted] in CR rate and ORR between epcoritamab and Pola + BR.

Table 41: Unadjusted and adjusted outcomes for epcoritamab (LBCL) versus Pola + BR (Liebers *et al.* RW data)

	Epcoritamab LBCL unadjusted (N=[redacted])	Epcoritamab LBCL adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs Pola + BR)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs Pola + BR)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CR: complete response; HR: hazard ratio; LBCL: large B-cell lymphoma; PFS: progression-free survival; ORR: overall response rate; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 29: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – LBCL, no prior CAR-T epcoritamab population)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab: RW: real-world.

Figure 30: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Liebers *et al.* RW data – LBCL, no prior CAR-T epcoritamab population

Abbreviations: CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; RW: real-world.

Scenario analysis A.4

A summary of the unadjusted and adjusted (nine reported variables adjusted for) outcomes for epcoritamab versus R-based CIT is presented in Table 42. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from SCHOLAR-1 are presented in Figure 31. No PFS KM data were available from SCHOLAR-1.

As presented in Table 42, the unadjusted OS HR for epcoritamab versus R-based CIT is [redacted]. Following adjustment, the adjusted OS HR for epcoritamab versus R-

based CIT is [redacted], demonstrating that epcoritamab provides a [redacted] treatment benefit versus R-based CIT.

Table 42: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT (SCHOLAR-1; nine reported variables adjusted for)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted[a] (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

[a] Scenario analysis in which all reported variables are adjusted for, compared to the base case, the additional baseline characteristics adjusted for include IPI score ≥3 and ≥3 lines of chemotherapy and ASCT.
Abbreviations: CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival; R: rituximab.

Figure 31: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population fully adjusted to SCHOLAR-1 (9 reported variables, no truncation)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; OS: overall survival; R: rituximab.

Scenario analysis A.5

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 43. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for Pola + BR from Northend *et al.* 3L+ are presented in Figure 32 and the unadjusted and

adjusted PFS KM curves for epcoritamab and the PFS KM for Pola + BR from Northend *et al.* 3L+ are presented in Figure 33.

As presented in Table 43, the unadjusted OS HR for epcoritamab versus Pola + BR [redacted] Following adjustment, the adjusted OS HR for epcoritamab versus Pola + BR is [redacted]. The unadjusted PFS HR for epcoritamab versus Pola + BR is [redacted]. Following adjustment, the adjusted PFS HR for epcoritamab versus Pola + BR is [redacted] These results demonstrate that, after adjustment, epcoritamab provides a [redacted] treatment benefit versus Pola + BR in terms of both OS and PFS.

Table 43: Unadjusted and adjusted outcomes for epcoritamab versus Pola + BR (Northend *et al.* 3L+; 11 reported variables adjusted for, with truncation)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted[a] (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; OS: overall survival.

Figure 32: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no ASCT epcoritamab population adjusted to Northend *et al* 3L+ (11 reported variables, with truncation)

Abbreviations: ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 33: Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no ASCT epcoritamab population adjusted to Northend *et al.* 3L+ (11 reported variables, with truncation)

Abbreviations: ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival; Pola-BR: polatuzumab vedotin with bendamustine plus rituximab.

B.1.2.3 Updated TE base case analysis B: patients eligible for intensive therapies

Updated TE base case analysis B (epcoritamab versus axi-cel): Patients eligible for intensive therapy

A summary of the unadjusted and adjusted outcomes for epcoritamab versus axi-cel is presented in Table 44. Alongside the unadjusted and adjusted KM curves for epcoritamab and axi-cel, in Figure 34 and Figure 35, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is a numerical benefit of epcoritamab versus axi-cel, in terms of both OS (unadjusted HR: [redacted] adjusted HR: ([redacted] and PFS (unadjusted HR: [redacted]; adjusted HR: ([redacted] However, this difference is [redacted].

There was [redacted] in CR rate and ORR between epcoritamab and axi-cel.

Table 44: Unadjusted and adjusted outcomes for epcoritamab (DLBCL, CAR-T eligible) versus axi-cel (ZUMA-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Response rates, %		
CR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

Figure 34: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival.

Figure 35: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival.

B.1.2.4 Scenario analyses: Patients eligible for intensive therapies

Scenario analysis B.1

A summary of the unadjusted and adjusted outcomes for epcoritamab versus axi-cel is presented in Table 45, alongside the unadjusted and adjusted KM curves for epcoritamab and axi-cel, in Figure 36 and Figure 37, for OS and PFS respectively.

Importantly, following adjustment, the results indicate that there is a numerical benefit of epcoritamab versus axi-cel, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted] and PFS (unadjusted HR: [redacted]; adjusted HR: [redacted]. However, this difference is [redacted].

Notably, there was [redacted] in CR rate and ORR between epcoritamab and axi-cel. These results indicate the efficacy of epcoritamab may be comparable to that of axi-cel after adjustment for eight reported variables; this was supported by UK clinical experts.

Table 45: Unadjusted and adjusted outcomes for epcoritamab (LBCL, CAR-T eligible) versus axi-cel (ZUMA-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; LBCL: large B-cell lymphoma; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

Figure 36: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; PFS: progression-free survival.

Figure 37: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; PFS: progression-free survival.

B.2 Additional supportive MAICs

In addition to the base case and scenario analyses presented in Appendix B.1, a number of additional supportive MAICs were conducted. Note that the output of these MAICs have not been incorporated into the cost-effectiveness model.

A summary of the additional supportive MAICs conducted is presented in Table 46, including the epcoritamab populations used in the analyses. For all MAICs conducted and presented as part of Technical Engagement, the epcoritamab efficacy data are based on the [redacted] data cut.

Table 46: Summary of additional supportive MAICs conducted

Epcoritamab population	Epcoritamab versus comparator	Comparator population adjusted to
Ineligible for, or choose not to receive, intensive therapy		

DLBCL, no prior CAR-T therapy (N=[redacted])	R-based CIT (SCHOLAR-1)	Fully adjusted to match SCHOLAR-1 (all reported variables matched, with truncation)
DLBCL, no prior CAR-T therapy (N=[redacted])	Pola + BR (Sehn *et al.* 3L+)	Fully adjusted to match Sehn *et al.* 3L+ (10 reported variables matched, with truncation)
LBCL, no prior CAR-T therapy (N=[redacted])	R-based CIT (SCHOLAR-1)	Adjusted to match SCHOLAR-1 (base case variables [n=7] adjusted for)
DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T (N=[redacted])	R-based CIT (Tomas *et al.*)	Adjusted to match Tomas *et al.* (5 reported variables matched, with truncation)
LBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T (N=[redacted])	R-based CIT (Tomas *et al.*)	Adjusted to match Tomas *et al.* (5 reported variables matched, with truncation)
DLBCL, prior CAR-T therapy, epcoritamab any-line after CAR-T (N=[redacted])	R-based CIT (Tomas *et al.*)	Adjusted to match Tomas *et al.* (5 reported variables matched, with truncation)
LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T (N=[redacted])	R-based CIT (Tomas *et al.*)	Adjusted to match Tomas *et al.* (5 reported variables matched, with truncation)
DLBCL, no prior ASCT (N=[redacted])	Pola + BR (Northend *et al.* 3L+)	Adjusted to match Northend *et al.* 3L+ (11 reported variables matched, without truncation)
DLBCL, no prior ASCT (N=[redacted])	Pola + BR (Northend *et al.* 3L+)	Adjusted to match Northend *et al.* 3L+ (13 reported variables matched, with truncation)
DLBCL, no prior ASCT (N=[redacted])	Pola + BR (Northend *et al.* 3L+)	Adjusted to match Northend *et al.* 3L+ (13 reported variables matched, without truncation)
Eligible for intensive therapy		
DLBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Fully adjusted to match ZUMA-1 (all reported variables matched; without truncation)
LBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1)	Fully adjusted to match ZUMA-1 (all reported variables matched without truncation)

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; MAIC: matching adjusted indirect comparisons; Pola + BR; polatuzumab vedotin with bendamustine plus rituximab R: rituximab.

B.2.1. Adjusted baseline characteristics

B.2.1.1 Patients ineligible for, or choose not to receive, intensive therapies

Patients ineligible for, or choose not to receive, intensive therapies: Fully adjusted versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab versus R-based CIT)

An additional analysis was conducted whereby all reported variables were adjusted for and truncation of weights was included, as the model did not converge if truncation of weights was not included.

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy population). An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 47.

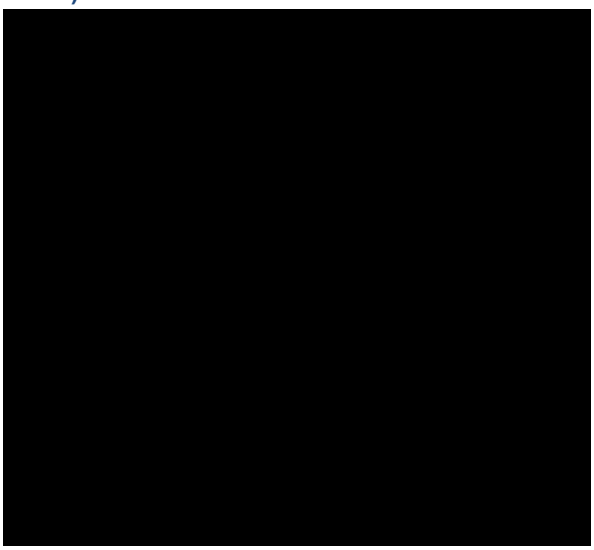
Table 47: Baseline characteristics for fully adjusted MAIC versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Unadjusted epcoritamab DLBCL, no CAR-T ([redacted])	Adjusted epcoritamab DLBCL, no CAR-T ([redacted])*	SCHOLAR-1 CIT (N=340)
Age			
Median (years)	[redacted]	[redacted]	55.0
≥65 years	[redacted]	[redacted]*	**16.5%***
Male	[redacted]	[redacted]*	**67.9%***
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III-IV	[redacted]	[redacted]*	**64.5%***
IPI score ≥3	[redacted]	[redacted]*	**27.7%***
Number of prior lines			
≥3 lines of chemo and ASCT	[redacted]	[redacted]*	**28.8%***
Primary refractory	[redacted]	[redacted]*	**37.1%***
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]*	**50.0%***
Relapse within 12 months of ASCT	[redacted]	[redacted]*	**21.8%***
SCT any time after refractory disease[a]	[redacted]	[redacted]*	**37.1%***

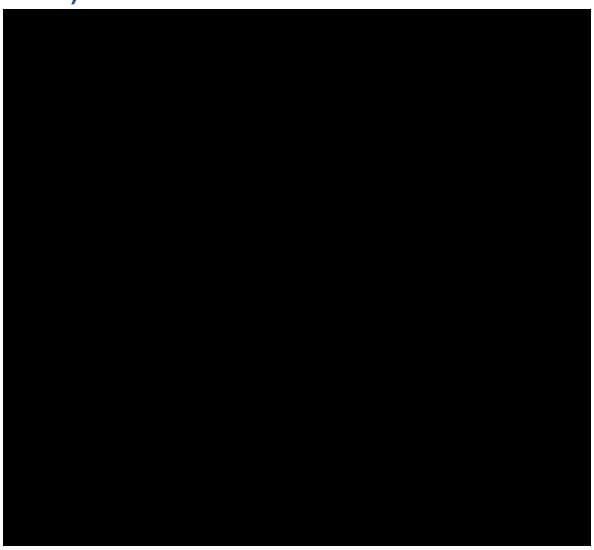
*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, IPI score ≥3, ≥3 lines of chemo and ASCT, primary refractory, refractory to ≥2 consecutive lines of therapy, relapse within 12 months of ASCT and SCT any time after refractory disease; weights truncated at 1% and 99%. [a] Model does not converge if SCT any time after refractory disease is also adjusted for (without truncation of weights).
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; MAIC: matching indirect treatment comparison; SCT: stem cell transplant

Figure 38: Adjustment weights distribution for fully adjusted MAIC versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

A) Without truncation



B) With truncation at 1% & 99%



Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

Patients ineligible for, or choose not to receive, intensive therapies: Fully adjusted to Sehn et al. 3L+ (10 reported variables matched, with truncation; epcoritamab versus Pola + BR)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T therapy population). As outlined above, EPCORE™ NHL-1 population was adjusted to match the synthetically generated Sehn *et al.* 3L+ survival data (described in Section B.2.8 of the CS) to match the decision problem. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 48.

Table 48: Baseline characteristics for fully adjusted MAIC versus Pola + BR (10 reported variables matched, with truncation; epcoritamab DLBCL population fully adjusted to Sehn et al. 3L+)

	Unadjusted epcoritamab (N=[redacted])	Epcoritamab adjusted to Sehn *et al.* 3L+ (N_{eff}=[redacted])	Sehn *et al.* 3L+ (N=29)[b, 4, 5]
Age			
Median (years)	[redacted]	[redacted]	65.0
≥65 years	[redacted]	[redacted]*	**51.7%***
Male	[redacted]	[redacted]*	**72.4%***
ECOG PS 0–1 (vs 2)	[redacted]	[redacted]*	**89.3%***
Disease stage III–IV	[redacted]	[redacted]*	**86.2%***
IPI score ≥3	[redacted]	[redacted]*	**55.2%***
Number of prior lines			
2 lines of prior therapy	[redacted]	[redacted]	37.9%

≥3 lines of chemo and ASCT	[redacted]	[redacted]*	**62.1%***
Refractory to last prior anti-CD20 agents[c]	[redacted]	[redacted]*	**51.7%***
Refractory to last prior anti-lymphoma therapy[d]	[redacted]	[redacted]*	**93.1%***
Prior ASCT	[redacted]	[redacted]*	**34.5%***

*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, IPI score ≥3, ≥3 lines of chemo and ASCT, refractory to last prior anti-CD20 agents, refractory to last prior anti-lymphoma therapy and prior ASCT; [b] Data from the EUnetHTA submission for Pola + BR were used to inform baseline characteristics of the 3L+ population. Data from Sehn *et al.* (2019) and Sehn *et al.* (2022) were used to estimate 3L+ survival curves and inform best response outcomes. [c] Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date in patients whose last prior regimen contained anti-CD20; [d] Definition based on Sehn *et al.* (2019): no response or progression or relapse within six months of last anti-lymphoma therapy end date.
Abbreviations: ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; MAIC: matching indirect treatment comparison; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab; SCT: stem cell transplant; 3L+: third-line and beyond.

Figure 39: Adjustment weights distribution for fully adjusted MAIC versus Pola + BR (10 reported variables matched, with truncation; epcoritamab DLBCL population fully adjusted to Sehn et al. 3L+)

A) Without truncation **B) With truncation at 1% & 99%**

[redacted]

Abbreviations: DLBCL: diffuse large-B-Cell lymphoma; MAIC: matching indirect treatment comparison; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted versus SCHOLAR-1 (base case variables matched, with truncation; epcoritamab versus R-based CIT)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, no prior CAR-T therapy population). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the SCHOLAR-1 population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 49.

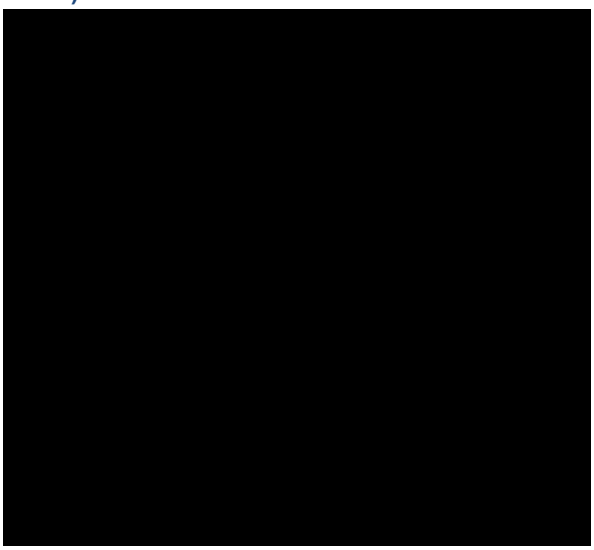
Table 49: Baseline characteristics for MAIC versus SCHOLAR-1 (base case variables matched; epcoritamab LBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Unadjusted epcoritamab LBCL, no CAR-T ([redacted])	Adjusted epcoritamab LBCL, no CAR-T ([redacted])	SCHOLAR-1 CIT (N=340)
Age			
Median (years)	[redacted]	[redacted]	55.0
≥ 65 years	[redacted]	[redacted]*	**16.5%***
Male	[redacted]	[redacted]*	**67.9%***
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III-IV	[redacted]	[redacted]*	**64.5%***
IPI score ≥3	[redacted]	[redacted]	27.7%
Number of prior lines			
≥3 lines of chemo and ASCT	[redacted]	[redacted]	28.8%
Primary refractory	[redacted]	[redacted]*	**37.1%***
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]*	**50.0%***
Relapse within 12 months of ASCT	[redacted]	[redacted]*	**21.8%***
SCT any time after refractory disease[a]	[redacted]	[redacted]	37.1%

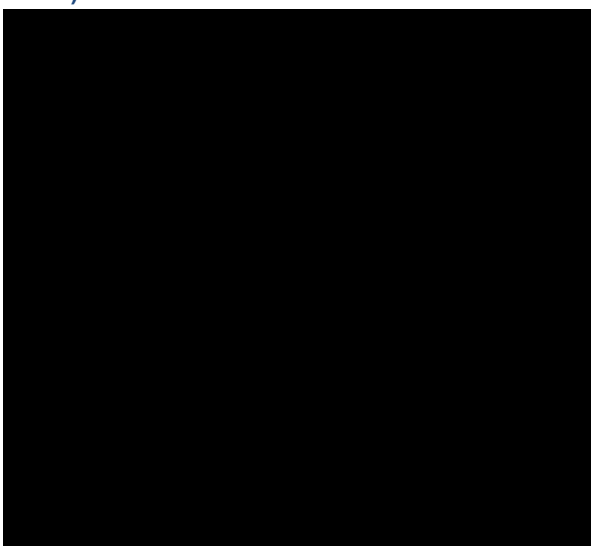
*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, primary refractory, refractory to ≥2 consecutive lines of therapy and relapse within 12 months of ASCT; weights truncated at 1% and 99%.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; MAIC: matching adjusted indirect treatment comparison; SCT: stem cell transplant

Figure 40: Adjustment weights distribution for MAIC versus SCHOLAR-1 (base case variables matched; epcoritamab LBCL, no prior CAR-T population adjusted to SCHOLAR-1)

A) Without truncation



B) With truncation at 1% & 99%



Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Tomas *et al*. population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 50.

Table 50: Baseline characteristics for fully adjusted MAIC versus R-based CIT (5 reported variables matched; DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	R-based CIT (N=17)
Age			
Median (years)	[redacted]	[redacted]	60 (55, 66) *
Age ≤ 65	[redacted]	[redacted]	12 (70.59%)
Age > 65	[redacted]	[redacted]	5 (29.41%)*
Number of prior lines of CAR-T			
<3	[redacted]	[redacted]	3 (17.65%)
≥3 lines	[redacted]	[redacted]	14 (82.35%)*
Primary refractory			
No	[redacted]	[redacted]	7 (41.18%)*
Yes	[redacted]	[redacted]	10 (58.82%)
Disease stage Ann harbor			

Stage I	[redacted]	[redacted]	2 (11.76%)
Stage II–IV	[redacted]	[redacted]	15 (88.24%)*
Prior transplant ASCT			
No	[redacted]	[redacted]	13 (76.47%)
Yes	[redacted]	[redacted]	4 (23.53%)*
LBCL origin			
De novo	[redacted]	[redacted]	14 (82.35%)
Transformed from low-grade	[redacted]	[redacted]	3 (17.65%)
Unknown	[redacted]	[redacted]	0 (0.00%)
NA	[redacted]	[redacted]	NR
Cell origin			
Germinal center B cells	[redacted]	[redacted]	5 (29.41%)
Non-Germinal center B cells	[redacted]	[redacted]	10 (58.82%)
Unknown	[redacted]	[redacted]	2 (11.76%)
Activated B-cell	[redacted]	[redacted]	NR
Not done	[redacted]	[redacted]	NR
N/A	[redacted]	[redacted]	NR
CAR-T received			
Axi-cel	[redacted]	[redacted]	45 (27 to 138)
Liso-cel	[redacted]	[redacted]	45 (27 to 138)
POC CAR-T	[redacted]	[redacted]	45 (27 to 138)
Tisa-cel	[redacted]	[redacted]	45 (27 to 138)
Median days from CAR-T to CIT/epcoritamab	[redacted]	[redacted]	45 (27, 138)

*Values adjusted for: median age, age (≥65 years), disease stage Ann harbor Stage II–IV, ≥3 lines of CAR-T, primary refractory, prior ASCT; weights truncated at 1% and 99%.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; MAIC: matching adjusted indirect treatment comparison; NR: not reported; liso-cel: lisocabtagene maraleucel; LBCL:large B-cell lymphoma; POC: point-of-care; R: rituximab; tisa-cel: tisagenlecleucel.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (LBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Tomas *et al*. population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 51.

Table 51: Baseline characteristics for fully adjusted MAIC versus R-based CIT (5 reported variables matched; LBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	R-based CIT (N=17)
Age			

Median (years)	[redacted]	[redacted]	60 (55, 66) *
Age ≤ 65	[redacted]	[redacted]	12 (70.59%)
Age > 65	[redacted]	[redacted]	5 (29.41%)*
Number of prior lines of CAR-T			
<3	[redacted]	[redacted]	3 (17.65%)
≥3 lines	[redacted]	[redacted]	14 (82.35%)*
Primary refractory			
No	[redacted]	[redacted]	7 (41.18%)
Yes	[redacted]	[redacted]	10 (58.82%)*
Disease stage Ann harbor			
Stage I	[redacted]	[redacted]	2 (11.76%)
Stage II–IV	[redacted]	[redacted]	15 (88.24%)*
Prior transplant ASCT			
No	[redacted]	[redacted]	13 (76.47%)
Yes	[redacted]	[redacted]	4 (23.53%)*
LBCL origin			
De novo	[redacted]	[redacted]	14 (82.35%)
Transformed from low-grade	[redacted]	[redacted]	3 (17.65%)
Unknown	[redacted]	[redacted]	0 (0.00%)
NA	[redacted]	[redacted]	NR
Cell origin			
Germinal center B cells	[redacted]	[redacted]	5 (29.41%)
Non-Germinal center B cells	[redacted]	[redacted]	10 (58.82%)
Unknown	[redacted]	[redacted]	2 (11.76%)
Activated B-cell	[redacted]	[redacted]	NR
Not done	[redacted]	[redacted]	NR
N/A	[redacted]	[redacted]	NR
CAR-T received			
Axi-cel	[redacted]	[redacted]	45 (27 to 138)
Liso-cel	[redacted]	[redacted]	45 (27 to 138)
POC CAR-T	[redacted]	[redacted]	45 (27 to 138)
Tisa-cel	[redacted]	[redacted]	45 (27 to 138)
Median days from CAR-T to CIT/epcoritamab	[redacted]	[redacted]	45 (27, 138)

*Values adjusted for: median age, age (≥65 years), disease stage Ann harbor Stage II–IV, ≥3 lines of CAR-T, primary refractory, prior ASCT; weights truncated at 1% and 99%.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; MAIC: matching adjusted indirect treatment comparison; NR: not reported; liso-cel: lisocabtagene maraleucel; LBCL:large B-cell lymphoma; POC: point-of-care; R: rituximab; tisa-cel: tisagenlecleucel.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Tomas *et al*. population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 52.

Table 52: Baseline characteristics for fully adjusted MAIC versus R-based CIT (all variables matched; DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	R-based CIT (N=17)
Age			
Median (years)	[redacted]	[redacted]	60 (55, 66) *
Age ≤ 65	[redacted]	[redacted]	12 (70.59%)
Age > 65	[redacted]	[redacted]	5 (29.41%)*
Number of prior lines of CAR-T			
<3	[redacted]	[redacted]	3 (17.65%)
≥3 lines	[redacted]	[redacted]	14 (82.35%)*
Primary refractory			
No	[redacted]	[redacted]	7 (41.18%)
Yes	[redacted]	[redacted]	10 (58.82%)*
Disease stage Ann harbor			
Stage I	[redacted]	[redacted]	2 (11.76%)
Stage II–IV	[redacted]	[redacted]	15 (88.24%)*
Prior transplant ASCT			
No	[redacted]	[redacted]	13 (76.47%)
Yes	[redacted]	[redacted]	4 (23.53%)*
LBCL origin			
De novo	[redacted]	[redacted]	14 (82.35%)
Transformed from low-grade	[redacted]	[redacted]	3 (17.65%)
Unknown	[redacted]	[redacted]	0 (0.00%)
NA	[redacted]	[redacted]	NR
Cell origin			
Germinal center B cells	[redacted]	[redacted]	5 (29.41%)
Non-Germinal center B cells	[redacted]	[redacted]	10 (58.82%)
Unknown	[redacted]	[redacted]	2 (11.76%)
Activated B-cell	[redacted]	[redacted]	NR
Not done	[redacted]	[redacted]	NR
N/A	[redacted]	[redacted]	NR
CAR-T received			

Axi-cel	[redacted]	[redacted]	45 (27 to 138)
Liso-cel	[redacted]	[redacted]	45 (27 to 138)
POC CAR-T	[redacted]	[redacted]	45 (27 to 138)
Tisa-cel	[redacted]	[redacted]	45 (27 to 138)
Median days from CAR-T to CIT/epcoritamab	[redacted]	[redacted]	45 (27, 138)

*Values adjusted for: median age, age (≥65 years), disease stage Ann harbor Stage II–IV, ≥3 lines of CAR-T, primary refractory, prior ASCT; weights truncated at 1% and 99%.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; MAIC: matching adjusted indirect treatment comparison; NR: not reported; liso-cel: lisocabtagene maraleucel; LBCL:large B-cell lymphoma; POC: point-of-care; R: rituximab; tisa-cel: tisagenlecleucel.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Tomas *et al*. population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 53.

Table 53: Baseline characteristics for fully adjusted MAIC versus R-based CIT (all variables matched; LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	R-based CIT (N=17)
Age			
Median (years)	[redacted]	[redacted]	60 (55, 66) *
Age ≤ 65	[redacted]	[redacted]	12 (70.59%)
Age > 65	[redacted]	[redacted]	5 (29.41%)*
Number of prior lines of CAR-T			
<3	[redacted]	[redacted]	3 (17.65%)
≥3 lines	[redacted]	[redacted]*	14 (82.35%)*
Primary refractory			
No	[redacted]	[redacted]	7 (41.18%)
Yes	[redacted]	[redacted]	10 (58.82%)*
Disease stage Ann harbor			
Stage I	[redacted]	[redacted]	2 (11.76%)
Stage II–IV	[redacted]	[redacted]	15 (88.24%)*
Prior transplant ASCT			
No	[redacted]	[redacted]	13 (76.47%)
Yes	[redacted]	[redacted]	4 (23.53%)*
LBCL origin			

De novo	[redacted]	[redacted]	14 (82.35%)
Transformed from low-grade	[redacted]	[redacted]	3 (17.65%)
Unknown	[redacted]	[redacted]	0 (0.00%)
NA	[redacted]	[redacted]	NR
Cell origin			
Germinal center B cells	[redacted]	[redacted]	5 (29.41%)
Non-Germinal center B cells	[redacted]	[redacted]	10 (58.82%)
Unknown	[redacted]	[redacted]	2 (11.76%)
Activated B-cell	[redacted]	[redacted]	NR
Not done	[redacted]	[redacted]	NR
N/A	[redacted]	[redacted]	NR
CAR-T received			
Axi-cel	[redacted]	[redacted]	45 (27 to 138)
Liso-cel	[redacted]	[redacted]	45 (27 to 138)
POC CAR-T	[redacted]	[redacted]	45 (27 to 138)
Tisa-cel	[redacted]	[redacted]	45 (27 to 138)
Median days from CAR-T to CIT/epcoritamab	[redacted]	[redacted]	45 (27, 138)

*Values adjusted for: median age, age (≥65 years), disease stage Ann harbor Stage II–IV, ≥3 lines of CAR-T, primary refractory, prior ASCT; weights truncated at 1% and 99%.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; MAIC: matching adjusted indirect treatment comparison; NR: not reported; liso-cel: lisocabtagene maraleucel; LBCL:large B-cell lymphoma; POC: point-of-care; R: rituximab; tisa-cel: tisagenlecleucel.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Northend et al. 3L+ (DLBCL, no prior ASCT; 11 reported variables matched, without truncation)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior ASCT). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Northend *et al*. 3L+ population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator population included in the analysis is presented in Table 54.

Table 54: Baseline characteristics for MAIC versus Pola + BR (11 variables matched, without truncation; DLBCL, no prior ASCT)

	Unadjusted epcoritamab DLBCL, no prior ASCT (N=[redacted])	Adjusted epcoritamab DLBCL, no prior ASCT (N_{eff}=[redacted])	Pola + BR (N=[redacted])
Median Age	[redacted]	[redacted]	[redacted]
Age ≥ 73	[redacted]	[redacted]*	[redacted]*
Male (mean)	[redacted]	[redacted]*	[redacted]*
ECOG 0 (mean)	[redacted]	[redacted]	[redacted]
ECOG 1 (mean)	[redacted]	[redacted]	[redacted]
ECOG 2 (mean)	[redacted]	[redacted]	[redacted]

ECOG 3 (mean)	[redacted]	[redacted]	[redacted]
Stage 3 (mean)	[redacted]	[redacted]*	[redacted]*
Stage 4 (mean)	[redacted]	[redacted]*	[redacted]*
IPI=3 (mean)	[redacted]	[redacted]*	[redacted]*
IPI >3 (mean)	[redacted]	[redacted]*	[redacted]*
Normal LDH at baseline (mean)	[redacted]	[redacted]	[redacted]
High LDH at baseline (mean)	[redacted]	[redacted]	[redacted]
Extranodal involvement at baseline (mean)	[redacted]	[redacted]	[redacted]
Bulky disease (mean)[a]	[redacted]	[redacted]*	[redacted]*
2 Prior treatment lines (mean)	[redacted]	[redacted]	[redacted]
3 Prior treatment lines (mean)	[redacted]	[redacted]	[redacted]
>3 Prior treatment lines (mean)	[redacted]	[redacted]	[redacted]
Prior CAR-T (mean)	[redacted]	[redacted]*	[redacted]*
Refractory to R-CHOP / Primary refractory (mean)	[redacted]	[redacted]*	[redacted]*
Refractoriness to any prior treatment (mean)	[redacted]	[redacted]*	[redacted]*
Refractoriness to last treatment (mean)	[redacted]	[redacted]*	[redacted]*

* Adjusted for age (≥73 years), male, disease stage, IPI score (3), IPI Score (>3) Bulky disease, prior CAR T, refractory to R-CHOP (Northend Pola-BR) / Primary refractory (EPCORE), refractory to any prior treatment, refractory to last treatment. [a] Due to differences in experimental design, bulky disease is defined as a tumour load >7 cm in EPCORE and ≥7.5 cm in Northend 3L+.
Abbreviations: ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor (CAR) T-cell therapy; DLBCL, diffuse large B-cell lymphoma; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; IPI, International Prognostic Index; R-CHOP: Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.

Figure 41: Adjustment weights distribution for MAIC versus Northend et al. 3L+ (11 reported variables matched, without truncation; epcoritamab DLBCL, no prior ASCT population)

Abbreviations: ASCT autologous stem cell transplant; LBCL: large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Northend et al. 3L+ (DLBCL, no prior ASCT; 13 reported variables matched, with truncation)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior ASCT). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Northend *et al*. 3L+ population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator population included in the analysis is presented in Table 55.

Table 55: Baseline characteristics for MAIC versus Pola + BR (13 variables matched, without truncation; DLBCL, no prior ASCT)

	Unadjusted epcoritamab DLBCL, no prior ASCT (N=[redacted])	Adjusted epcoritamab DLBCL, no prior ASCT (N_{eff}=[redacted])	Pola + BR (N=[redacted])
Age			
Median Age	[redacted]	[redacted]	[redacted]
Age ≥ 73	[redacted]	[redacted]*	[redacted]*
Male (mean)	[redacted]	[redacted]*	[redacted]*
ECOG (mean)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
Disease stage (mean)			
Stage 3	[redacted]	[redacted]*	[redacted]*
Stage 4	[redacted]	[redacted]*	[redacted]*
IPI score (mean)			
3	[redacted]	[redacted]*	[redacted]*
>3	[redacted]	[redacted]*	[redacted]
Normal LDH at baseline (mean)	[redacted]	[redacted]	[redacted]
High LDH at baseline (mean)	[redacted]	[redacted]	[redacted]
Extranodal involvement at baseline (mean)	[redacted]	[redacted]	[redacted]
Bulky disease (mean)a	[redacted]	[redacted]*	[redacted]*
Prior treatment lines (mean)			
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]*	[redacted]*
>3	[redacted]	[redacted]*	[redacted]*
Prior CAR-T (mean)	[redacted]	[redacted]*	[redacted]*
Refractory to R-CHOP / Primary refractory (mean)	[redacted]	[redacted]*	[redacted]*

Refractory to any prior treatment (mean)	[redacted]	[redacted]*	[redacted]*
Refractory to last treatment (mean)	[redacted]	[redacted]*	[redacted]*

* Adjusted for age (>=73 years), male, disease stage, IPI score (3), IPI Score (>3) Bulky disease, 3 prior treatment lines, >3 prior treatment lines, CAR-T, refractory to R-CHOP (Northend Pola-BR) / Primary refractory (EPCORE), refractory to any prior treatment, refractory to last treatment. [a] Due to differences in experimental design, bulky disease is defined as a tumour load >7 cm in EPCORE and ≥7.5 cm in Northend 3L+.
Abbreviations: CAR-T: Chimeric antigen receptor T-cell; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; Pola + BR: Polatuzumab vedotin with rituximab and bendamustine; R-CHOP: Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.

Figure 42: Adjustment weights distribution for MAIC versus Northend et al. 3L+ (13 reported variables matched, with truncation; epcoritamab DLBCL, no prior ASCT population)

A) Without truncation **B) With truncation at 1% & 99%**

[redacted]

Abbreviations: ASCT autologous stem cell transplant; LBCL: large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Northend et al. 3L+ (DLBCL, no prior ASCT; 13 reported variables matched, without truncation)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior ASCT). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the Northend *et al*. 3L+ population. An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator population included in the analysis is presented in Table 56.

Table 56: Baseline characteristics for MAIC versus Pola + BR (13 variables matched, without truncation; DLBCL, no prior ASCT)

	Unadjusted epcoritamab DLBCL, no prior ASCT (N=[redacted])	Adjusted epcoritamab DLBCL, no prior ASCT (N_{eff}=[redacted])	Pola + BR (N=[redacted])
Age			
Median Age	[redacted]	[redacted]	[redacted]
Age ≥ 73	[redacted]	[redacted]*	[redacted]*

Male (mean)	[redacted]	[redacted]*	[redacted]*
ECOG (mean)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
Disease stage (mean)			
Stage 3	[redacted]	[redacted]*	[redacted]*
Stage 4	[redacted]	[redacted]*	[redacted]*
IPI score (mean)			
3	[redacted]	[redacted]*	[redacted]*
>3	[redacted]	[redacted]*	[redacted]*
Normal LDH at baseline (mean)	[redacted]	[redacted]	[redacted]
High LDH at baseline (mean)	[redacted]	[redacted]	[redacted]
Extranodal involvement at baseline (mean)	[redacted]	[redacted]	[redacted]
Bulky disease (mean)a	[redacted]	[redacted]*	[redacted]*
Prior treatment lines (mean)			
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]*	[redacted]*
>3	[redacted]	[redacted]*	[redacted]*
Prior CAR-T (mean)	[redacted]	[redacted]*	[redacted]*
Refractory to R-CHOP / Primary refractory (mean)	[redacted]	[redacted]*	[redacted]*
Refractoriness to any prior treatment (mean)	[redacted]	[redacted]*	[redacted]*
Refractoriness to last treatment (mean)	[redacted]	[redacted]*	[redacted]*

* Adjusted for age (>=73 years), male, disease stage, IPI score (3), IPI Score (>3) Bulky disease, 3 prior treatment lines, >3 prior treatment lines, CAR-T, refractory to R-CHOP (Northend Pola-BR) / Primary refractory (EPCORE), refractory to any prior treatment, refractory to last treatment. [a] Due to differences in experimental design, bulky disease is defined as a tumour load >7 cm in EPCORE and ≥7.5 cm in Northend 3L+.
Abbreviations: CAR-T: Chimeric antigen receptor T-cell; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; Pola + BR: Polatuzumab vedotin with rituximab and bendamustine; R-CHOP: Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.

Figure 43: Adjustment weights distribution for MAIC versus Northend et al. 3L+ (13 reported variables matched, without truncation; epcoritamab DLBCL, no prior ASCT population)

Abbreviations: ASCT autologous stem cell transplant; LBCL: large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

B.2.1.2 Patients eligible for intensive therapies

Patients eligible for intensive therapy: Fully adjusted to ZUMA-1 (all reported variables matched; epcoritamab versus axi-cel; DLBCL population)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (DLBCL, no prior CAR-T, eligible for CAR-T). The unadjusted and adjusted baseline characteristics for the comparison of epcoritamab versus axi-cel (all reported variables matched) are presented in Table 57.

Table 57: Baseline characteristics for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab DLBCL, CAR-T eligible population fully adjusted to match axi-cel)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Axi-cel, ZUMA-1 (N=101)
Age			
Median, years	[redacted]	[redacted]	58.0
≥65 years	[redacted]	[redacted]*	**23.8%***
Male	[redacted]	[redacted]*	**67.3%***
DLBCL (including TFL)	[redacted]	[redacted]	92.1%
ECOG PS 0 or 1 (versus 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III–IV	[redacted]	[redacted]*	**85.1%***
IPI score ≥3	[redacted]	[redacted]*	**45.5%***
Number of prior lines of treatment			

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])	Axi-cel, ZUMA-1 (N=101)
≥3 prior lines of treatment	[redacted]	[redacted]*	**69.3%***
History of primary refractory disease	[redacted]	[redacted]*	**25.7%***
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]*	**53.5%***
Refractory to second-line or subsequent therapy	[redacted]	[redacted]*	**76.2%***
Relapse after ASCT within 12 months	[redacted]	[redacted]*	**20.8%***

*Values adjusted for: age (≥65 years), male, ECOG PS, disease stage, IPI score ≥3, ≥3 prior lines of treatment, history of primary refractory disease, history of resistance to two consecutive lines of therapy, refractory to second-line or subsequent therapy, and relapse after ASCT within 12 months.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; MAIC: matching indirect treatment comparison; TFL: transformed follicular lymphoma.

Figure 44: Adjustment weights distribution for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab DLBCL, CAR-T eligible population fully adjusted to match axi-cel)

A) Without truncation

B) With truncation at 1% & 99%

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

Patients eligible for intensive therapies: Fully adjusted to ZUMA-1 (all reported variables matched; epcoritamab versus axi-cel; LBCL population)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, no prior CAR-T therapy, eligible for CAR-T therapy population). An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the axi-cel population included in the analysis is presented in Table 58.

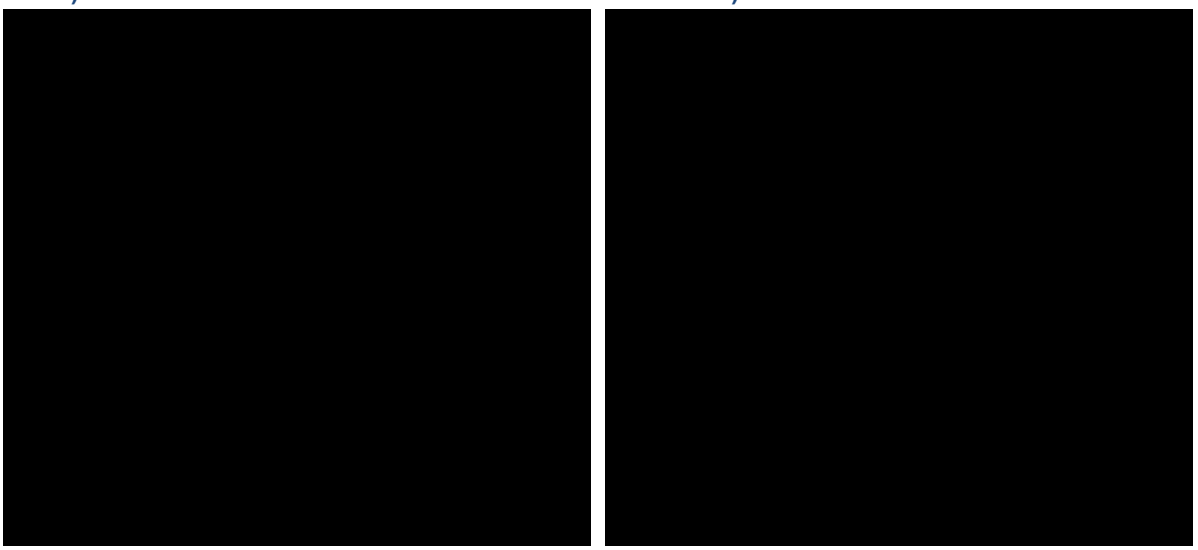
Table 58: Baseline characteristics for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab LBCL, CAR-T eligible population fully adjusted to match axi-cel)

	Unadjusted epcoritamab (N=[redacted])	Adjusted epcoritamab (N_{eff}=[redacted])[a]	Axi-cel, ZUMA-1 (N=101)
Age			
Median, years	[redacted]	[redacted]	58.0
≥65 years	[redacted]	[redacted]*	**23.8%***
Male	[redacted]	[redacted]*	**67.3%***
DLBCL (including TFL)	[redacted]	[redacted]*	**92.1%***
ECOG PS 0 or 1 (versus 2)	[redacted]	[redacted]*	**100.0%***
Disease stage III–IV	[redacted]	[redacted]*	**85.1%***
IPI score ≥3	[redacted]	[redacted]*	**45.5%***
Number of prior lines of treatment			
≥3 prior lines of treatment	[redacted]	[redacted]*	**69.3%***
History of primary refractory disease	[redacted]	[redacted]*	**25.7%***
History of resistance to two consecutive lines of therapy	[redacted]	[redacted]*	**53.5%***
Refractory to second-line or subsequent therapy	[redacted]	[redacted]*	**76.2%***
Relapse after ASCT within 12 months	[redacted]	[redacted]*	**20.8%***

*Values adjusted for: age (≥65 years), male, DLBCL (including TFL), ECOG PS, disease stage, IPI score ≥3, ≥3 prior lines of treatment, history of primary refractory disease, history of resistance to two consecutive lines of therapy, refractory to second-line or subsequent therapy, and relapse after ASCT within 12 months.
Abbreviations: ASCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; MAIC: matching indirect treatment comparison; TFL: transformed follicular lymphoma.

Figure 45: Adjustment weights distribution for fully adjusted MAIC versus axi-cel (all reported variables matched; epcoritamab LBCL, CAR-T eligible population fully adjusted to match axi-cel)

A) Without truncation **B) With truncation at 1% & 99%**



Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large-B-Cell lymphoma; MAIC: matching indirect treatment comparison.

B.2.1. Efficacy results

B.2.1.1 Patients ineligible for, or choose not to receive, intensive therapies

Patients ineligible for, or choose not to receive, intensive therapy: Fully adjusted to SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab versus R-based CIT)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 59. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from SCHOLAR-1 are presented in Figure 46. No PFS KM data were available from SCHOLAR-1.

As presented in Table 59, the unadjusted OS HR for epcoritamab versus R-based CIT is 0 [redacted]. Following adjustment, the adjusted OS HR for epcoritamab versus R-based CIT is [redacted], demonstrating that epcoritamab provides a [redacted] treatment benefit versus R-based CIT.

Due to the [redacted], the results of this analysis are considered to be clinically implausible. This is likely due to the very small effective sample size (N_{eff}=[redacted]) in this analysis. As such, as reported in Appendix B.1, an additional MAIC was conducted in which all reported variables, except SCT any time after refractory disease, were adjusted for, and the results of that MAIC are considered to be more robust compared with this the MAIC presented here.

Table 59: Unadjusted and adjusted outcomes for fully adjusted MAIC versus SCHOLAR-1 (all reported variables matched, with truncation; epcoritamab DLBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; HR: hazard ratio; ORR: overall response rate; OS: overall survival; MAIC: matching indirect treatment comparison; R: rituximab.

Figure 46: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 (all reported variables, with truncation)

Abbreviations: CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; DLBCL: diffuse large B-Cell lymphoma; KM: Kaplan–Meier; OS: overall survival; R: rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Fully adjusted to Sehn et al. 3L+ (10 reported variables, with truncation; epcoritamab versus Pola + BR)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 60, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 47 and Figure 48, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is a numerical benefit of epcoritamab versus Pola + BR, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted]; adjusted HR: [redacted]). However, this difference is [redacted].

There was [redacted] in CR rate and ORR between epcoritamab and Pola + BR after adjustment.

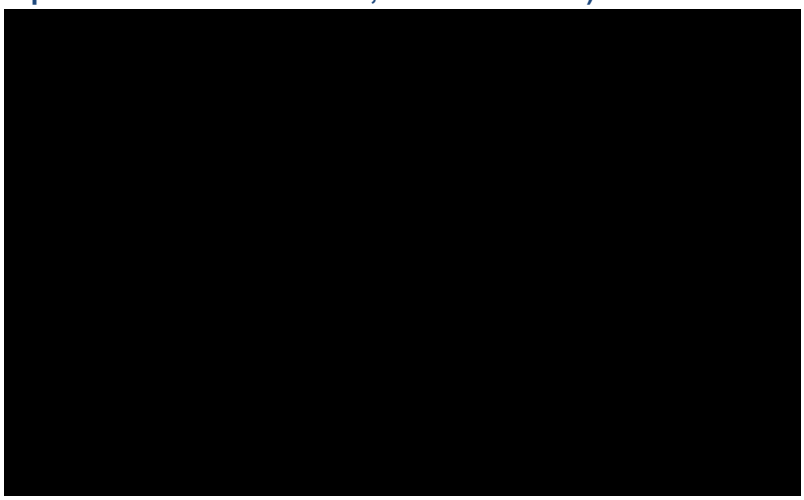
When discussed with UK clinical experts, UK clinical experts stated that the results of these MAICs are not aligned with their expectations of the comparative efficacy of epcoritamab and Pola + BR in UK clinical practice. Moreover, it is not clinically plausible for epcoritamab to demonstrate efficacy that is comparable to both Pola + BR and axi-cel.

Table 60: Unadjusted and adjusted outcomes for fully adjusted MAIC versus Pola + BR (10 reported variables matched, with truncation; DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+)

	Epcoritamab DLBCL, no prior CAR-T unadjusted (N=[redacted])	Epcoritamab DLBCL, no prior CAR-T adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs Pola + BR)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs Pola + BR)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; MAIC: matching indirect treatment comparison; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 47: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population (10 reported variables matched, with truncation)



Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; MAIC: matching indirect treatment comparison; epco: epcoritamab; KM: Kaplan–Meier; OS: overall survival.

Figure 48: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – DLBCL, no prior CAR-T epcoritamab population (10 reported variables matched, with truncation)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; epco: epcoritamab; KM: Kaplan–Meier; MAIC: matching indirect treatment comparison; PFS: progression-free survival.

Patients ineligible for, or choose not to receive, intensive therapy: Adjusted to SCHOLAR-1 (base case variables matched; epcoritamab versus R-based CIT)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 61. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from SCHOLAR-1 are presented in Figure 49. No PFS KM data were available from SCHOLAR-1.

As presented in Table 61, the unadjusted OS HR for epcoritamab versus R-based CIT is [redacted]. Following adjustment, the adjusted OS HR for epcoritamab versus R-based CIT is [redacted];, demonstrating that epcoritamab provides a [redacted] treatment benefit versus R-based CIT.

Table 61: Unadjusted and adjusted outcomes for MAIC versus SCHOLAR-1 (base case variables matched [n=7]; epcoritamab LBCL, no prior CAR-T population adjusted to SCHOLAR-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs R-based CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; HR: hazard ratio; LBCL: large B-Cell lymphoma; MAIC: matching indirect treatment comparison; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R: rituximab.

Figure 49: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – LBCL, no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 (base case variables matched)

Abbreviations: CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; EPCO: epcoritamab; KM: Kaplan–Meier; LBCL: large B-Cell lymphoma; OS: overall survival; R: rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus CIT is presented in Table 62. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from Tomas *et al* are presented in Figure 50. No PFS KM data were available from Tomas *et al*.

Both single HRs and piecewise HRs, whereby one HR was calculated up to the point of the crossing of the epcoritamab and R-based CIT hazard curves ([redacted]) and a second HR was calculated after this timepoint, are presented. The timepoint was based on the assessment of the PH approach. Following adjustment, the OS HR for epcoritamab versus CIT for up to [redacted] is [redacted] After [redacted] the adjusted OS HR is [redacted] This demonstrates that both prior to and after [redacted] there is a treatment benefit in favour of epcoritamab versus R-based CIT, and this difference is [redacted]. When a single HR is generated following adjustment, there is a numerical treatment benefit associated with epcoritamab, but the difference is [redacted]

Table 62: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (DLBCL; prior CAR-T therapy, epcoritamab 1L post CAR-T)

	Epcoritamab unadjusted (N=[redacted])		Epcoritamab adjusted (N_{eff}=[redacted])	
	Before [redacted]	After [redacted]	Before [redacted]	After [redacted]
Survival, HR (95% CI)				

	Epcoritamab unadjusted (N=[redacted])		Epcoritamab adjusted (N_{eff}=[redacted])	
	Before [redacted]	After [redacted]	Before [redacted]	After [redacted]
OS	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; DLBCL: diffuse large B-Cell lymphoma; HR: hazard ratio; OS: overall survival; R: rituximab.

Figure 50: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T

[redacted]

Abbreviations: DLBCL: diffuse large B-cell lymphoma; CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (LBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 63. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from Tomas *et al* are presented in Figure 51. No PFS KM data were available from Tomas *et al*.

The adjusted OS HR for epcoritamab versus R-based CIT for up to [redacted] is [redacted] After [redacted] the adjusted OS HR is [redacted] This demonstrates that both prior and after [redacted] there is a treatment benefit in favour of epcoritamab versus R-based CIT, and this difference is [redacted].

Table 63: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (LBCL; prior CAR-T therapy, epcoritamab 1L post CAR-T)

	Epcoritamab unadjusted (N=[redacted])		Epcoritamab adjusted (N_{eff}=[redacted])	
	Before [redacted]	After [redacted]	Before [redacted]	After [redacted]
Survival, HR (95% CI)				
OS	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; LBCL: large B-Cell lymphoma; HR: hazard ratio; OS: overall survival; R: rituximab.

Figure 51: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – DLBCL, prior CAR-T therapy, epcoritamab 1L post CAR-T

Abbreviations: CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 64. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from Tomas *et al* are presented in Figure 52. No PFS KM data were available from Tomas *et al*.

The adjusted OS HR for epcoritamab versus R-based CIT for up to [redacted] is [redacted] After [redacted] the adjusted OS HRs is [redacted]. This demonstrates that both prior and after [redacted] there is a treatment benefit in favour of epcoritamab versus R-based CIT and this difference is [redacted].

Table 64: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (DLBCL; prior CAR-T therapy, epcoritamab any-line post CAR-T)

	Epcoritamab unadjusted (N=[redacted])		Epcoritamab adjusted (N_{eff}=[redacted])	
	Before [redacted]	After [redacted]	Before [redacted]	After [redacted]
Survival, HR (95% CI)				
OS	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; DLBCL: diffuse large B-Cell lymphoma; HR: hazard ratio; OS: overall survival; R: rituximab.

Figure 52: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – DLBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T

Abbreviations: DLBCL: diffuse large B-cell lymphoma; CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Tomas et al. (LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus R-based CIT is presented in Table 65. The unadjusted and adjusted OS KM curves for epcoritamab and the OS KM for R-based CIT from Tomas *et al* are presented in Figure 53. No PFS KM data were available from Tomas *et al*.

The adjusted OS HR for epcoritamab versus R-based CIT for up to [redacted] is [redacted] After [redacted] the adjusted OS HR is [redacted] This demonstrates that both prior and after [redacted] there is a treatment benefit in favour of epcoritamab versus R-based CIT (although this is [redacted]).

Table 65: Unadjusted and adjusted outcomes for MAIC versus *Tomas et al.* (LBCL; prior CAR-T therapy, epcoritamab any-line post CAR-T)

	Epcoritamab unadjusted (N=[redacted])		Epcoritamab adjusted (N_{eff}=[redacted])	
	Before [redacted]	After [redacted]	Before [redacted]	After [redacted]
Survival, HR (95% CI)				
OS	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; LBCL: large B-Cell lymphoma; HR: hazard ratio; OS: overall survival; R: rituximab.

Figure 53: Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (*Tomas et al.*) – LBCL, prior CAR-T therapy, epcoritamab any-line post CAR-T

Abbreviations: CAR-T: chimeric antigen receptor T-cell; EPCO: epcoritamab; KM: Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Northend et al. 3L+ (DLBCL, no prior ASCT; 11 reported variables matched, without truncation)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 66, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 54 and Figure 55, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is [redacted] treatment benefit of epcoritamab versus Pola + BR, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted] adjusted HR: [redacted]).

Table 66: Unadjusted and adjusted outcomes for MAIC versus Pola + BR based on Northend *et al.* 3L+ (11 reported variables matched, without truncation; DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+)

	Epcoritamab DLBCL, no prior ASCT unadjusted (N=[redacted])	Epcoritamab DLBCL, no prior ASCT adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; MAIC: matching indirect treatment comparison; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 54: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (11 reported variables matched, without truncation)

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 55: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (11 reported variables matched, without truncation)

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Northend et al. 3L+ (DLBCL, no prior ASCT; 13 reported variables matched, with truncation)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 67, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 56 and Figure 57, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is [redacted] treatment benefit of epcoritamab versus Pola + BR, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted] adjusted HR: [redacted]).

Table 67: Unadjusted and adjusted outcomes for MAIC versus Pola + BR based on Northend *et al.* 3L+ (13 reported variables matched, with truncation; DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+)

	Epcoritamab DLBCL, no prior ASCT unadjusted (N=[redacted])	Epcoritamab DLBCL, no prior ASCT adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; MAIC: matching indirect treatment comparison; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 56: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, with truncation)

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 57: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, with truncation)

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Patients ineligible for, or choose not to receive, intensive therapies: Adjusted to Northend et al. 3L+ (DLBCL, no prior ASCT; 13 reported variables matched, without truncation)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus Pola + BR is presented in Table 68, alongside the unadjusted and adjusted KM curves for epcoritamab and Pola + BR, in Figure 58 and Figure 59, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is [redacted] treatment benefit of epcoritamab versus Pola + BR, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted] adjusted HR: [redacted]).

Table 68: Unadjusted and adjusted outcomes for MAIC versus Pola + BR based on Northend *et al.* 3L+ (13 reported variables matched, without truncation; DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+)

	Epcoritamab DLBCL, no prior ASCT unadjusted (N=[redacted])	Epcoritamab DLBCL, no prior ASCT adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; MAIC: matching indirect treatment comparison; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 58: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, without truncation)

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 59: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Northend *et al.* 3L+) – DLBCL, no prior ASCT epcoritamab population (13 reported variables matched, without truncation)

Abbreviations: 3L+: third treatment line and beyond; ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

B.2.1.2 Patients eligible for intensive therapies

Patients eligible for intensive therapy: Fully adjusted to ZUMA-1 (all reported variables matched; epcoritamab versus axi-cel; DLBCL population)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus axi-cel is presented in Table 69, alongside the unadjusted and adjusted KM curves for epcoritamab and axi-cel, in Figure 60 and Figure 61, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is a numerical benefit of epcoritamab versus axi-cel, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]) and PFS (unadjusted HR: [redacted]; adjusted HR[redacted]). However, this difference is [redacted].

There was [redacted] in CR rate and ORR between epcoritamab and axi-cel.

Table 69: Unadjusted and adjusted outcomes for fully adjusted MAIC versus axi-cel (all reported variables matched; DLBCL, CAR-T eligible adjusted to ZUMA-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; MAIC: matching adjusting indirect treatment comparison; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

Figure 60: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched)

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival.

Figure 61: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched)

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival.

Patients eligible for intensive therapies: Fully adjusted to ZUMA-1 (all reported variables matched; epcoritamab versus axi-cel; LBCL population)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus axi-cel is presented in Table 70, alongside the unadjusted and adjusted KM curves for epcoritamab and axi-cel, in Figure 62 and Figure 63, for OS and PFS respectively.

Following adjustment, the results demonstrate that there is a numerical benefit of epcoritamab versus axi-cel, in terms of both OS (unadjusted HR: [redacted]; adjusted HR: [redacted]

[redacted]) and PFS (unadjusted HR: [redacted]; adjusted HR: [redacted]). However, this difference is [redacted].

There was [redacted] in CR rate and ORR between epcoritamab and axi-cel.

Table 70: Unadjusted and adjusted outcomes for fully adjusted MAIC versus axi-cel (all reported variables matched; LBCL, CAR-T eligible adjusted to ZUMA-1)

	Epcoritamab unadjusted (N=[redacted])	Epcoritamab adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)		
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs axi-cel)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; HR: hazard ratio; LBCL: large B-cell lymphoma; MAIC: matching adjusted indirect comparisons; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

Figure 62: Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched)

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival.

Figure 63: Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, CAR-T therapy eligible epcoritamab population (all reported variables matched)

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; KM: Kaplan–Meier; PFS: progression-free survival.

Appendix C Time-to-event analyses

C.1 Overview

As outlined in the CS (Document B, Section B.3.2.2) parametric models for PFS, OS and ToT were fitted to the KM curves from the EPCORE™ NHL-1 trial (Appendix C.2) and the comparator data (Appendix C.4) in line with NICE DSU TSD14.[5] The parametric distributions for were selected based on statistical goodness of visual fit to the observed data, feedback form UK clinicians and comparison with long-term data in the published literature where available. When goodness of fit statistics did not provide clear differentiation for models, clinical plausibility (and alignment to MAIC outcomes) was prioritised when selecting extrapolation.

C.2 Epcoritamab

C.2.1. Updated base case analysis A: DLBCL, no prior CAR-T adjusted to the SCHOLAR-1 population (epcoritamab versus R-based CIT)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the SCHOLAR-1 population is provided in Figure 64.

Figure 64: KM plot of PFS, OS and TTD used in updated base case analysis A (data cut-off)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to SCHOLAR-1, and evaluated based on AIC and BIC values, which are presented in Table 71.

The exponential and log-normal distribution performs best in terms of AIC and BIC. However, all distributions could be considered viable on the basis of goodness of fit statistics due to minimal differences in the AIC/BIC values.

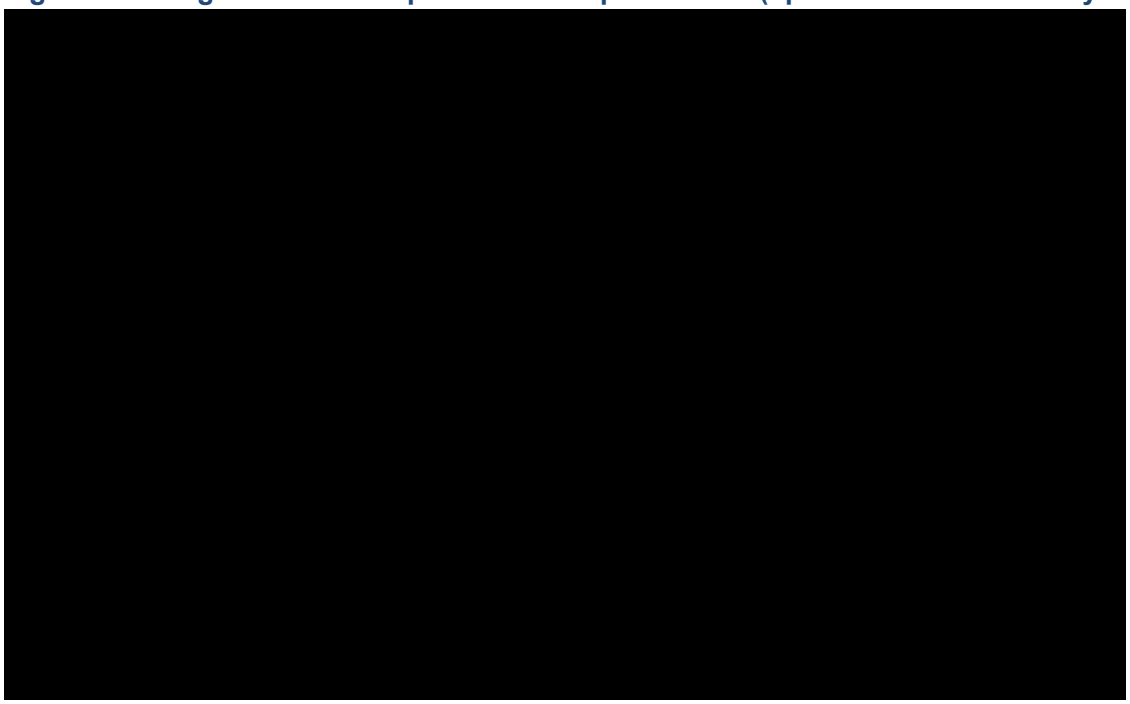
Table 71: Goodness of fit statistics for OS (AIC and BIC; updated base case analysis A)

Distribution	AIC	BIC
Exponential		
Log-normal		
Gompertz		
Log-logistic		
Weibull		
Gamma		
Generalised gamma		

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 65. The corresponding survival estimates at several landmarks are presented in Table 72. During validation interviews with UK clinical experts, the clinical experts expressed a preference for the long-term extrapolations of the generalised gamma or the lognormal extrapolations. As such, based on the lognormal extrapolation demonstrating a better statistical fit than the generalised gamma extrapolation, the lognormal extrapolation was selected to model OS for epcoritamab in base case analysis A. The loglogistic extrapolation was also explored in a scenario analysis.

Figure 65: Long-term OS extrapolations for epcoritamab (updated base case analysis A)



Abbreviations: OS: overall survival.

Table 72: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (updated base case analysis A)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to SCHOLAR-1. These were evaluated based on AIC and BIC values, which are presented in Table 73. Based on AIC and BIC criteria, the generalised gamma extrapolation demonstrates the best statistical fit.

Table 73: Goodness of fit statistics for PFS (AIC and BIC; updated base case A)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 66. The corresponding survival estimates at several landmarks are presented in Table 74. During interviews with UK clinical experts, the clinical experts commented that the Gompertz and generalised gamma extrapolations produced clinically plausible long-term PFS estimates for epcoritamab, with some experts also noting that the loglogistic and lognormal extrapolations could be considered plausible. As such, as the extrapolation that demonstrates the best statistical fit and clinically plausible long-term outcomes, the generalised gamma extrapolation was selected to model PFS for epcoritamab in base case analysis A, with the lognormal extrapolation considered in a scenario analysis.

Figure 66: Long-term PFS extrapolations for epcoritamab (updated base case analysis A)

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A.
Abbreviations: PFS: progression-free survival.

Table 74: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (updated base case analysis A)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted DLBCL population from EPCORE™ NHL-1 are presented in Table 75. Based

on AIC and BIC, the Gompertz and lognromal distributions show the best statistical fit to the observed data, however there are minimal differences in the statistical fit of all extrapolations.

Table 75: Goodness of fit statistics for TTD (AIC and BIC; updated base case analysis A)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in the updated base case analysis A.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 67. The corresponding TTD estimates at several landmarks are presented in Table 76. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years. As such, in line with feedback from UK clinical experts, the exponential extrapolation was selected to model TTD for epcoritamab in base case analysis A, with the gamma extrapolation explored in a scenario analysis.

Figure 67: Long-term TTD extrapolations for epcoritamab (updated base case analysis A)

Abbreviations:
TTD: time to treatment discontinuation.

Table 76: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (updated base case analysis A)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	NA	NA	NA	NA
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

C.2.2. Scenario analysis A.1: DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+ (epcoritamab versus Pola + BR)

Epcoritamab efficacy

In scenario analysis A.1 (patients ineligible for, or choose not to receive, intensive therapies), the epcoritamab DLBCL population adjusted to match the synthetically generated Sehn *et al.* 3L+ survival data was used to inform comparative efficacy estimates of epcoritamab versus Pola + BR. A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the SCHOLAR-1 population is provided in Figure 64.

Figure 68: KM plot of PFS, OS and TTD used in scenario analysis A.1 (data cut-off)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to synthetically generated Sehn *et al.* 3L+ survival data, and evaluated based on AIC and BIC values, which are presented in Table 71.

The exponential and log-normal distributions perform best in terms of AIC and BIC. The log-logistic and Gompertz models can also be considered as good fitting models in terms of both AIC and BIC scores.

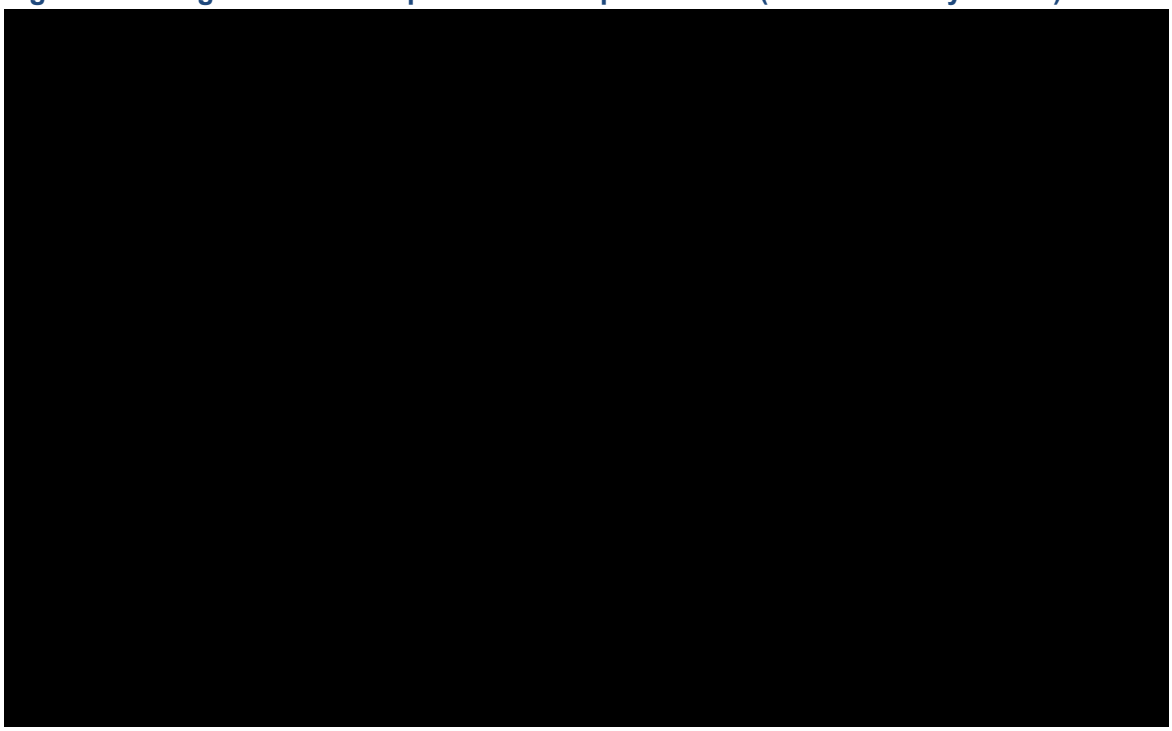
Table 77: Goodness of fit statistics for OS (AIC and BIC; scenario analysis A.1)

Distribution	AIC	BIC
Log-normal		
Log-logistic		
Gompertz		
Weibull		
Generalised gamma		
Gamma		
Exponential		

The generalised gamma extrapolation was selected to model OS for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 69. The corresponding survival estimates at several landmarks are presented in Table 72. During interviews with UK clinical experts, the experts stated that the long-term OS estimates provided by the generalised gamma model represent clinically plausible estimates, with the loglogistic and lognormal models also producing plausible long-term estimates. As such, the generalised gamma extrapolation was selected to model OS for epcoritamab in scenario analysis A.1, with the loglogistic model selected for use in a scenario analysis.

Figure 69: Long-term OS extrapolations for epcoritamab (scenario analysis A.1)



Abbreviations: OS: overall survival.

Table 78: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)						
Exponential						
Gamma						
Generalised gamma						
Gompertz						
Log-logistic						
Log-normal						

Distribution	Month					
	12	24	48	60	120	180
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in scenario analysis A.1.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to synthetically generated Sehn *et al.* 3L+ survival data. These were evaluated based on AIC and BIC values, which are presented in Table 79.

The log-normal model performs best in terms of both AIC and BIC score, with the generalised gamma model also demonstrating a good statistical fit.

Table 79: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.1)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 66. The corresponding survival estimates at several landmarks are presented in Table 74. During interviews with UK clinical experts, the experts stated that the generalised gamma extrapolation produces the most clinically plausible long-term estimates, with the Gompertz model also being considered clinically plausible. As such, the generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1.

Figure 70: Long-term PFS extrapolations for epcoritamab (scenario analysis A.1)

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1.
Abbreviations: PFS: progression-free survival.

Table 80: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted DLBCL population from EPCORE™ NHL-1 are presented in Table 75.

The log-normal distribution performs best in terms of AIC and BIC scores. The log-logistic and generalised gamma can also be considered to provide good fit in terms of AIC score, and the log-logistic also performed well in terms of BIC score.

Table 81: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis A.1)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 67. The corresponding TTD estimates at several landmarks are presented in Table 76. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years. As such, in line with feedback from UK clinical experts, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.1, with the gamma extrapolation explored in a scenario analysis.

Figure 71: Long-term TTD extrapolations for epcoritamab (scenario analysis A.1)

Abbreviations: TTD: time to treatment discontinuation.

Table 82: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.1.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

C.2.3. Scenario analysis A.2: DLBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR)

Epcoritamab efficacy

In this scenario analysis, IPD from the DLBCL population from EPCORE™ NHL-1 adjusted to Liebers *et al.* RW data were the source of the long-term time-to-event outcomes for the epcoritamab arm. A KM plot of PFS, OS and TTD for the DLBCL population adjusted to Liebers *et al.* RW data from EPCORE™ NHL-1 is provided in in Figure 72.

Figure 72: KM plot of PFS, OS and TTD in the DLBCL population (N=139) from EPCORE™ NHL-1 adjusted to Liebers et al. RW data, used in scenario analysis A.2 ([redacted] data cut-off)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation; RW: real-world.

Overall survival: Extrapolation selection

The same seven parametric distributions were also fitted to the OS KM data of the DLBCL population from EPCORE™ NHL-1 trial adjusted to match Liebers *et al.* RW data, and evaluated based on AIC and BIC values, which are presented in Table 83. The log-normal distribution performs best in terms of both AIC and BIC.

Table 83: Goodness of fit statistics for OS (AIC and BIC; Scenario A.2)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.2.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 73. The corresponding survival estimates at several landmarks are presented in Table 84. Based on consideration of feedback from UK clinical experts for the

expected survival of patients receiving epcoritamab (as outlined in Appendix C.2.2) and statistical fit, the lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.2.

Figure 73: Long-term OS extrapolations for epcoritamab (Scenario analysis A.2)

Abbreviations: OS: overall survival.

Table 84: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.2)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.2.
Abbreviations: CI: confidence intervals; NA: not available; OS: overall survival.

Progression-free survival: Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the DLBCL population from EPCORE™ NHL-1 trial adjusted to match Liebers *et al.* RW data. These were evaluated based on AIC and BIC values, which are presented in Table 85.

The best statistical fit based on both AIC and BIC is provided by the generalised gamma model, but the log-normal model also provides a good statistical fit.

Table 85: Goodness of fit statistics for PFS (AIC and BIC; Scenario analysis A.2)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.2.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 74. The corresponding survival estimates at several landmarks are presented in Table 86. Based on consideration of feedback from UK clinical experts for the expected survival of patients receiving epcoritamab (as outlined in Appendix C.2.2) and statistical fit, the generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.2.

Figure 74: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.2)

Abbreviations: PFS: progression-free survival.

Table 86: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.2)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.2.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the DLBCL population from EPCORE™ NHL-1 adjusted to match Liebers *et al.* RW data are presented in Table 87. The log-normal distribution performs best in terms of AIC and BIC

score. The log-logistic, model can also be considered to provide good fit in terms of AIC and BIC score.

Table 87: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.2)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.2.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 75. The corresponding TTD estimates at several landmarks are presented in Table 88. In line with the reasoning provided in Appendix C.2.2, the exponential model was selected to model TTD for epcoritamab in scenario analysis A.2.

Figure 75: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.2)

Abbreviations: TTD: time to treatment discontinuation.

Table 88: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.2)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.2.
Abbreviations: CI: confidence intervals; NA: not available; TTD: time to treatment discontinuation. survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; HR: hazard ratio.

C.2.4. Scenario analysis A.3: LBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR)

Epcoritamab efficacy

In this scenario analysis, IPD from the LBCL population from EPCORE™ NHL-1 adjusted to match Liebers *et al.* RW data were the source of the long-term time-to-event outcomes for the epcoritamab arm. A KM plot of PFS, OS and TTD for the LB LBCL population from EPCORE™ NHL-1 adjusted to match Liebers *et al.* RW data is provided in Figure 76.

Figure 76: KM plot of PFS, OS and TTD in the LBCL population (N=157) from EPCORE™ NHL-1 adjusted to match Liebers *et al.* RW data, used in scenario analysis A.3 (data cut-off)

Abbreviations: LBCL: large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; progression-free survival; TTD: time to treatment discontinuation; RW: real-world.

Overall survival: Extrapolation selection

The same seven parametric distributions were also fitted to the OS KM data of the LBCL population from EPCORE™ NHL-1 trial adjusted to match Liebers *et al.* RW data, and evaluated based on AIC and BIC values, which are presented in Table 89. The log-normal distribution performs best in terms of both AIC and BIC.

Table 89: Goodness of fit statistics for OS (AIC and BIC; Scenario analysis A.3)

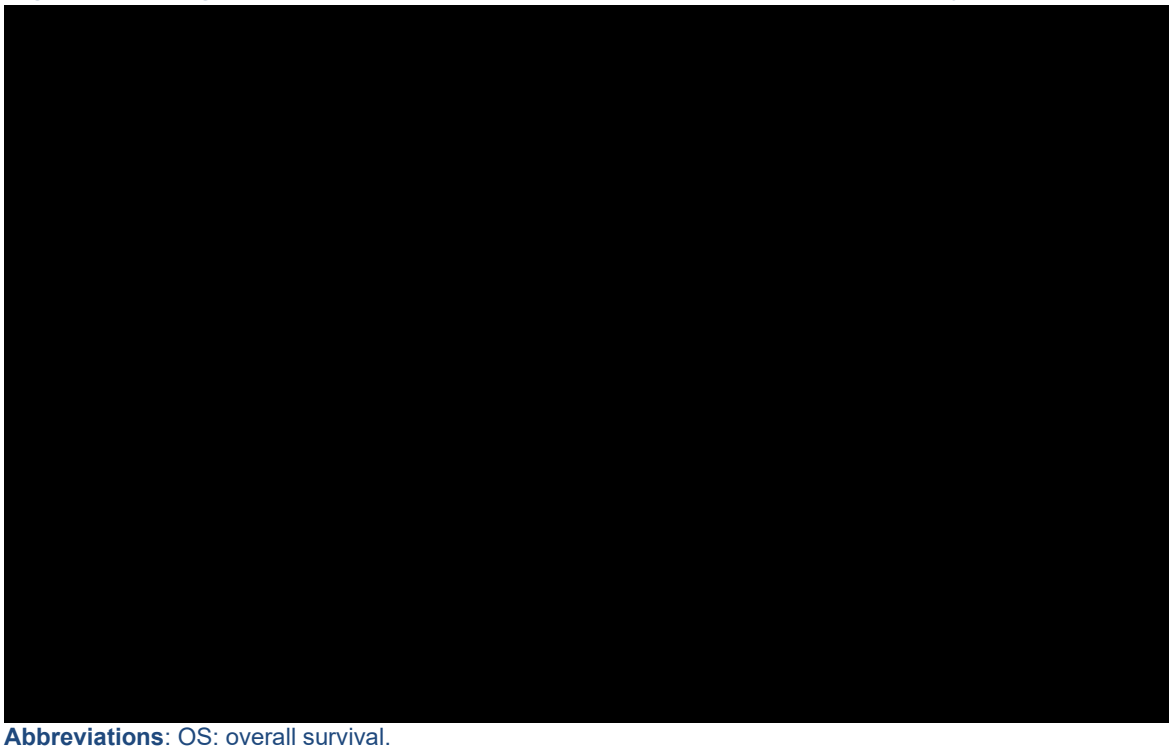
Distribution	AIC	BIC
Log-normal		
Log-logistic		
Gompertz		
Generalised gamma		
Exponential		
Weibull		
Gamma		

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.3.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 77. The corresponding survival estimates at several landmarks are

presented in Table 90. In line with the reasoning outlined in Appendix C.2.3, the lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.3.

Figure 77: Long-term OS extrapolations for epcoritamab (Scenario analysis A.3)



Abbreviations: OS: overall survival.

Table 90: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.3)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.3.
Abbreviations: CI: confidence intervals; NA: not available; OS: overall survival.

Progression-free survival*: *Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the LBCL population from EPCORE™ NHL-1 trial adjusted to match Liebers *et al.* RW data. These were evaluated based on AIC and BIC values, which are presented in Table 91. The generalised gamma model performs best in terms of both AIC and BIC score.

Table 91: Goodness of fit statistics for PFS (AIC and BIC; Scenario analysis A.3)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.3.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 78. The corresponding survival estimates at several landmarks are presented in Table 92. In line with the reasoning outlined in Appendix C.2.3, the generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.3.

Figure 78: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.3)

Abbreviations: PFS: progression-free survival.

Table 92: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.3)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.3.
Abbreviations: CI: confidence intervals; NA: not available; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the LBCL population from EPCORE™ NHL-1 adjusted to match Liebers *et al.* RW data are presented in Table 93. The log-normal distribution performs best in terms of AIC and BIC score. The log-logistic, Gompertz and generalised gamma can also be considered to provide good fit in terms of AIC and BIC score.

Table 93: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.3)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.3.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 79. The corresponding TTD estimates at several landmarks are presented in Table 94. In line with the reasoning outlined in Appendix C.2.3, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.3.

Figure 79: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.3)

Abbreviations: TTD: time to treatment discontinuation.

Table 94: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.3)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.3 .
Abbreviations: CI: confidence intervals; NA: not available; TTD: time to treatment discontinuation.

C.2.5. Scenario analysis A.4: DLBCL, no prior CAR-T fully adjusted to SCHOLAR-1 (epcoritamab versus R-based CIT)

Epcoritamab efficacy

In this scenario analysis, IPD from the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 fully adjusted (nine reported variables) to match SCHOLAR-1 were the source of the long-term time-to-event outcomes for the epcoritamab arm. A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 fully adjusted to match SCHOLAR-1 is provided in Figure 80.

Figure 80: KM plot of PFS, OS and TTD in the DLBCL population (N=[redacted] from EPCORE™ NHL-1 fully adjusted to match SCHOLAR-1, used in scenario analysis A.4 ([redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS IRC: progression-free survival-Independent Review Committee; TTD: time to treatment discontinuation.

Overall survival

The same seven parametric distributions were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 fully adjusted (nine reported variables) to match SCHOLAR-1, and evaluated based on AIC and BIC values, which are presented in Table 95.

The exponential distribution performs best both in terms of AIC and BIC. However, all the distributions except generalised gamma could be considered viable based on goodness of fit statistics.

Table 95: Goodness of fit statistics for OS (AIC and BIC; Scenario analysis A.4)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.4.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 81. The corresponding survival estimates at several landmarks are presented in Table 96. In line with the reasoning outlined in Appendix C.2.1, the lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.4.

Figure 81: Long-term OS extrapolations for epcoritamab (Scenario analysis A.4)

Abbreviations: OS: overall survival.

Table 96: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.4)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.4.
Abbreviations: CI: confidence intervals; NA: not available; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 fully adjusted (nine reported variables) to match SCHOLAR-1. These were evaluated based on AIC and BIC values, which are presented in Table 97.

The generalised gamma model performs best both in terms of AIC and BIC, with the log-normal, log-logistic and Gompertz models also demonstrating a good statistical fit.

Table 97: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.4)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis A.4.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 82. The corresponding survival estimates at several landmarks are presented in Table 98. In line with feedback from UK clinical experts and consideration of

statistical fit, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis A.4.

Figure 82: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.4)

Abbreviations: PFS: progression-free survival.

Table 98: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.4)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis A.4.
Abbreviations: CI: confidence intervals; NA: not available; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 fully adjusted (nine reported variables) to match SCHOLAR-1 are presented in Table 99.

The log-normal and log-logistic distributions perform best both in terms of AIC and BIC. However, all the distributions except generalised gamma could be considered viable based on goodness of fit statistics.

Table 99: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.4)

Distribution	AIC	BIC
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The exponential extrapolation was selected to model OS for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 83. The corresponding TTD estimates at several landmarks are presented in Table 100. In line with the reasoning outlined in Appendix C.2.1, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.4.

Figure 83: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.4)

Abbreviations: TTD: time to treatment discontinuation.

Table 100: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.4)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.4.
Abbreviations: CI: confidence intervals; NA: not available; TTD: time to treatment discontinuation.

C.2.6. Scenario analysis A.5: DLBCL, no prior ASCT adjusted to Northend *et al.* 3L+ RW data (epcoritamab versus Pola + BR)

Epcoritamab efficacy

In this scenario analysis, IPD from the DLBCL population from EPCORE™ NHL-1 adjusted to Northend *et al.* 3L+ RW data were the source of the long-term time-to-event outcomes for the epcoritamab arm. A KM plot of PFS, OS and TTD for the DLBCL population adjusted to Northend *et al*. 3L+ RW data from EPCORE™ NHL-1 is provided in in Figure 84.

Figure 84: KM plot of PFS and OS in the DLBCL, no prior ASCT population from EPCORE™ NHL-1 adjusted to Northend *et al*. 3L+ RW data (N=[redacted]), used in scenario analysis A.5 ([redacted] data cut-off)

Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation; RW: real-world.

Overall survival: Extrapolation selection

The same seven parametric distributions were also fitted to the OS KM data of the DLBCL population from EPCORE™ NHL-1 trial adjusted to match Northend et al. 3L+ RW data, and evaluated based on AIC and BIC values, which are presented in Table 101. The exponential distribution performs best both in terms of AIC and BIC. However, all the distributions can be considered viable in terms of AIC but not necessarily BIC.

Table 101: Goodness of fit statistics for OS (AIC and BIC; Scenario analysis A.5)

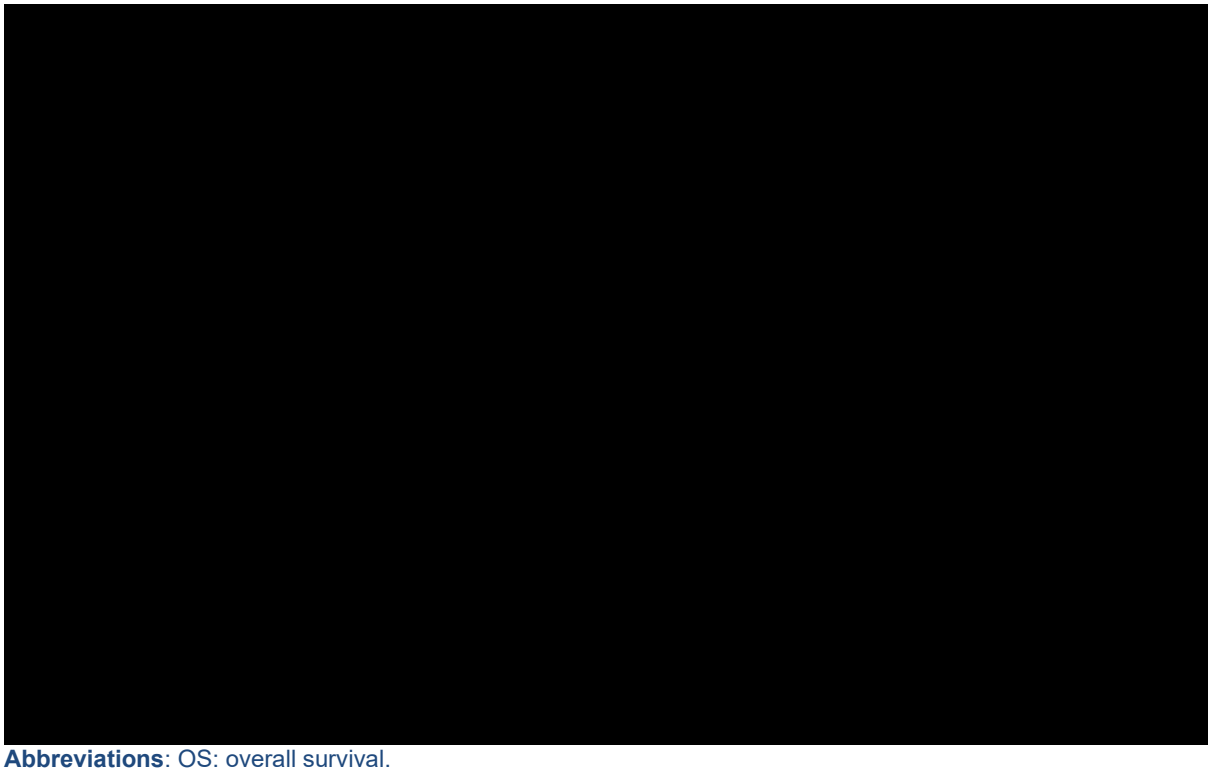
Exponential	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

Exponential	AIC	BIC
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis A.5.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 85. The corresponding survival estimates at several landmarks are presented in Table 102. During interviews with UK clinical experts, clinical experts stated that the Gompertz extrapolation provides the most clinically plausible long-term estimates of OS for epcoritamab. As such, in line with feedback from UK clinical experts and in line with AIC and BIC criteria, the Gompertz model was selected to model OS for epcoritamab in scenario analysis A.5.

Figure 85: Long-term OS extrapolations for epcoritamab (Scenario analysis A.5)



Abbreviations: OS: overall survival.

Table 102: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.5)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Month					
	12	24	48	60	120	180
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis A.5.
Abbreviations: CI: confidence intervals; NA: not available; OS: overall survival.

Progression-free survival: Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the DLBCL population from EPCORE™ NHL-1 trial adjusted to match Northend et al. 3L+ RW data. These were evaluated based on AIC and BIC values, which are presented in Table 103. The log-normal model performs best in terms of AIC whereas the exponential model performs best in terms of BIC. All the other models except generalised gamma can also be considered viable based on goodness of fit statistics.

Table 103: Goodness of fit statistics for PFS (AIC and BIC; Scenario analysis A.5)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis A.5.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 86. The corresponding survival estimates at several landmarks are presented in Table 104. During interviews with UK clinical experts, clinical experts stated that the Gompertz extrapolation provides the most clinically plausible long-term estimates of PFS for epcoritamab, with one clinical expert noting that the estimates from the Gompertz extrapolation are pessimistic compared to their expectations. As such, in line with this feedback, the Gompertz model was selected to model PFS for epcoritamab in scenario analysis A.5.

Figure 86: Long-term PFS extrapolations for epcoritamab (Scenario analysis A.5)

Abbreviations: PFS: progression-free survival.

Table 104: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.5)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis A.5.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the DLBCL population from EPCORE™ NHL-1 adjusted to match Northend *et al*. 3L+ RW data are presented in Table 87. The log-normal distribution performs best in terms of AIC and

BIC score. The log-logistic model performs best both in terms of AIC and BIC. All the other models except generalized gamma and gamma distributions all demonstrate a good statistical fit.

Table 105: Goodness of fit statistics for TTD (AIC and BIC; Scenario analysis A.5)

Distribution	AIC	BIC
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.5.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 75. The corresponding TTD estimates at several landmarks are presented in Table 88. In line with the reasoning outlined in Appendix C.2.1, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.5, with the gamma extrapolation explored in a scenario analysis.

Figure 87: Long-term TTD extrapolations for epcoritamab (Scenario analysis A.5)

Abbreviations: TTD: time to treatment discontinuation.

Table 106: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Scenario analysis A.5)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.5.
Abbreviations: CI: confidence intervals; NA: not available; TTD: time to treatment discontinuation. survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; HR: hazard ratio.

C.2.7. Updated TE base case analysis B: DLBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T, CAR-T eligible EPCORE™ NHL-1 population adjusted to the ZUMA-1 population is provided in Figure 88.

Figure 88: KM plot of PFS, OS and TTD used in the updated base case analysis B (data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS IRC: progression-free survival-Independent Review Committee; TTD: time to treatment discontinuation.

Overall survival: *Extrapolation selection*

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the adjusted DLBCL population from EPCORE™ NHL-1 trial, and evaluated based on AIC and BIC values, which are presented in Table 107.

The generalised gamma distribution performs best in terms of AIC and BIC, and the exponential, log-normal and Gompertz models could also be considered in terms of goodness of fit.

Table 107: Goodness of fit statistics for OS (AIC and BIC; updated base case analysis B)

Distribution	AIC	BIC
Generalised gamma		
Exponential		
Log-normal		
Gompertz		
Log-logistic		
Weibull		
Gamma		

The Gompertz extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 89. The corresponding survival estimates at several landmarks are

presented in Table 108. During interviews with UK clinical experts, the experts stated that long-term estimates provided by the generalised gamma or lognormal extrapolations could be considered clinically plausible. When considered in comparison with the axi-cel selected extrapolations (Appendix C.4.5) and to ensure the extrapolations reflect the results of the MAIC of epcoritamab versus axi-cel, the Gompertz extrapolation was selected to model OS for epcoritamab in updated base case B.

Figure 89: Long-term OS extrapolations for epcoritamab (updated base case analysis B)

Abbreviations: OS: overall survival.

Table 108: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (updated base case analysis B)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.

Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival: *Extrapolation selection*

Seven parametric distributions were fitted to the PFS KM data of the adjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 trial. These were evaluated based on AIC and BIC values, which are presented in Table 109. The generalised gamma demonstrates the best statistical fit.

Table 109: Goodness of fit statistics for PFS (AIC and BIC; updated base case analysis B)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 90. The corresponding survival estimates at several landmarks are presented in Figure 90and Table 110. During interviews with UK clinical experts, the experts stated that long-term estimates provided by the generalised gamma or loglogistic extrapolations could be considered clinically plausible. When considered in comparison with the axi-cel selected extrapolations (Appendix C.4.5) and to ensure the extrapolations reflect the results of the MAIC of epcoritamab versus axi-cel, the Gompertz extrapolation was selected to model PFS for epcoritamab in updated base case B

Figure 90: Long-term PFS extrapolations for epcoritamab (updated base case analysis B)

Abbreviations: PFS: progression-free survival.

Table 110: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (updated base case analysis B)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in updated base case analysis B. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 are presented in Table 111.

Table 111: Goodness of fit statistics for TTD (AIC and BIC; updated base case analysis B)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The exponential extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 91. The corresponding TTD estimates at several landmarks are presented in Table 112. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years. As such, in line with feedback from UK clinical experts, the exponential extrapolation was selected to model TTD for epcoritamab in updated base case analysis B, with the gamma extrapolation explored in a scenario analysis.

Figure 91: Long-term TTD extrapolations for epcoritamab (updated base case analysis B)

Abbreviations: TTD: time to treatment discontinuation.

Table 112: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (updated base case analysis B))

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model PFS for epcoritamab in the updated base case analysis B. For all timepoints, the model cycle prior to the timepoint of interest is used to inform the survival estimate (e.g. the 12-month estimate is based on model cycle 13 [11.50 months]).
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

C.2.8. Scenario analysis B.1: LBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the LBCL, no prior CAR-T, CAR-T eligible EPCORE™ NHL-1 population adjusted to the ZUMA-1 population is provided in Figure 92.

Figure 92: KM plot of PFS, OS and TTD used in scenario analysis B.1 (data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS IRC: progression-free survival-Independent Review Committee; TTD: time to treatment discontinuation.

Overall survival

Assessment of the PH assumption: Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the adjusted LBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 trial, and evaluated based on AIC and BIC values, which are presented in Table 113.

Table 113: Goodness of fit statistics for OS (AIC and BIC; scenario analysis B.1)

Distribution	AIC	BIC
Exponential		
Gompertz		
Log-normal		
Generalised gamma		
Log-logistic		
Weibull		
Gamma		

The Gompertz extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 93. The corresponding survival estimates at several landmarks are

presented in Table 114. In line with the reasoning outlined in Appendix C.2.7, the Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.1.

Figure 93: Long-term OS extrapolations for epcoritamab (scenario analysis B.1)

The Gompertz extrapolation was selected to model OS for epcoritamab in the updated base case analysis B.1.
Abbreviations: OS: overall survival.

Table 114: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.2.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reported; OS: overall survival.

Progression-free survival*: *Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the adjusted LBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1 trial. These were evaluated based on AIC and BIC values, which are presented in Table 115. The generalised gamma demonstrates the best statistical fit, based on both AIC and BIC criteria.

Table 115: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis B.1)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in In line with the reasoning outlined in Appendix C.2.7, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.Figure 94. The corresponding survival estimates at several landmarks are presented in Table 116. In line with the reasoning outlined in Appendix C.2.7, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.Figure 94: Long-term PFS extrapolations for epcoritamab (scenario analysis B.1)

Abbreviations: PFS: progression-free survival.

Table 116: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reported; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the adjusted LBCL population from EPCORE™ NHL-1 are presented in Table 117.

Table 117: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis B.1)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis B.2.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 95. The corresponding TTD estimates at several landmarks are presented in Table 118. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years. As such, in line with feedback from UK clinical experts, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.1, with the gamma extrapolation explored in a scenario analysis.

Figure 95: Long-term TTD extrapolations for epcoritamab (scenario analysis B.1)

Abbreviations: TTD: time to treatment discontinuation.

Table 118: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation, including the durable remission assumption (scenario analysis B.1)

Distribution	Month					
	12	24	48	60	120	180
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis B.1.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

C.3 Comparators (proportional hazards approach)

As outlined in the original CS, in the base case analyses, the long-term time-to-event outcomes for the comparator arms were derived by applying HRs, derived from the MAICs, to the extrapolated outcomes of epcoritamab. This approach is outlined as a potential modelling approach in NICE DSU TSD14, if the PH assumption is justified.

An overview of the assessment of the PH assumption, and the HRs and CIs that were applied to the epcoritamab curves to derive the time-to-event outcomes for the comparators arms in the cost-effectiveness model are provided in the following section for both the base case analyses and the scenario analyses explored.

C.3.1. Updated base case analysis A: DLBCL, no prior CAR-T adjusted to the SCHOLAR-1 population (epcoritamab versus R-based CIT)

Assessment of the PH assumption for OS

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus R-based CIT are presented in Figure 96 and Figure 97. The log-cumulative hazard plot shows crossing of the treatment arms within the first month of the trial period (≤0 month on the natural log scale), after which the cumulative hazards move parallel over time, suggesting proportionality of the hazard curves for OS. The Schoenfeld residual curve shows almost zero slope, except towards the end, suggesting the covariate is time independent for most of the time. As such, the proportional hazards assumption is likely not violated, as supported by the Grambsch and Therneau test of OS (p>0.05).

Figure 96: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 97: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the R-based CIT arm in the cost-effectiveness model is presented in Table 119.

As outlined in the CS, ToT for R-based CIT is assumed equal to PFS. This assumption has a minimal impact on the total cost associated with R-based CIT. For the R-based CIT arm, the HR for PFS was assumed to be the same as the HR derived for OS, as no PFS KM data are reported from SCHOLAR-1. This is consistent with the approach taken in TA559 and feedback from UK clinical and health economic experts supported the plausibility of this assumption.[6]

Table 119: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (updated base case A)

Outcome	HR (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[b]
Source of comparator efficacy	SCHOLAR-1[7]

[a] The R-based CIT PFS HR is assumed equal to the derived OS HR. [b] As R-based CIT is administered for a fixed number of doses or cycles and based on feedback from UK clinical experts, ToT for R-based CIT is assumed equal to PFS.
Abbreviations: CI: confidence interval; CIT: chemoimmunotherapy; HR: hazard ratio; OS: overall survival; R: rituximab.

C.3.2. Scenario analysis A.1: DLBCL, no prior CAR-T adjusted to Sehn *et al.* 3L+ (epcoritamab versus Pola + BR)

Assessment of PH assumption

Overall survival

The log-cumulative hazard plot and the Schoenfeld residual curve for OS are presented in Figure 98 and Figure 99. The log-cumulative hazard plot shows crossing of the hazard curves at approximately [redacted], suggestion non-proportionality of the hazard curves for OS. The Schoenfeld residual curve demonstrates a patter over time, suggestion the covariate is not time independent. This suggests that the proportional hazards assumption may be violated. However, this is not consistent with with the Grambsch and Therneau test of OS (p-value >0.05) which indicates that the PHA cannot be rejected.

Figure 98: Log-cumulative hazard curve – Epcoritamab versus Pola + BR

Abbreviations: Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 99. Schoenfeld residual curve – Epcoritamab versus Pola + BR

Abbreviations: Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS are presented in Figure 100 and Figure 101. The log-cumulative hazard curves of both treatment arms cross at [redacted] and converge around [redacted]. This suggests non-proportionality of the hazard curves for PFS. The Schoenfeld residual curve shows a pattern over time, which suggests the covariate is not time independent. Hence, proportional hazards may be violated. However, this is not consistent with the Grambsch and Therneau test of PFS (p-value >0.05), which indicates that the proportional hazards assumption cannot be rejected.

Figure 100: Log-cumulative hazard curve – Epcoritamab versus Pola + BR

Abbreviations: Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Figure 101: Schoenfeld residual curve – Epcoritamab versus Pola + BR

Abbreviations: Pola + BR: polatuzumab vedotin with bendamustine plus rituximab.

Comparator efficacy

The unadjusted and adjusted outcomes for epcoritamab (DLBCL population adjusted to synthetically generated Sehn *et al.* 3L+ survival data) versus Pola + BR for the time-to-event driven outcomes are presented in Table 120.

Table 120: Unadjusted and adjusted outcomes for epcoritamab (DLBCL population adjusted to Sehn et al. 3L+) versus Pola + BR (Sehn *et al.* 3L+)

Outcome	HR (95% CI)	
	Before [redacted]	After [redacted]
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]
Source of comparator efficacy	Sehn *et al.* 3L+[7]	

[a] As outlined in the CS, for epcoritamab versus Pola + BR, a piecewise HR approach is used. The first HR is used until [redacted], after which the second HR is used.
Abbreviations: CI: confidence interval; CR: complete response; HR: hazard ratio; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with bendamustine.

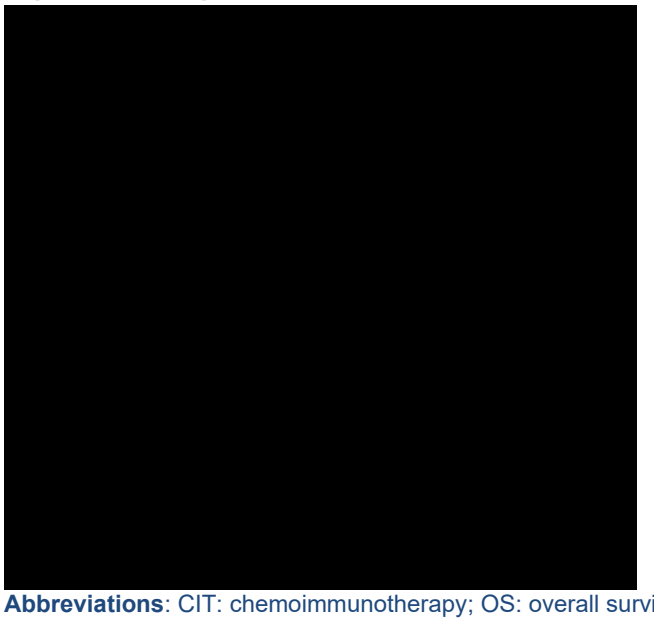
C.3.3. Scenario analysis A.2: DLBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus Pola + BR are presented in Figure 102 and Figure 103. The log-cumulative hazard plot shows crossing of both treatment arms within the first month [redacted]). After [redacted], the cumulative hazards move parallel over time, suggesting proportionality of the hazard curves for OS. In the Schoenfeld residual curve, a pattern over time can be observed, suggesting the covariate is not time independent. Hence, proportional hazards may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p >0.05), which indicates that the proportional hazards assumption cannot be rejected. As such, the proportional hazards assumption is not violated.

Figure 102: Log-cumulative hazard curve – OS (epcoritamab versus Pola +BR)



Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 103: Schoenfeld residual curve – OS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus Pola + BR are presented in Figure 104 and Figure 105. The log-cumulative hazard plot shows that both treatment arms cross within the first 1.5 months of the trial. After 1.5 months, the cumulative hazards seem to diverge over time, suggesting non-proportionality of the hazard curves for PFS. The Schoenfeld residual curve shows a pattern over time, which suggests the covariate is not time independent. Hence, proportional hazards may be violated. This is also consistent with the Grambsch and Therneau test of PFS ($p<0.05$), which indicates that the proportional hazards assumption can be rejected.

Figure 104: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 105: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the Pola + BR arm in the cost-effectiveness model is presented in Table 121.

Table 121: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (Pola + BR)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]

ToT	N/A[a]
Source of comparator efficacy	Liebers *et al.* RW data[8]

[a] As Pola + BR is administered for a fixed number of doses of cycles and there is a lack of published data for ToT, ToT for Pola + BR is assumed equal to PFS, based on feedback from UK clinical experts.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; HR: hazard ratio.

C.3.4. Scenario analysis A.3: LBCL, no prior CAR-T adjusted to Liebers *et al.* RW data (epcoritamab versus Pola + BR)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus Pola + BR are presented in Figure 106 and Figure 107. The log-cumulative hazard plot shows crossing of both treatment arms cross within the first month. After 1 month, the cumulative hazards move parallel over time, suggesting proportionality of the hazard curves for OS. The Schoenfeld residual curve shows a pattern over time, suggesting the covariate is not time independent. Hence, the proportional hazards assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p>0.05), which indicates that the proportional hazards assumption cannot be rejected.

Figure 106: Log-cumulative hazard curve – OS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 107: Schoenfeld residual curve – OS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus Pola + BR are presented in Figure 108 and Figure 109. The log-cumulative hazard plot shows that both treatment arms cross within 1.5 months (~0.5 month on the natural log scale). However, after 1.5 months, the cumulative hazards seem to diverge over time, suggesting non-proportionality of the hazard curves for PFS. The Schoenfeld residual curve shows evidence of a pattern over time, which suggests the covariate is not time independent. Hence, the proportional hazards assumption may be violated. This is also consistent with the Grambsch and Therneau test of PFS ($p<0.05$), which indicates that the proportional hazards assumption can be rejected.

Figure 108: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 109: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the Pola + BR arm in the cost-effectiveness model is presented in Table 122.

Table 122: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (Pola + BR)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	Liebers *et al.* RW data[8]

As Pola + BR is administered for a fixed number of doses or cycles and based on feedback from UK clinical experts, ToT for Pola + BR is assumed equal to PFS.
Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; HR: hazard ratio.

C.3.5. Scenario analysis A.4: DLBCL, no prior CAR-T fully adjusted to SCHOLAR-1 (epcoritamab versus R-based CIT)

Assessment of the PH assumption for OS

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus R-based CIT are presented in Figure 110 and Figure 111. The log-cumulative hazard plot shows both treatment arms cross twice within the first 1.3 months of the trial period (i.e., within 0.3 month on the natural log scale). However, after 1 month, the cumulative hazards move parallel over time, suggesting proportionality of the hazard curves for OS. The Schoenfeld residual curve has almost zero slope except towards the end, suggesting the covariate is time independent for most of the time. Hence, the proportional hazards assumption may not be violated. This is also

consistent with the Grambsch and Therneau test of OS (p>0.05), which indicates that there is not enough evidence to reject the proportional hazards assumption.

Figure 110: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R-based CIT: rituximab-based chemoimmunotherapy.

Figure 111: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the R-based CIT arm in the cost-effectiveness model is presented in Table 123.

Table 123: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (R-based CIT)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
TTD	N/A[b]

Source of comparator efficacy	SCHOLAR-1

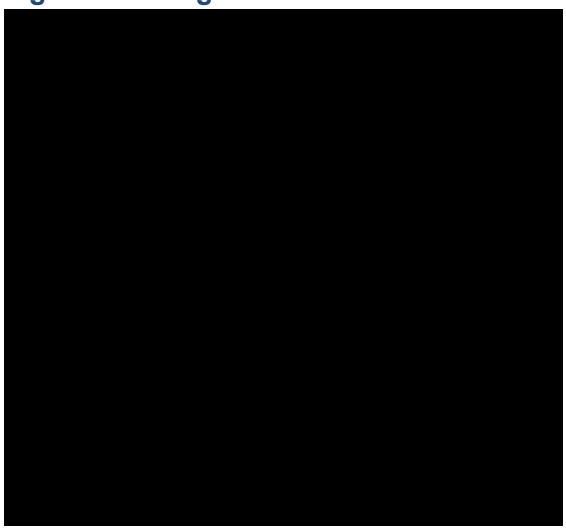
[a] The R-based CIT PFS HR is assumed equal to the derived OS HR. [b] As R-based CIT is administered for a fixed number of doses or cycles and based on feedback from UK clinical experts, ToT for R-based CIT is assumed equal to PFS.
Abbreviations: CI: confidence interval; HR: hazard ratio; N/A: not applicable; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; TTD: time to treatment discontinuation.

C.3.6. Scenario analysis A.5: DLBCL, no prior ASCT adjusted to Northend et al. 3L+ RW data (epcoritamab versus Pola + BR)

Assessment of the PH assumption for OS

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus Pola + BR are presented in Figure 112 and Figure 113. The log-cumulative hazard plot shows both treatment arms cross within the first 1.3 months of the trial period (≤0.3 month on the natural log scale). After 1.3 months, the cumulative hazards move parallel over time, suggesting proportionality of the hazard curves for OS. The Schoenfeld residual plot shows a pattern over time, which suggests the covariate is not time independent. Hence, the proportional hazards assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p>0.05) indicating that the proportional hazards assumption cannot be rejected.

Figure 112: Log-cumulative hazard curve – OS (epcoritamab versus Pola + BR)



Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; R-based CIT: rituximab-based chemoimmunotherapy.

Figure 113: Schoenfeld residual curve – OS (epcoritamab versus Pola + BR)

Abbreviations: OS: overall survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus Pola + BR are presented in Figure 114 and Figure 115. The log-cumulative hazard plot shows both treatment arms cross within the first 1.3 months of the trial period (≤0.3 month on the natural log scale). After 1.3 months, the cumulative hazards move parallel over time, suggesting proportionality of the hazard curves for PFS. The Schoenfeld residual curve shows evidence of a pattern over time, which suggests the covariate is not time independent. Hence, proportional hazards may be violated. However, this is not consistent with the Grambsch and Therneau test of PFS (p>0.05), which indicates that the proportional hazards assumption cannot be rejected.

Figure 114: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 115: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the R-based CIT arm in the cost-effectiveness model is presented in Table 124.

Table 124: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (Pola + BR)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
TTD	NA[a]
Source of comparator efficacy	Northend *et al.*

[a] As Pola + BR is administered for a fixed number of doses or cycles and based on feedback from UK clinical experts, ToT is assumed equal to PFS.
Abbreviations: CI: confidence interval; HR: hazard ratio; N/A: not applicable; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; TTD: time to treatment discontinuation.

C.3.7. Updated base case analysis B: DLBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel)

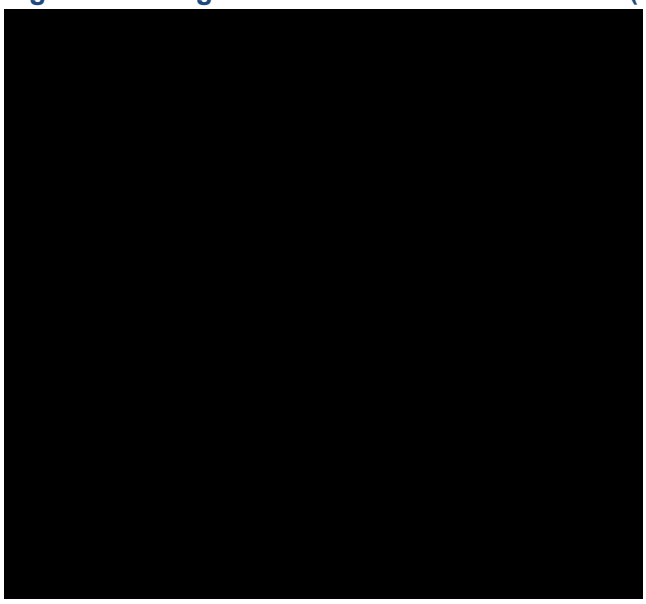
Assessment of PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus axi-cel are presented in Figure 116 and Figure 117. The log-cumulative hazard plot shows both treatment arms cross at around 2.7 months (~1 month on the natural log scale) and around 7.4 months (~2 months on the natural log scale). Therefore, this suggests non-proportionality of the

hazard curves for OS. The Schoenfeld residuel curve shows a pattern over time, suggesting the covariate is not time independent. Hence, the proportional hazards assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p>0.05), which indicates that the proportional hazards assumption cannot be rejected.

Figure 116: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)



Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 117: Schoenfeld residual curve – OS (epcoritamab versus axi-cel)

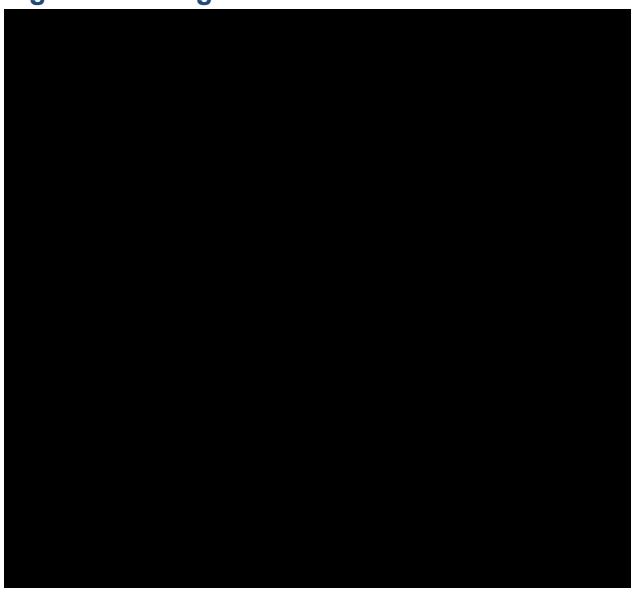
Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus axi-cel are presented in Figure 118 and Figure 119. The log-cumulative hazard plot shows both treatment arms cross at multiple time points, around 1.1 months (~0.1 month on the natural log scale), around 2.7 months (~1 month on the natural log scale), and around 20.1 months (~3 months on the natural log scale). Therefore, this suggests non-proportionality of the hazard

curves for PFS. The Schoenfeld residual curve shows evidence of a pattern over time, which suggests the covariate is not time independent. Hence, the proportional hazards assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of PFS (p>0.05) which indicates that the proportional hazards assumption cannot be rejected.

Figure 118: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)



Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 119: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the axi-cel arm in the cost-effectiveness model is presented in Table 130.

Table 125: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – updated base case analysis B

Outcome	HR (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	ZUMA-1[9]

[a] ToT is not applicable for axi-cel as it is administered as a single-dose.
Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

C.3.8. Scenario analysis B.1: LBCL, no prior CAR-T, CAR-T eligible adjusted to ZUMA-1 population (epcoritamab versus axi-cel)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus R-based CIT are presented in Figure 120 and Figure 121. The log-cumulative hazard plot shows both treatment arms cross between 1.7 to 2.7 months (between 0.5 to 1 month on the natural log scale) and then around 7.4 months (~2 months on the natural log scale). Therefore, this suggests non-proportionality of the hazard curves for OS. The Schoenfeld residual curve shows evidence of a pattern over time, suggesting the covariate is not time independent. Hence, the proportional hazards assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p>0.05) which indicates that the proportional hazards assumption cannot be rejected.

Figure 120: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Figure 121: Schoenfeld residual curve – OS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; OS: overall survival; R: rituximab.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus axi-cel are presented in Figure 122 and Figure 123. The log-cumulative hazard plot shows both treatment arms cross at multiple time points, around 1.2 months (~0.2 month on the natural log scale), around 2.7 months (~1 month on the natural log scale), and around 20.1 months (~3 months on the natural log scale). Therefore, this suggests non-proportionality of the hazard curves for PFS. The Schoenfeld residual curve shows a pattern over time, suggesting the covariate is not time independent. Hence, the proportional hazards assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of PFS (p>0.05) which indicates that the proportional hazards assumption cannot be rejected.

Figure 122: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; R: rituximab.

Figure 123: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel)

Abbreviations: CIT: chemoimmunotherapy; PFS: progression-free survival; R: rituximab.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the axi-cel arm in the cost-effectiveness model is presented in Table 130.

Table 126: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model – scenario analysis B.1

Outcome	HR (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	ZUMA-1[9]

[a] ToT is not applicable for axi-cel as it is administered as a single-dose.
Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

C.4 Comparators (independent modelling approach)

In response to the EAG's request, AbbVie have conducted additional analyses to allow each comparator to be modelled via independent extrapolation of the survival data from SCHOLAR1, ZUMA1 and Sehn et al (3L+), respectively. In the updated base case analysis A and B, R-based CIT and axi-cel are modelled via independent extrapolation.

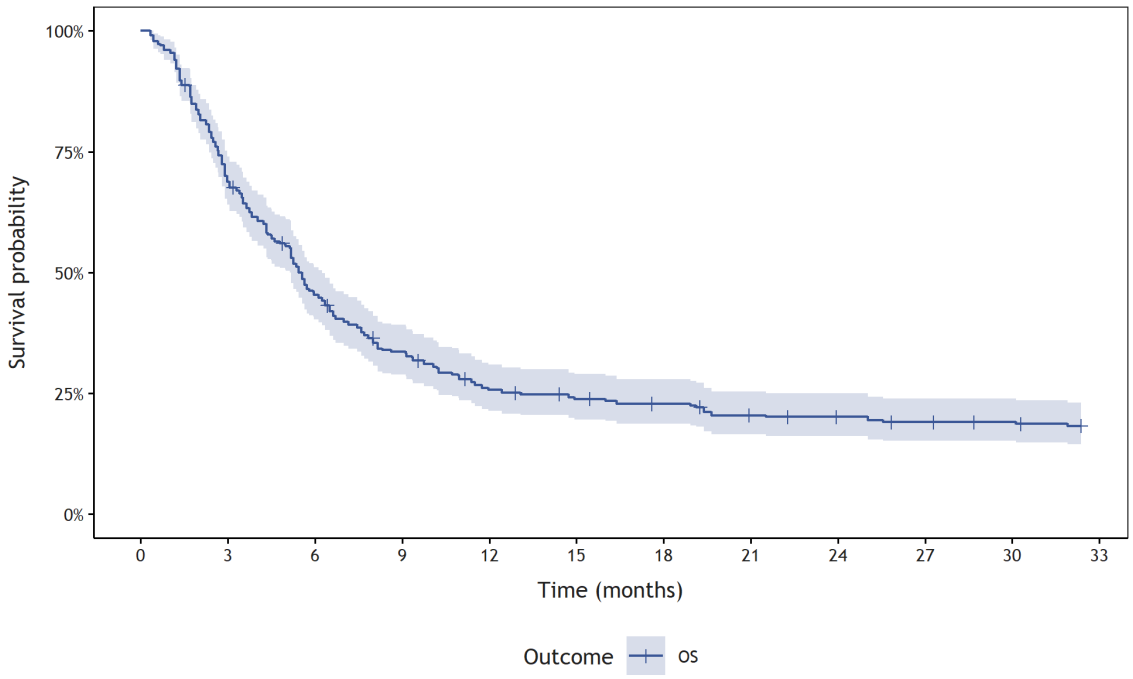
The time-to-event analyses for each comparator are provided in the following section.

C.4.1. R-based CIT based on SCHOLAR-1

Overview

The results presented in this section are for R-based CIT from SCHOLAR-1. A KM plot of OS for the CIT from SCHOLAR-1 is provided in Figure 124.

Figure 124: KM plot of OS for R-based CIT based on SCHOLAR-1



Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data for R-based CIT, and evaluated based on AIC and BIC values, which are presented in Table 127. The generalised gamma distribution performs best in terms of AIC and BIC. The rest of the distributions have a significantly higher AIC and BIC values as compared to the generalised gamma distribution, suggesting a worse statistical fit.

Table 127: Goodness of fit statistics for OS (AIC and BIC; R-based CIT independent extrapolation)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

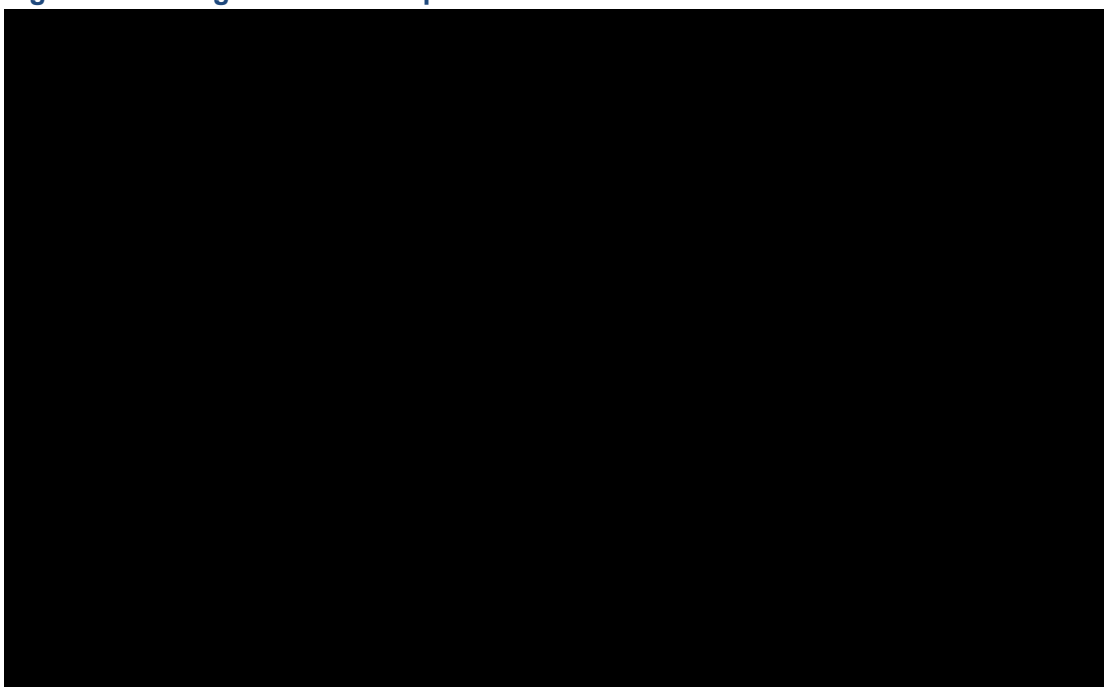
Distribution	AIC	BIC
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for R-based CIT.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 125. The corresponding survival estimates at several landmarks are presented in Table 128.

When comparing the landmark OS estimates based on each extrapolation with the observed OS based on SCHOLAR-1, the generalised gamma provides predicted survival estimates within the 95% CI of observed survival estimates for both 12 and 24 months. During interviews with UK clinical experts, the experts stated that the lognormal or generalised gamma extrapolations provide clinically plausible estimates for R-based CIT. When asked to provide estimates of OS for R-based CIT at 5 years, the experts estimated a range of 5–10%, with the lower plausible limit estimated being 0%. Based on this feedback and considering the statistical fit of the extrapolations, the lognormal extrapolation was selected to model OS for R-based CIT, with the loglogistic and Gompertz extrapolations explored in scenario analyses.

Figure 125: Long-term OS extrapolations for R-based CIT



Abbreviations: OS: overall survival.

Table 128: Predicted and observed OS for R-based CIT at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for R-based CIT.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Progression-free survival

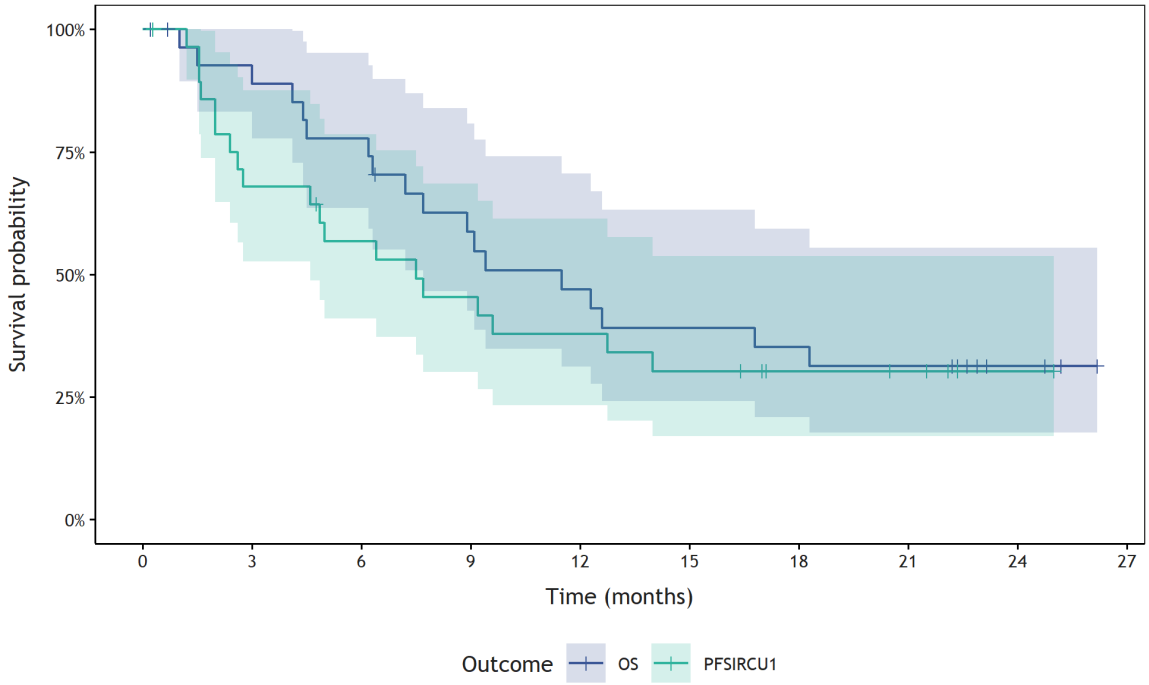
As highlighted in the CS, PFS data for R-based CIT are not available from SCHOLAR-1. As such, PFS for R-based CIT is modelled by applying the HR for OS that was derived from the MAIC of epcoritamab versus R-based CIT (based on SCHOLAR-1), as outlined in Appendix C.3.

C.4.2. Pola + BR based on Sehn *et al.* 3L+

Overview

The results presented in this section are for Pola + BR from synthetically generated Sehn *et al*. 3L+ comparator data. The KM curves of the OS and PFS endpoints for Pola + BR from the Sehn *et al*. 3L+ synthetically generated survival data are presented in Figure 126.

Figure 126: KM plot of PFS and OS for Pola + BR based on Sehn *et al.* 3L+



Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data for Pola + BR, and evaluated based on AIC and BIC values, which are presented in Table 129. The exponential, log-normal, and log-logistic distributions perform best in terms of AIC and BIC.

Table 129: Goodness of fit statistics for OS (AIC and BIC; Pola + BR independent extrapolation)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Distribution	AIC	BIC
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The loglogistic extrapolation was selected to model OS for Pola + BR.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 127. The corresponding survival estimates at several landmarks are presented in Table 130. During interviews with UK clinical experts, the experts stated that the loglogistic, lognormal or generalised gamma extrapolations provide clinically plausible long-term estimates for Pola + BR, based on their experience in UK clinical practice. As such, the loglogistic extrapolation was selected to model OS for Pola + BR, with the lognormal and generalised gamma extrapolations explored in scenario analyses.

Figure 127: Long-term OS extrapolations for Pola + BR

Abbreviations: OS: overall survival.

Table 130: Predicted and observed OS for Pola + BR at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The loglogistic extrapolation was selected to model OS for Pola + BR.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Progression-free survival

The same seven parametric distributions explored in the original submission were also fitted to the PS KM data of for Pola + BR, and evaluated based on AIC and BIC values, which are presented in Table 131. The generalised gamma model performs best both in terms of AIC and BIC compared to the rest of the distributions.

Table 131: Goodness of fit statistics for PFS (AIC and BIC; Pola + BR independent extrapolation)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The gamma extrapolation was selected to model PFS for Pola + BR.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS are presented in Figure 128 The corresponding survival estimates at several landmarks are presented in Table 132. All the distributions overestimate the observed median PFS (7.4 months) except the generalised gamma distribution. During interviews with UK clinical experts, the experts stated that the gamma, exponential, lognormal or loglogistic distributions provide the most plausible estimates based on their experience in UK

clinical practice. As such, the gamma extrapolation was selected to model PFS for Pola + BR, with the lognormal extrapolation explored in a scenario analysis.

Figure 128: Long-term PFS extrapolations for Pola + BR

The gamma extrapolation was selected to model PFS for Pola + BR.
Abbreviations: PFS: progression-free survival.

Table 132: Predicted and observed PFS for Pola + BR at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

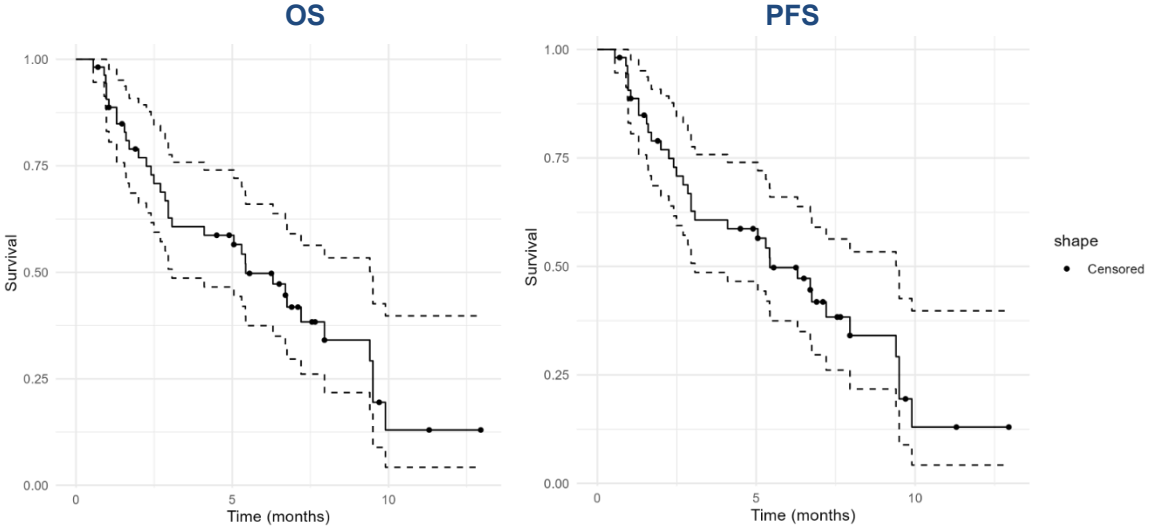
The gamma extrapolation was selected to model PFS for Pola + BR.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

C.4.3. Pola + BR based on Liebers et al. RW data

Overview

The results presented in this section are for the Pola + BR from Liebers *et al.* comparator data. The KM curves of the OS and PFS endpoints for Pola + BR from Liebers *et al.* RW data are presented in Figure 126.

Figure 129: KM plot of PFS and OS for Pola + BR based on Liebers *et al.* RW data



Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data for Pola + BR, and evaluated based on AIC and BIC values, which are presented in Table 133. The exponential, log-normal, and log-logistic distributions perform best in terms of AIC and BIC. However, all distributions could be considered viable based on goodness of fit statistics.

Table 133: Goodness of fit statistics for OS (AIC and BIC; Pola + BR independent extrapolation)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for Pola + BR.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 130. The corresponding survival estimates at several landmarks are presented in Table 134. In order to most closely align with feedback from UK clinical experts on the estimated survival of patients receiving Pola + BR (as outlined in Appendix C.4.2), and consideration of statistical fit, the lognormal extrapolation was selected to model OS for Pola + BR.

Figure 130: Long-term OS extrapolations for Pola + BR

Abbreviations: OS: overall survival.

Table 134: Predicted and observed OS for Pola + BR at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for Pola + BR.

Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reported; OS: overall survival.

Progression-free survival

The same seven parametric distributions explored in the original submission were also fitted to the PS KM data of for Pola + BR, and evaluated based on AIC and BIC values, which are presented in Table 135. The lognormal extrapolation performs best in terms of both AIC and BIC.

Table 135: Goodness of fit statistics for PFS (AIC and BIC; Pola + BR independent extrapolation)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for Pola + BR.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS are presented in Figure 131. The corresponding survival estimates at several landmarks are presented in Table 136. In order to most closely align with feedback from UK clinical experts on the estimated survival of patients receiving Pola + BR (as outlined in Appendix C.4.2), and consideration of statistical fit, the lognormal extrapolation was selected to model PFS for Pola + BR.

Figure 131: Long-term PFS extrapolations for Pola + BR

Abbreviations: PFS: progression-free survival.

Table 136: Predicted and observed PFS for Pola + BR at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for Pola + BR.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reported; PFS: progression-free survival.

C.4.4. Pola + BR based on Northend et al. 3L+ RW data

Epcoritamab efficacy

The results presented in this section are for the Pola + BR from Northend *et al* 3L+ comparator data. The KM curves of the OS and PFS endpoints for Pola + BR from Northend *et al* 3L+ are presented in Table 132.

Figure 132: KM plot of PFS and OS for Pola + BR, based on Northend et al 3L+

Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; RW: real-world.

Overall survival: Extrapolation selection

The same seven parametric distributions were also fitted to the OS KM data of the DLBCL population from EPCORE™ NHL-1 trial adjusted to match Northend *et al*. RW data, and evaluated based on AIC and BIC values, which are presented in Table 101. The log-normal distribution performs best both in terms of AIC and BIC.

Table 137: Goodness of fit statistics for OS (AIC and BIC; Pola + BR independent extrapolation)

Distribution	AIC	BIC
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for Pola + BR, based on Northend et al 3L+.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 85. The corresponding survival estimates at several landmarks are

presented in Table 102. During interviews with UK clinical experts, the experts stated that the generalised gamma or Gompertz extrapolations provide the most clinically plausible long-term estimates for Pola + BR based on their experience in UK clinical practice. As such, the generalised gamma extrapolation was selected to model OS for Pola + BR, with the Gompertz extrapolation explored in a scenario analysis.

Figure 133: Long-term OS extrapolations for Pola + BR (Pola + BR independent extrapolation)

Abbreviations: OS: overall survival.

Table 138: Predicted and observed OS for Pola + BR at several landmarks for each extrapolation (Pola + BR independent extrapolation)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for Pola + BR, based on Northend et al 3L+.
Abbreviations: CI: confidence intervals; NA: not available; OS: overall survival.

Progression-free survival: Extrapolation selection

Seven parametric distributions were fitted to the PFS KM data of the DLBCL population from EPCORE™ NHL-1 trial adjusted to match Northend *et al*. RW data. These were evaluated based on AIC and BIC values, which are presented in Table 103. The generalised gamma distribution performs best in terms of AIC whereas the log-normal distribution performs best in terms of BIC. The log-logistic and exponential distributions can also be considered viable based on goodness of fit statistics.

Table 139: Goodness of fit statistics for PFS (AIC and BIC; Pola + BR independent extrapolation)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The loglogistic extrapolation was selected to model PFS for Pola + BR, based on Northend et al 3L+.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 86. The corresponding survival estimates at several landmarks are presented in Table 104. During interviews with UK clinical experts, the experts stated that the loglogistic or Gompertz extrapolations provide the most clinically plausible long-term estimates for Pola + BR based on their experience in UK clinical practice. As such, the loglogistic extrapolation was selected to model PFS for Pola + BR, with the Gompertz extrapolation explored in a scenario analysis.

Abbreviations: PFS: progression-free survival.

Table 140: Predicted and observed PFS for Pola + BR at several landmarks for each extrapolation (Pola + BR independent extrapolation)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

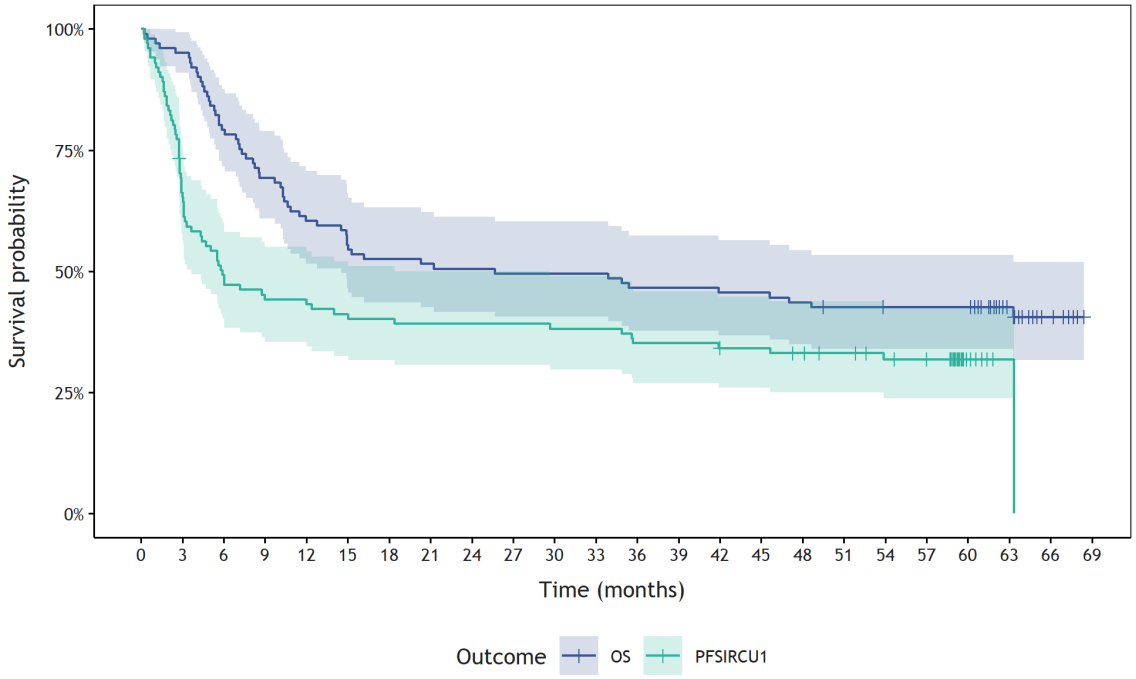
The loglogistic extrapolation was selected to model PFS for Pola + BR, based on Northend et al 3L+.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

C.4.5. Axi-cel based on ZUMA-1

Overview

The results presented in this section are for the axi-cel adjusted to ZUMA-1 comparator IPD. A KM plot of PFS and OS for axi-cel from ZUMA-1 is provided in Figure 134. Although PFS based on ZUMA-1 drops to [redacted], axi-cel is not modelled such that PFS equals [redacted] this is assumed to be due to low number of patients at risk.

Figure 134: KM plot of PFS and OS for axi-cel, based on ZUMA-1



Abbreviations: DLBCL: diffuse large B-cell lymphoma; KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival

Extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the axi-cel data adjusted to ZUMA-1, and evaluated based on AIC and BIC values, which are presented in Table 141. The Gompertz distribution performs best in terms of AIC and BIC. The rest of the distributions have a significantly higher AIC and BIC values compared to the Gompertz distribution, suggesting a worse statistical fit.

Table 141: Goodness of fit statistics for OS (AIC and BIC; axi-cel independent extrapolation)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Distribution	AIC	BIC
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for axi-cel.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 135 presents the long-term extrapolations for OS. The corresponding survival estimates at several landmarks are presented in Table 142. During interviews with UK clinical experts, the experts stated that the generalised gamma, loglogistic or lognormal extrapolations provide the most clinically plausible long-term estimates for axi-cel based on their experience in UK clinical practice. However, when asked to provide estimates for the proportion of patients alive after receiving axi-cel at 5 years, the experts provided a range of 40–45% as the most likely value. As such, in order to align with estimates provided by the experts, the Gompertz extrapolation was selected to model OS for axi-cel.

Figure 135: Long-term OS extrapolations for axi-cel (axi-cel independent extrapolation)

Abbreviations: OS: overall survival.

Table 142: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (axi-cel independent extrapolation)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in the updated base case analysis A.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Progression-free survival

Seven parametric distributions were also fitted to the PFS KM curve for the axi-cel adjusted to ZUMA-1 data. These were evaluated based on AIC and BIC values, which are presented in Table 143. The generalised gamma distribution performs best in terms of AIC and BIC. The rest of the distributions have a significant higher AIC and BIC values compared with the generalised gamma distribution, suggesting a worse statistical fit.

Table 143: Goodness of fit statistics for PFS (AIC and BIC; axi-cel independent extrapolation)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS axi-cel.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS are presented in Figure 136. The corresponding survival estimates at several landmarks are presented in Figure 136. During interviews with UK clinical experts, the experts stated that the generalised gamma extrapolation provides the most clinically plausible long-term estimates for axi-cel based on their experience in UK clinical practice.

However, when asked to provide estimates for the proportion of patients progression-free after receiving axi-cel at 5 years, the experts provided a range of 32–36% as the most likely value. As such, in order to align mostly closely with estimates provided by the experts, the Gompertz extrapolation was selected to model PFS for axi-cel.

Figure 136: Long-term PFS extrapolations for axi-cel

The Gompertz extrapolation was selected to model PFS for axi-cel.
Abbreviations: PFS: progression-free survival.

Table 144: Predicted and observed PFS for axi-cel at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for axi-cel.
Abbreviations: CI: confidence intervals; NA: not applicable; NR: not reached; OS: overall survival.

Appendix D Additional responses related to Pola + BR

As highlighted in the CS, Pola + BR is only a relevant treatment option for a minority of patients with R/R LBCL after two or more lines of therapy, following the recommendation of polatuzumab vedotin and rituximab in combination with cyclophosphamide, hydroxydaunorubicin and prednisone at first-line.[10, 11] For the minority of patients who are ineligible to receive intensive therapies and are polatuzumab-naïve, Pola + BR would remain a treatment option at third-line. However, when asked in February 2023, UK clinicians stated that they would expect less than 5% of patients with R/R LBCL at third-line to receive Pola + BR within the next 24 months (approximately February 2025).[10]

As such, AbbVie do not consider Pola + BR to be a relevant comparator and all responses to key issues identified by the EAG that relate to Pola + BR are provided in the following sections.

D.1 Key Issue 4 and Key Issue 9

Limitations of Sehn *et al.* as the data source informing the MAIC versus Pola + BR

Overestimation of the efficacy of Pola + BR

As highlighted by the EAG, a major limitation of Sehn *et al.* is that the efficacy data overestimate the efficacy of Pola + BR compared with UK clinical practice. It is important to note that this biases considerably against epcoritamab and the results of this MAIC are therefore unlikely to be an accurate representation of the comparative efficacy of epcoritamab versus Pola + BR in UK clinical practice.

In line with feedback from UK clinical experts that Northend *et al.* more accurately reflects the outcomes associated with Pola + BR in UK clinical practice, AbbVie requested efficacy data for the subgroup of patients in this dataset that have received two or more prior lines of therapy (hereafter referred to as Northend *et al.* 3L+) and have conducted a number of MAICs of epcoritamab versus Pola + BR using these data. Detailed information related to all MAICs conducted are presented in Appendix B.1.1.2 and Appendix B.2. A summary of the results of the MAIC versus Sehn *et al.* 3L+ and the MAIC versus Northend *et al.* 3L+ are presented in Table 145.

The results of the MAIC versus Northend *et al.* 3L+ in which all clinically important variables are adjusted for demonstrates a [redacted] treatment benefit of epcoritamab versus Pola + BR in terms of both OS and PFS and clearly demonstrate that the MAICs versus Sehn *et al.* 3L+ are heavily biased against epcoritamab.

Table 145: Comparison of MAIC results for epcoritamab versus Pola + BR, based on Sehn *et al.* 3L+ and Northend *et al.* 3L+

Epcoritamab population	Comparator data source	Adjusted OS and PFS HR (95% CI)	
		Up to [redacted]	After [redacted]
DLBCL, no prior CAR-T	Sehn et al. 3L+[a]	OS: [redacted] PFS: [redacted]	OS: [redacted] PFS: [redacted]

DLBCL, no prior ASCT	Northend et al. RW data 3L+	OS: [redacted]

[a] For the MAIC versus Sehn *et al.* 3L+ informing scenario analysis A.1, piecewise HRs were generated as outlined in the CS Appendices.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; OS: overall survival.

Lack of adjustment for all baseline characteristics

Additionally, the EAG highlight that the proportion of primary refractory patients in the Sehn *et al.* (2019) population is not reported. AbbVie agree that this represents a source of uncertainty in this MAIC but, as noted by the EAG, the lack of reporting for certain factors in Sehn *et al.* is an uncertainty that is beyond the control of AbbVie. Although the proportion of primary refractory patients cannot be directly adjusted for, adjusting for other related factors (such as refractory to last prior anti-CD20 agents) is likely to result in the proportion of primary refractory patients in the EPCORE™ NHL-1 and the Sehn *et al.* 3L+ populations being similar.

Although AbbVie maintain that adjusting for all clinically important variables (rather than all reported variables) represents the most robust approach, to further explore any uncertainty surrounding this, AbbVie have also provided additional supportive MAICs in which epcoritamab is fully adjusted to comparator populations. These analyses are further discussed in response to Key Issue 7.

Limitation of the MAIC for epcoritamab versus Pola + BR to the DLBCL population

The EAG are concerned that the results of MAIC of epcoritamab (DLBCL, no prior CAR-T population) versus Pola + BR do not cover the full LBCL population detailed in the original decision problem. AbbVie wish to highlight that this MAIC accurately reflects the use of Pola + BR and the anticipated use of epcoritamab, due to the NICE recommendation of Pola + BR as a treatment for R/R DLBCL and [redacted].[12]

D.2 Key Issue 7

As highlighted in response to Key Issue 7, AbbVie have conducted MAICs versus Pola + BR in which all reported baseline characteristics are adjusted for. AbbVie maintain that the MAICs used to inform scenario analyses A.1–A.3 and A.5 provide the most robust estimates of comparative efficacy, but additional MAICs have been provided as supportive analyses.

A comparison of the results of the fully adjusted MAICs versus Sehn *et al*. 3L+ and Northend *et al.* 3L+, alongside AbbVie's preferred MAICs, are presented in Table 146.

Table 146: Comparison of MAIC results for epcoritamab versus Pola + BR, based on Sehn *et al.* 3L+ and Northend *et al.* 3L+

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted OS and PFS HR (95% CI)	
			Up to [redacted]	After [redacted]
DLBCL, no prior CAR-T	Sehn et al. 3L+	7; no truncation [a] (N_{eff}=[redacted]	OS: [redacted] PFS: [redacted]	OS: [redacted] PFS: [redacted]

		10; with truncation (N_{eff}=[redacted]	OS:[redacted] PFS:[redacted]
DLBCL, no prior ASCT	Northend et al. RW data 3L+	11; with truncation (N_{eff}=[redacted]	OS: [redacted]
		13; with truncation (N_{eff}=[redacted]	OS: [redacted] PFS: [redacted]

[a] For the MAIC versus Sehn *et al.* 3L+ informing scenario analysis A.1, piecewise HRs were generated as outlined in the CS Appendices.
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; OS: overall survival.

D.3 Key Issues 11–14

For the comparison of epcoritamab versus Pola + BR, the EAG state that the OS and PFS curves for Pola + BR are likely to considerably underpredict OS and PFS in the long-term when compared with the observed data in Sehn *et al.* However, as highlighted in response to Key Issue 9 and acknowledged by the EAG, data reported by Sehn *et al.* substantially overpredict the survival of patients receiving Pola + BR compared with UK RWE. As such, Sehn *et al.* does not represent a robust source to assess the external validity of the long-term OS and PFS estimates for Pola + BR.

As highlighted in response to Key Issues 4 and 9, AbbVie have obtained OS and PFS estimates for Pola + BR based on Northend *et al.* 3L+, presented in Figure 137. These data from Northend *et al.* 3L+ represents a more suitable source to externally validate the OS and PFS estimates for Pola + BR in the cost-effectiveness model, compared with Sehn *et al.* In all scenario analyses conducted comparing epcoritamab with Pola + BR (based on Sehn *et al.* 3L+, Liebers *et al.* RW data or Northend *et al.* 3L+ RW data), the landmark OS and PFS estimates are broadly aligned with the estimates observed in the Northend *et al.* 3L+ UK RWE, but both generally overestimate OS and PFS. As such, in the scenario analyses of epcoritamab versus Pola + BR, the long-term estimates for Pola + BR are representative of UK clinical practice within the patient population of interest in this submission.

Figure 137: PFS and OS KM curves for Pola + BR, split by treatment line (2L versus 3L+), based on UK RWE

[redacted]

Abbreviations: 2L: second line; ≥3L: third line and beyond.

References

1. AbbVie Data on File. EPCORE™ NHL-1 CSR. April 2023. .
2. AbbVie Data on File. EPCORE™ NHL-1 CSR. January 2022. .
3. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-638.
4. EUnetHTA. PTJA06 – Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. Available at: https://www.eunethta.eu/ptja06/ [Accessed: 09 December 2022].
5. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-165.
6. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. Final appraisal document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document [Accessed: 1 November 2022].
7. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood advances 2021;5:4149-4155.
8. Liebers N, Duell J, Fitzgerald D, et al. Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas. Blood Adv 2021;5:2707-2716.
9. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
10. AbbVie Data on File. Epcoritamab for Treating Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL). UK Medical Advisory Board – Meeting Report. 22 February 2023.
11. AbbVie Data on File. Epcoritamab in Large B-Cell Lymphoma: Clinical Validation Interviews. December 2022–May 2023.
12. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Available at: https://www.nice.org.uk/guidance/ta649 [Accessed: 31 Mar23].

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

The company has not provided any of the fully-adjusted MAIC, with independently fitted curves in the model for the Pola+BR or the axi-cel comparisons but have included this for R-based CIT. This is an inconsistent approach and we would need to have these curves in the model as these are likely to be our preferred MAIC curves, and at the very least, these are likely to form very important scenarios for the committee to consider. We will need these as soon as possible.

As outlined by AbbVie in response to Key Issue 7 and Clarification Question A15, AbbVie maintain that the MAICs in which all clinically important variables are adjusted for (based on feedback from UK clinical experts on the most important prognostic factors and treatment effect modifiers) provide the most robust estimates of comparative efficacy. The MAICs were conducted in accordance with NICE Decision Support Unit TSD18 and following feedback from UK clinical experts; in particular, treatment effect modifiers and prognostic factors were identified via an evidence-based process including consideration of peer-reviewed published indirect treatment comparisons (ITCs) and previous NICE evaluations in the indication of interest, empirical testing of prognostic status in the EPCORE™ NHL-1 trial and input from UK clinical experts. Moreover, the outputs of the MAICs were validated by UK clinical experts in terms of the balance in baseline characteristics between the adjusted epcoritamab populations and the comparator populations, and the comparative efficacy estimates.

Regardless, in response to the original request from the EAG, AbbVie conducted a series of additional MAICs (using the [redacted] data cut from EPCORE™ NHL-1 for epcoritamab) versus R-based CIT (based on SCHOLAR-1), axi-cel (based on ZUMA-1) and Pola + BR (based on Sehn *et al.* 3L+, Liebers *et al.*, and Northend *et al.* 3L+), in which all reported variables (or the maximum number of variables that is feasible) are adjusted for. When all variables are adjusted for, the effective sample size of the epcoritamab population is decreased (to N_{eff}=[redacted], N_{eff}=[redacted] and N_{eff}=[redacted] for the comparisons versus R-based CIT, axi-cel and Pola + BR [based on Sehn *et al.* 3L+], respectively). Broadly, the results of the MAICs requested by the EAG are consistent with the results of AbbVie's preferred MAICs. For the comparisons of epcoritamab versus R-based CIT and epcoritamab versus axi-cel, the results suggest increased comparative efficacy for epcoritamab versus the comparators (when compared with the MAICs informing the base case analyses versus R-based CIT and axi-cel). For the fully adjusted MAIC versus Pola + BR (based on Sehn *et al.* 3L+ and Northend *et al.* 3L+), the results suggest a slightly increased treatment benefit for Pola + BR (when compared with the MAICs informing scenario analyses A.1 and A.5), [redacted].

To support the development of the Technical Engagement response, AbbVie conducted teleconference interviews with three UK clinical experts. As part of these interviews, the clinicians were presented the MAICs conducted in response to requests from the EAG (using the [redacted] data cut from EPCORE™ NHL-1 for epcoritamab) and were asked to provide their thoughts on the additional baseline characteristics adjusted for and the plausibility of the results. All clinicians raised concerns regarding the decreased effective sample sizes when all reported variables were adjusted for and many clinicians noted that the additional variables adjusted for are unlikely to provide substantial benefit in terms of achieving better balance in important prognostic variables and treatment effect modifiers. When shown the results of these MAICs, the clinicians expressed concern over the clinical plausibility of all of the fully adjusted MAICs. In particular, the clinical experts noted that the results of the fully adjusted MAIC versus axi-cel were likely overly optimistic for epcoritamab and they questioned the clinical plausibility of the treatment benefit of Pola + BR suggested by the fully adjusted MAICs of epcoritamab versus Pola + BR. It is apparent that this methodology has the potential to introduce bias and the comparative efficacy estimates are associated with increased uncertainty.

Due to time constraints and prioritisation of requested analyses during Technical Engagement, the requested MAICs were run but scenario analyses informed by the fully adjusted MAICs for all comparators were not performed, given that AbbVie do not agree with the requested methodology or clinical plausibility of the results. However, to demonstrate that the methodology requested by the EAG has a minimal impact on the cost-effectiveness results, AbbVie conducted an exemplary scenario analysis for epcoritamab versus R-based CIT in which the fully adjusted MAIC is used to inform the populations in the model and each treatment arm is independently extrapolated (scenario analysis A.4). This scenario analysis decreased the incremental cost-effectiveness ratio (ICER) from £26,915 to £25,485 (Table 21, Technical Engagement response), demonstrating that AbbVie's base case approach represents a conservative approach and this should not have a substantial impact on decision-making. Of the base case comparators, the fully adjusted MAIC versus R-based CIT was selected to conduct the exemplary scenario analysis as UK clinical experts heavily questioned the plausibility of the results of the fully adjusted MAIC versus axi-cel, due to these results being overly optimistic in favour of epcoritamab. However, based on the results of the fully adjusted MAIC versus axi-cel which show an increased treatment benefit of epcoritamab in terms of both OS and PFS (compared with the base case MAIC), it is likely that cost-effectiveness of epcoritamab versus axi-cel would improve.

Based on the above, AbbVie have not updated the model to include the outputs of the fully adjusted MAICs versus axi-cel and Pola + BR but full results of these MAICs are presented in Appendix B of the Technical Engagement response for consideration by the EAG and NICE Committee.

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Post-Technical Engagement Severity and Cost Calculations

In line with the method used in the original submission, the expected quality-adjusted life expectancy for the general population was calculated in line with the methods provided by Schneider *et al.* (2022).[102] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2017–2019.[95] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D, as reported by Hernandez Alava et al. (2022) through the NICE DSU.[103] A summary of the QALY shortfall calculations for each analysis is presented in Table 1.

Table 1: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with the condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Ineligible for, or choose not to receive, intensive therapy			
Base case A: epcoritamab versus R-based CIT[a]			
[redacted]	0.86	[redacted]	94.00%
Scenario analysis A.1: epcoritamab versus Pola + BR (based on Sehn *et al.* 3L+)			
[redacted]	1.36	[redacted]	88.27%
Scenario analysis A.2: epcoritamab versus Pola + BR (based on Liebers *et al.* RW data; epcoritamab DLBCL population)			
[redacted]	0.52	[redacted]	94.50%
Scenario analysis A.3: epcoritamab versus Pola + BR (based on Liebers *et al.* RW data; epcoritamab LBCL population)			
[redacted]	0.51	[redacted]	94.81%
Scenario analysis A.5: epcoritamab versus Pola + BR (based on Northend *et al.* 3L+ RW data)			
[redacted]	[redacted]	[redacted]	93.80%
Base case population B: eligible for intensive therapy			
[redacted]	5.60	[redacted]	60.90%

[a] As base case A represents the primary comparison for epcoritamab versus R-based CIT, the severity modifier calculations based on scenario analysis A.4 have not been provided.
Abbreviations: axi-cel: axicabtagene ciloleucel; QALY: quality-adjusted life year; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R-based CIT: rituximab-based chemoimmunotherapy.

The average cost of a course of treatment with epcoritamab and each comparator in each analysis is presented in Table 2.

Table 2: Average duration of a course of treatment with epcoritamab and comparators

Analysis	Average cost of a course of treatment with epcoritamab (list price)	Average cost of a course of treatment with the comparator (list price)
Population A		
Base case A: epcoritamab versus R-based CIT[a]	[redacted]	£3,277
Scenario analysis A.1: epcoritamab versus Pola + BR (based on Sehn *et al.* 3L+)	[redacted]	£67,104
Scenario analysis A.2: epcoritamab versus Pola + BR (based on Liebers *et al.* RW data; epcoritamab DLBCL population)	[redacted]	£54,702
Scenario analysis A.3: epcoritamab versus Pola + BR (based on Liebers *et al.* RW data; epcoritamab LBCL population)	[redacted]	£54,702
Scenario analysis A.5: epcoritamab versus Pola + BR (based on Northend *et al.* 3L+ RW data)	[redacted]	£54,357
Population B		
Base case population B: eligible for intensive therapy	[redacted]	£346,982[b]

[a] As base case A represents the primary comparison for epcoritamab versus R-based CIT, the average cost of a course of treatment with epcoritamab in scenario analysis A.4 has not been provided. b For axi-cel, drug acquisition costs are captured in the one-time drug acquisition costs; as such, the value reported above refers to the one-time drug administration and monitoring costs.

Abbreviations: axi-cel: axicabtagene ciloleucel; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R-based CIT: rituximab-based chemoimmunotherapy.

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

1. **The EAG presents the impact of switching on the LTR assumption in the model for each comparator, 2 years after the end of treatment. The EAG could not conduct the same analysis for epcoritamab as the company's model did not directly track which patients stopped treatment with epcoritamab (as opposed to the comparator treatments which have a fixed duration).**

As highlighted previously, the dosing of epcoritamab differs from currently available treatments; epcoritamab is received continuously until unacceptable toxicity or progression whereas currently available treatments are all received for a fixed duration. As such, patients in the epcoritamab arm would always be on-treatment according to modelled time to treatment discontinuation (TTD) whilst progression-free and it is not possible to apply an external long-term remission assumption two years after patients discontinue treatment with epcoritamab in the current model.

However, in case the External Assessment Group (EAG) wish to present the impact of assuming the external long-term remission assumption, the cost-effectiveness model has been updated such that TTD is decoupled from long-term remission; this means that the long-term remission assumption only impacts progression-free survival (PFS) and overall survival (OS), whilst TTD follows the extrapolated TTD curve.

AbbVie have conducted analyses using the updated cost-effectiveness model, in which the long-term remission assumption is applied two years after treatment initiation (to allow consistency between the epcoritamab and comparator arms). The results of these analyses are presented in Table 1.

Table 1: Long-term remission analyses (probabilistic; epcoritamab PAS price)

Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT		[redacted]	[redacted]	£26,915	[redacted]	[redacted]
LTR assumed to be captured within selected extrapolations	LTR applied 2 years after treatment initiation[a]	[redacted]	[redacted]	£14,945	[redacted]	[redacted]
Base case population B versus axi-cel		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
LTR assumed to be captured within selected extrapolations	LTR applied 2 years after treatment initiation[a]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

[a] The cost-effectiveness model has been updated such that TTD is decoupled from long-term remission.
Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; Incr.: incremental; LTR: long term remission; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy; TTD: time to treatment discontinuation.

2. **Assesses the potential impact of using the population from EPCORE™ NHL-1 that matches the definition of population A in the CS (i.e., patients ineligible to receive CAR-T), both to conduct the MAICs and the utility analysis for population A.**

The epcoritamab population used in the matching adjusted indirect treatment comparisons (MAICs) and utility analysis for population A (epcoritamab versus rituximab-based chemoimmunotherapy (R-based CIT), based on SCHOLAR-1, and polatuzumab vedotin with rituximab and bendamustine (Pola + BR; based on Sehn *et al.* 3L+) included patients who had diffuse large B-cell lymphoma (DLBCL) and had

received no prior chimeric antigen receptor T-cell (CAR-T) therapy (N=[redacted]). This population was selected to more closely align with the comparator populations, as the SCHOLAR-1 and Sehn *et al.* studies were conducted prior to the availability of CAR-T therapies, hence did not include any patients that had previously received CAR-T therapy.[1, 2,]

As highlighted by the EAG, it is unclear whether the comparator populations were restricted to patients ineligible for intensive therapies. As the phrasing of 'ineligible for intensive therapies' is an artefact of alignment with clinical practice since the approval of CAR-T therapies and considering the populations included in the trials, it is unlikely that criteria were included to specifically select patients who were ineligible for intensive therapies. As such, AbbVie maintain that it is not appropriate for the epcoritamab population to be restricted to those ineligible for intensive therapies without applying the same restriction to the comparator populations; conducting such an analysis would introduce bias of unknown magnitude and direction. Given that AbbVie do not have access to the comparator trials' individual patient data, such an adjustment is unfeasible, and therefore, the current analyses represent the fairest comparison based on the available data.

3. Assesses the potential impact of conducting the utility analysis for population B in the DLBCL population.

As stated in the Technical Engagement response, all base case analyses were updated to align with the anticipated license population for epcoritamab. This included updating the MAIC informing base case B to the MAIC of epcoritamab (DLBCL, no prior CAR-T, CAR-T eligible population) versus axi-cel. In addition, the population informing the utility values was updated to the DLBCL, no prior CAR-T population of the EPCORE™ NHL-1 trial. For scenario analysis B.1 (epcoritamab LBCL, no prior CAR-T, CAR-T eligible population versus axi-cel), utility values derived from the LBCL population from EPCORE™ NHL-1 are used to align as closely as possible to the population informing the efficacy data.

As such, AbbVie have not conducted a utility analysis using the DLBCL, no prior CAR-T, CAR-T eligible population from EPCORE™ NHL-1; if the sample size of patients in the DLBCL, no prior CAR-T population was restricted further to those ineligible for intensive therapies it would be insufficient to derive robust utilities from. Moreover, it is more appropriate to derive health state-specific utilities, rather than based on eligibility for CAR-T therapy. Regardless, there are not expected to be any large discrepancies between utilities of the DLBCL, no prior CAR-T population and the same population restricted further to those ineligible for intensive therapies specifically.

To address the EAG's concerns regarding the utility values being derived from a population that is not specifically CAR-T eligible, a scenario analyses has been conducted in which the utility values for population B are informed by ZUMA-1, which is a CAR-T eligible population. These utility values have been previously accepted by the NICE Committee in recent appraisals for R/R DLBCL (TA649, ID3695 and TA559).[3-5]

The results for this scenario analysis are presented in Table 2. Changing the utility values to those based on a CAR-T eligible population has minimal impact on the cost-effectiveness results and epcoritamab remains dominant versus axi-cel. As such, the source of utility values for population B should not be considered a significant source of uncertainty.

Table 2: Health state values scenario analyses (probabilistic; epcoritamab PAS price)

Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population B versus axi-cel		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Utility values derived from the DLBCL, no prior CAR-T population of EPCORE™ NHL-1	Utility values informed by the ZUMA-1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; incr.: incremental; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

4. **Investigates what is driving the uncertainty in QALYs and costs seen in the PSA results – potentially confirming the EAG view that it comes from the uncertainty embedded in the survival curves used by the company, and the fact that these are key drivers of the economic results.**

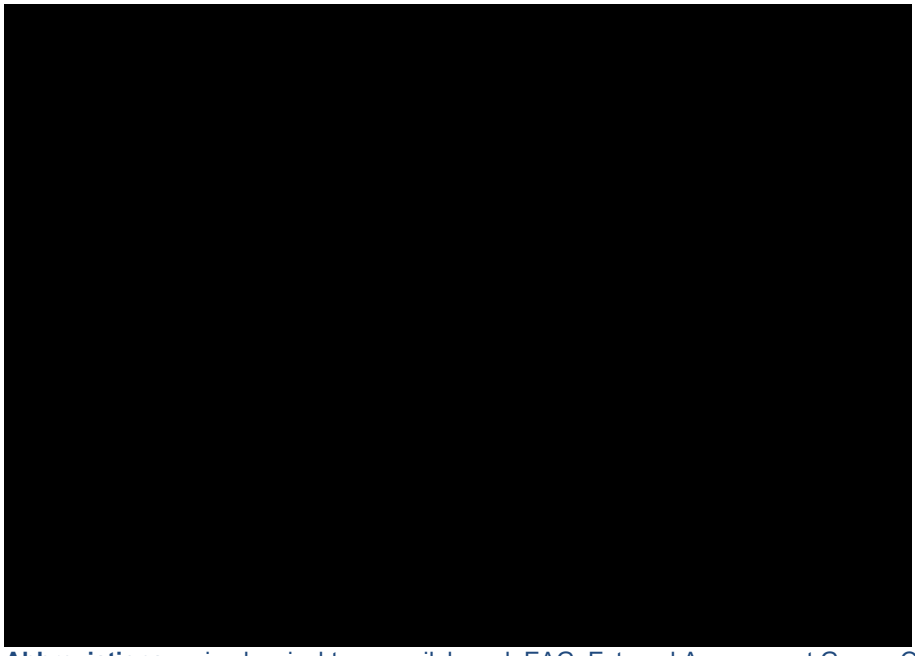
As requested by the EAG, AbbVie have investigated the cause of the uncertainty in the quality-adjusted life years (QALYs) and costs observed in the probabilistic sensitivity analysis (PSA) scatter plots for the epcoritamab arm, particular for the comparison of epcoritamab versus axi-cel. The variation observed in the scatter plots is potentially a result of the underlying uncertainty in the MAICs used to inform the cost-effectiveness analyses, as is expected for any indirect treatment comparison. This is particular the case for the MAIC of epcoritamab (DLBCL, no prior CAR-T, CAR-T eligible population) versus axi-cel, as demonstrated by the wide 95% confidence intervals associated with the point estimates from this MAIC. As outlined previously, AbbVie conducted a range of MAICs using different epcoritamab populations; when the effective sample size in the epcoritamab arm is decreased the variation in QALYs and costs observed in the scatter plot for the epcoritamab arm is increased, and vice versa.

Based on the updated base case analyses post-Technical Engagement, the probability of cost-effectiveness at a £30,000 willingness-to-pay threshold for epcoritamab versus R-based CIT, Pola + BR (based on Sehn *et al.*) and axi-cel is [redacted]%, [redacted]% and [redacted]% respectively. As a standard approach in cost-utility analysis, this probability of cost-effectiveness accounts for the degree of uncertainty in QALYs and costs for the epcoritamab arm (and comparator arms), and as this probability remains high, the uncertainty associated with the economic analysis should not have a significant impact on decision-making.

5. **The option in the model to reintroduce the LTR for axi-cel at 2 years (when the EAG-preferred curves are used) generates higher QALYs associated with the PFS state for axi-cel than epcoritamab, even though the proportion of patients in the PFS epcoritamab curve remains higher (or the same) as that of axi-cel throughout the model. In the limited time available, the EAG could not fully explore the cause of this error or correct it in the model. Therefore, the EAG recommends that the company provides a corrected version of the model for this scenario before the first committee meeting.**

After clarifying that the EAG are referring to scenario analysis 8 presented in Table 35 of the EAG report (applying the long-term remission assumption for axi-cel at two years), AbbVie are unable to match the discrepancy observed by the EAG or the results presented for this scenario analysis. When applying the long-term remission assumption for axi-cel at two years (but all other settings remaining the same as AbbVie's base case analysis B), the QALYs associated with the PFS health state are [redacted] for epcoritamab compared with axi-cel ([redacted] versus 4.243). However, based on the shape of the PFS curves for epcoritamab and axi-cel, these results are expected; in this scenario, the curves are [redacted], after which the epcoritamab curve is [redacted] than the axi-cel curve (Figure 1).

Figure 1: Base case analysis B, with the long-term remission assumption applied to axi-cel (at two years; scenario analysis 8 from Table 35 of the EAG report): PFS and OS extrapolations for epcoritamab and axi-cel



Abbreviations: axi-cel: axicabtagene ciloleucel; EAG: External Assessment Group; OS: overall survival; PFS: progression-free survival.

It is possible that the discrepancy observed by the EAG occurred when the utility estimate applied to patients in long-term remission was set to apply age-related general population mortality (on the Utilities tab, F24), rather than to equal the PFS utility value. When AbbVie conduct scenario analysis 8 presented in Table 35 of the EAG report, with the addition of the long-term remission utilities being set to age-related general population mortality, the QALYs associated with the PFS health state for axi-cel are higher than those for epcoritamab (4.598 versus 4.519), whilst the PFS curves follow the same shape as outlined above (Figure 1). However, this is due to the increased utility value applied to patients in long-term remission, thereby increasing the QALYs accrued in the PFS health state in the axi-cel arm. AbbVie are unable to match the results presented for scenario analysis 8 in the EAG report.

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood advances 2021;5:4149-4155.
2. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-165.
3. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Available at: https://www.nice.org.uk/guidance/ta649/resources/polatuzumab-vedotin-with-rituximab-and-bendamustine-for-treating-relapsed-or-refractory-diffuse-large-bcell-lymphoma-pdf-82609146587077 [Accessed: 10 October 2022].
4. NICE. Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10645/documents [Accessed: 25 November 2022].
5. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. Final appraisal document. Available at: https://www.nice.org.uk/guidance/ta559/documents/final-appraisal-determination-document [Accessed: 1 November 2022].

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 16 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

NICE National Institute for Health and Care Excellence

1. Your name	David Lewis
2. Name of organisation	Plymouth Hospitals NHS Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? X A specialist in the treatment of people with relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments? ☐ A specialist in the clinical evidence base for relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐x Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The achievement of durable remission and disease control with minimal symptom burden. Ideal outcome is cure with a good quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	At least a partial response (defined by 50% reduction In lymph node size) is generally considered a clinically significant response. Achievement of complete response (CR) is preferable, as demonstrated by the superior outcomes of patients achieving a CR in studies, with longer remissions and some patients potentially cured.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments?	Yes. Whilst there have been significant advances in the treatment of relapsed/refractory high grade B NHL there is still unmet need. CAR-T is a potentially curative option but not all patients can access CAR-T, due to rapid disease kinetics, co-morbidities, or manufacturing problems. Furthermore there are other reasons eg geographical, lack of social support, whereby CAR-T may not be an acceptable option for some patients. Roughly 60% of patients will relapse post CAR-T therapy and there is currently no effective treatment option for those patients. Epcoritamab can overcome many of these factors as it is a treatment that can be delivered with minimal delay and is relatively well tolerated compared with CAR-T, and can be delivered in local hospitals as opposed to regional CAR-T centres

11. How is relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	New BSH guidelines are being drafted due to rapid changes over the last few years Standard pathway for current patients: 1st line - Pola-RCHP. If patients relapse within 1 year (70% of relapses occur in the 1st year) and are considered fit for ASCT then they are eligible for 2nd line CAR-T (axi-cel). If relapse > 1year, then patients who are fit for ASCT will have high dose chemo and ASCT. For those patients not fit for ASCT there are a number of tx options - including R-Gem-OX, R-benda-pola or a number of other palliative chemo regimens Third line patients can have CAR-T (if no prior CAR-T in 2nd line) if considered fit enough, or palliative chemotherapy Epcoritamab would be used after relapse following CAR-T therapy (either 3rd line or 4th line depending on patient's route to CAR-T) or 3rd line in patients who do not have CAR-T 3rd line either due to patients wishes to have local treatment or because CAR-T is unsuitable
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology is deliverable by haematology units with a chemotherapy unit, as opposed to CAR-T which needs to be delivered by specialised centres. Whilst the side effect profile of this technology is similar to CAR-T it is much more mild and is predictable as the vast majority off cytokine release syndrome (CRS) occurs on cycle 1 D15. There will be some training and education requirements to safely deliver this treatment, mainly around the recognition, grading and management of CRS - there are well defined treatment algorithms The treatment itself is easy to administer as it is a subcutaneous injection

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, absolutely. There are currently no effective treatments in this clinical setting, whereas epcoritamab induces a CR in approximately 40% of patients even with prior CAR-T treatment, and the responses appear durable with minimal toxicity and good quality of life. This represents a significant improvement compared with currently available treatments in both length and quality of life
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Subgroup analysis of the GEN-01 study shows good responses regardless of prior treatment or histological subtype, such as prior CAR-T treatment. Some patients who cannot access CAR-T due to social/geographical constraints may benefit relatively more from epcoritamab
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Compared with CAR-T it is much easier to deliver as it has no manufacturing delay, and can be given in local hospitals. CRS is an important side effect which will require training but should be manageable. In the majority of instances this technology will be given in preference to palliative chemotherapy. It is easier to give than chemotherapy as it is a subcutaneous injection. Some training will be required on eg management of cytokine release syndrome.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Response assessments will be as standard for high grade lymphoma, with CT and PET/CT to assess response treatment and diagnose relapse. Treatment will be stopped if lymphoma progression is diagnosed.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	It is certainly easier to administer compared to CAR-T as it is a subcutaneous, "off the shelf" injection. There is also no requirement to travel to a CAR-T centre which is a significant problem for a number of patients and places stress and is major burden for patients who have to travel a long way and may be socially isolated. Patients undergoing CAR-T also have uncertainty in their treatment pathway due to time taken to manufacture the product and requirement for bridging therapy and possible disease progression whilst waiting manufacture.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes. This treatment can induce durable Complete responses in a group of patients for which no standard of care options are available post CAR-T and also allows a highly effective treatment option for patients unsuitable for CAR-T or who do not want to travel to regional CAR-T centres. This represents a step-change.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effect of this technology is cytokine release syndrome which may require an admission on C1 D15.Otherwise trial data suggests that the AE profile is not particularly burdensome and there are minimal toxicities once patients are established on treatment.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In terms of inclusion criteria the trial is representative of clinical practice as it included patients who were relapsed post ASCT, or ineligible for ASCT and also allowed relapse after prior CAR-T therapy. The most important outcomes are CR rate, PFS and OS and all of these are measured in the trial No further AEs outside of a trial context have come to light
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA872 for axi-cel and TA649 for Pola + BR]?	No
23. How do data on real-world experience compare with the trial data?	Currently no RWD have been published.

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Epcoritamab will allow more equality of access compared with CAR-T due to geographical limitations of CAR-T and the difficulties (social support, economic, travel) that some patients have with accessing CAR-T

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. The population in the decision problem may be broader than that covered by the trial. The trial was limited to:
- **those that failed (or were ineligible for) prior autologous stem cell transplant**
- **had ECOG scores 0 to 2**
 	
- What is the approximate size of the population in UK clinical practice with relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments that would be eligible for epcoritamab who:
  - have not had prior autologous stem cell transplant? (%)
  - have ECOG scores of 3 or greater? (%)
	Trial populations are inevitably selected populations and the "real world" population may include some patients that would not have fulfilled the trial inclusion criteria.
	
	The GEN-01 study did allow patients to have 2 lines of therapy, and an autoSCT did not have to be part of their prior treatment so I don't think that is an issue. Patients at 3rd line treatment would generally be considered "auto-ineligible" as they would have been offered it in prior lines of treatment if it was a good treatment option.
	
	Whilst 2nd line CAR-T cells cannot be considered in this appraisal as they are not baseline commissioned the reality is that in UK practice the majority (approx 70%) of patients who have relapsed high grade B NHL will have 2nd line CAR-T in preference to an autologous stem cell transplant
	
	Some patients with R/R lymphoma will have ECOG>=3 at the time of relapse, possibly due to the lymphoma, and some of these may be considered eligible for treatment with epcoritamab. This will be a relatively low number though, approx 5%.

2. Issues associated with the paper used to inform data for SCHOLAR-1 in the matching-adjusted indirect comparisons (MAIC) vs rituximab-based chemoimmunotherapy (R-based CIT)	

3. Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used Questions related to R-based CIT: - What forms of R-based CIT are used most in UK clinical practice? - Is the company's choice of rituximab, gemcitabine and oxaliplatin (R-GEMOX) in their model an appropriate proxy of other types of R-based CIT in terms of a similar clinical effect and cost/resources associated with treatment? - Are you aware of any additional data sources for clinical efficacy data for R-based CIT (other than SCHOLAR-1)?	There isn't a universally accepted standard of care R/R high grade B NHL 3rd line setting. R-chemo approaches are not considered particularly effective but are given in a palliative setting. R Gem-OX is a frequently used regimen and is a reasonable comparator. R-benda-pola is likely to be used less as R-Pola-CHP is now available 1st line for the majority of patients and most patients who relapse will already have had polatuzumab.
4. The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population	I think it is unlikely that the histological subtype is particularly important in the 3rd line setting, and only 5% had non DLBCL subtypes
5. Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment - What proportion of people would you expect have epcoritamab as 4th line after CAR-T at 3rd line? - Do you think that the effectiveness of epcoritamab would differ between people who have received prior CAR-T and people who have not received prior CAR-T?	As mentioned above, the majority of patients with high grade B NHL from now will have 1st line Pola-R-CHP. If 2nd line tx is required, 70% will get CAR-T. Of those, most patients will be eligible for 3rd line ecporitamab if they relapse and would receive this at 3rd line. Of the 30% of R/R patients who do not have 2nd line CAR-T, they will receive 2nd line high dose chemo followed by autologous SCT. If they subsequently relapse (approx 50%) they will be eligible for 3rd line CAR-T. Approximately 60% of these will relapse and may be eligible for 4th line epcoritamab.

6. It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments	The Epcore NHL-1 study included patients treated with >=2 prior lines of treatment, and patients had to have had relapsed post prior ASCT or be ineligible for ASCT, so these patients would not usually be considered eligible for intensive treatments at that time. 34.5% of patients in the Pola-BR study had had prior ASCT, so presumably had been considered fit for intensive treatment previously.

7. Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons
 	
- Would the following factors influence the prognosis of people with relapsed or refractory large B-cell lymphoma?
  o Refractory to last anti-lymphoma treatment
  o IPI score ≥3
  o ≥3 lines of chemo and ASCT
  o SCT any time after refractory disease
	Subgroups of patients within the GEN01 study have been analysed and the data has been presented at BSH meeting. None of the factors such as prior treatment had any effect on the response rates to epcoritamab.
	
	All of the factors mentioned are poor prognosis factors. At the point of 3rd line therapy for high grade B NHL there are no real “good prognosis” groups.

8. All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1	
9. Limitations of Sehn *et al.* for the MAIC vs Pola + BR Are the results of pola + BR in relapsed or refractory DLBCL reported in Sehn *et al.* (NCT02257567) reflective of UK clinical practice?	

10. Limitations of ZUMA-1 for the MAIC vs axi-cel	ZUMA-1 was a Phase II single arm study. The primary analysis was performed on the infused patient population as opposed to the ITT population. This may introduce a bias in favour of the ZUMA-1 population

11. Implementation of when the long-term remission assumption starts in the model
 	
- Is it reasonable to assume that people with relapsed or refractory disease after 2 or more systemic treatments will enter long-term remission (i.e. no further disease progression) if their disease has not progressed after a certain time point?
- At what time point would people enter long-term remission, for example:
  o 2 years after treatment initiation?
  o 2 years after end of treatment?
  o Another time point?
- Would the time point at which long-term remission begins differ for people treated with epcoritamab (vs comparator treatments), noting that epcoritamab does not have a stopping rule and is indicated to be given until progression or unacceptable toxicity?
- Would people in long-term remission require regular follow-up and, if so, how frequent and what would follow-up entail?
- How would you expect quality of life (utility values) for people in long-term remission to compare with:
	This is a novel treatment in a group of patients with no standard of care options.
	
	I would generally consider the absence of relapsed disease at 2 years after completion of treatment as an important milestone - we know that relapses after this timepoints are rare in high grade lymphoma
	
	We know from the GEN-01 study that the achievement of CR usually happens quite early in the treatment course at 2-3 months. A smaller number of patients will convert from a PR to a CR later in the treatment course. If CR is achieved, about 2/3 of patients remain in CR at 15 months.
	
	Regarding the time to assess response, this is similar between epcoritamab and SOC treatments such as R-chemo, in which I'd also expect any responses to be seen at 2-months. I would not expect durable responses with R-chemo in this setting.
	
	People on epcoritamab would require ongoing follow up assuming epcoritamab is given as per trial protocol in which case it is given to progression, but the follow up would be limited. We do not know if it may be possible to interrupt or stop epcoritamab, or give limited duration treatment in certain patients who achieve CR, but this may become clear in the future.
	
	I would expect quality of life to be significantly improved compared to those patients on R-chemo, for 2 reasons. Lymphoma related symptoms will be dramatically improved in those patients who have a reponse to epcoritamab. Treatment related toxicity is likely to be significantly better than if patients have chemotherapy.

○ people who have not yet progressed at an earlier stage (i.e. 1 year after treatment initiation)? ○ age-matched general population? - How would you expect survival for people in long-term remission to compare with age-matched general population?	

12. Estimation of overall survival in the model	
13. Estimation of progression-free survival in the model.	
14. Estimation of time to treatment discontinuation in the model.	
15. The population(s) used to derive utilities used in the model (in relation to eligibility for CAR-T).	
16. Treatment and administration costs of comparators in the model. - How many cycles of R-based CIT are typically used in UK? (company assume 8 cycles but EAG notes several UK centres only allow up to 6)	We consider clinical perspectives may particularly help to address this issue. We would usually give 6 cycles of R-chemo.

17. Subsequent treatments in the model.
 	
- What subsequent treatments would you expect for people who received 3rd line treatment with:
  o epcoritamab?
  o R-based CIT?
  o pola + BR?
  o axi-cel?
- Would eligibility for subsequent therapies after 3rd line treatment with epcoritamab differ between:
  o those ineligible for or who chose not to take intensive therapies like CAR-T
  o those eligible for intensive therapies like CAR-T?
- What proportion of people who had epcoritamab as 3rd line treatment would go on to have CAR-T?
	We consider clinical perspectives may particularly help to address this issue.
	
	A lot of this depends on what treatment was given in prior lines.
	
	3rd line post epco - palliative chemotherapy/best supportive management. It does depend however on what treatment they received in prior lines (ie Pola-RCHP vs RCHOP 1st line, 2nd line Axi-cel or High dose chemotherapy).
	
	Post R-based CIT: Palliative chemo/best supportive management
	
	Post Pola-BR - if prior 1st line RCHOP and 2nd line high dose chemo +- ASCT, then 4th line - CAR-T
	
	Post 3rd line Axi-cel - if prior polaRCHP, then GDP, I would offer R-chemo (eg R GEM-OX)
	
	In terms of eligibility for subsequent lines of treatment, there may be a small number of patients who may be considered candidates for allogeneic stem cell transplant, and these are more likely to be the CAR-T eligible patients. Most patients will not fall into this category
	
	The number of patients with 3rd line epcoritamab who go on to CAR-T will be low as most patients who do not have CAR-T 2nd or 3rd line will have strong clinical or other reasons not to have it at that stage

18. Disease follow-up costs in the model. - Would the frequency of follow-up of people receiving epcoritamab change depending on how long they had been receiving epcoritamab for?	Yes. The patient will still have to attend for the sc injection 4 weekly but once a CR has been obtained the clinical follow up could be reduced. Certainly in terms of imaging etc I would not perform further routine scans once a CR has been attained.

Additional question: The company considers pola + BR not to be one of the main comparators. This is because they considered pola + BR would no longer be used for those who previously had polatuzumab as part of pola + R-CHP (following February 2023 guidance on pola + R-CHP in untreated patients). - What proportion of people would you expect to be eligible for pola + BR as 3rd line treatment in current practice?	The majority of patients will receive R-PolaCHP as 1st line treatment. We know that if relapses occur, the majority (approx 70%) occur in the 1st year after treatment. Most clinicians will not offer polatuzumab to patients who relapse after initial Pola-RCHP. The 30% of patients with later relapses may be considered candidates for Pola-BR
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Epcoritamab is a highly effective novel treatment that has a high response rate of 40%, which is sustained, even in very heavily pretreated patients with very limited treatment options
It is an easily deliverable treatment by any haematology centre that can give standard chemotherapy treatments
Whilst it does cause some side effects, these occur in a predictable time frame and are manageable without intensive care support (as opposed to CAR-T treatment)
Patients feel well on treatment and it does not appear to cause late toxicity
Because this treatment can be given by any heamatology centre, it will be easy to achieve equality of access to it, as opposed to CAR-T treatment which can be difficult for some patients to access

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 16 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Wendy Osborne
2. Name of organisation	Newcastle upon Tyne Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? x☐ A specialist in the treatment of people with relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments? ☐ A specialist in the clinical evidence base for relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐x Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is to obtain a durable remission and, in some patients, cure. In those patients in whom cure is not achieved then we want to achieve as long as possible with disease control and minimal symptoms allowing a good quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any reduction in lymphoma volume is significant but the most important is achieving a complete response as some of these will lead to cure. If a partial response is achieved, then this will usually lead to the patient living longer and having better symptom control but most people with a partial response eventually do go on an progress. A complete response in large cell lymphoma is important as a proportion of patients will be cured and those that will have usually have a longer duration of response compared to those in a partial response.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments?	This is an area of lymphoma care in which there is still a large unmet need. In a 3rd line and beyond setting the current option is CAR T treatment, the data of which are not intention to treat data. Of all the patients who reach CAR T infusion, 60-65% of them will progress and if no further treatment available are likely to die from large cell lymphoma in a short number of months. There are also patients who aren't considered eligible because the disease kinetics are such that the clinician predicts that they cannot wait for the 6 weeks of apheresis and manufacturing time required for CAR T. There are also pts who progress in the bridging period and don't reach infusion in CAR T. In my experience the toxicity with epcoritamab is less than CAR T and so I would consider this as an option for patients who aren't fit enough for CAR T. Although we are fortunate enough to have many CAR T centres in the UK, there are still some patients who do not want to travel and stay 1 month near a CAR T centre and therefore choose to not be referred for CAR T. Epcoritamab can be delivered in local hospitals and therefore will expand equity of access to T cell engagers.
11. How is relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments currently treated in the NHS?	The BSH guidelines are out of date and are currently being rewritten but are not yet published. The standard pathway is well defined.

• Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	If a patient is auto fit and relapse within 12 months of first line polaRCHP then they will have Axi-cel 2nd line on the CDF. If they are auto fit and relapse after 12 months then they will have 2nd line high dose chemo and an auto.If the patient is auto unfit they will have rgemox if planning 3rd line CAR T or will have Rbenda pola (if the pt hasn't had pola first line) or oral palliative chemo (eg DECC) if not planning CAR T 3rd line. Third line patients will either have CAR T or palliative chemo depending on patients wishes and if it is considered likely that we can keep the patient stable whilst the CAR Ts are being manufactured. If epcoritamab is approved it will be used 3rd line, for pts who had CAR T 2nd line or for those patients who may prefer having treatment close to home and not travelling to a CAR T centre. It will also be used 4th line for those patients who relapse post CAR T.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology is similar to CAR T but significantly easier to deliver which will mean that more patients will choose to access it as they will not have to travel to a CAR T centre. The main side effect is cytokine release syndrome which is predictable and treatable with tocilizumab. Hospitals which can manage patients with neutropenic sepsis can manage CRS and this is why bispecifics have been successfully delivered in a clinical trial setting in hospitals geographically isolated from large CAR T centres or allo centres. Epcoritamab can be delivered in secondary care in all centres which deliver chemo at risk of neutropenic sepsis (eg RCHOP). There will be some additional training to ensure CRS is managed appropriately and this has already started as more bispecifics are being used in trials in both haematology and oncology. ICANS is very rare and very different to CAR T, patients can still drive and do not need a carer with them due to the infrequent nature of ICANS
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	Yes, the response rates are high and about 40% achieve CR for which many are durable. This includes a high-risk population, more than a third of which have had prior CAR T. In my clinical experience using bispecifics in clinical trials the

• Do you expect the technology to increase health-related quality of life more than current care?	patients have minimal side effects, particularly after the first cycle and they describe excellent quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The data shows response even across high-risk subgroups (eg double hit lymphoma, relapse post CAR T). There are patients which choose to not travel away from home for a month for CAR T and these patients could benefit from epcoritamab because it could be delivered in their local hospital.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier thatn3rd line CAR T. If epcoritamab is to be used for relapse post 2nd line CAR T rather than instead of CAR T in a non-CAR T centre then hospital staff will need to be trained in the management of CRS but this is straightforward to do. There is no requirement for apheresis, stem cell lab and central line insertions, remaining within 2 hours of CAR T centre, care giver present for 1st month, no driving for 2 months as there are for CAR T.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A scan (either CT or PET) will identify that the patient has unfortunately progressed and now needs 3rd line treatment. CT or PET will also be used when the patient is on epcoritamab to assess response and if clear progression then treatment stopped. No other testing is required, just imaging which is done at present to identify progression.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Qualitative data from CAR T and palliative care teams (Stenson et al) have shown that the requirements for a patient to be 2 hours (previously 1 hour) from a CAR T centre for a month is very difficult for patients. Waiting for apheresis slots and manufacturing time is also reported as causing high levels of stress. Bridging treatment for CAR T is toxic whether chemo or radiotherapy is used. Epcoritamab will not have this negative impact because of the ability to administer straight after seeing the patient.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Bispecific antibodies are innovative and allow the benefits of lymphoma response by T cell activation without the need for apheresis, manufacture, and long inpatient stays for patients. It also allows true "intention to treat" data whereby you would be able to see the patient in clinic and if eligible start treatment within a few days. This technology allow access irrespective of geography in the UK and also access for those patients who have rapid progression of lymphoma who are not stable enough to wait for CAR T manufacture.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Step up dosing mitigates against CRS and is all done as an outpatient. At first full dose an overnight stay is required to monitor or treat for CRS (or a long day unit day) but the patients' quality of life is otherwise good for this targeted treatment.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In the UK the trials are currently focusing on achieving durable responses for patients who relapse and using T cell engagers either as bispecific antibodies or cellular therapies is a primary focus of this research. The most important outcomes are PFS, CR rates and durability of the CR as well as the low toxicity profile suggesting that the months gained (if durable response not achieved) allow the patients to remain out of hospital and have good quality of life. I am not aware of any adverse events not reported.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA872 for axi-cel and TA649 for Pola + BR]?	No

23. How do data on real-world experience compare with the trial data?	Limited real-world data as licence only just obtained although would predict that RWD will be published in the next 12 months.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	In my experience patients who live a long way from a CAR T centre and potentially those who have less income to pay for travel may access 3rd line CAR T less and so epcoritamab may reduce some of these inequalities.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. The population in the decision problem may be broader than that covered by the trial. The trial was limited to: - **those that failed (or were ineligible for) prior autologous stem cell transplant** - **had ECOG scores 0 to 2** - What is the approximate size of the population in UK clinical practice with relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments that would be eligible for epcoritamab who: o have not had prior autologous stem cell transplant? (%)	We consider clinical perspectives may particularly help to address this issue. In a 3rd line setting most patients would be considered auto ineligible because we would only do an auto in a second line setting and even if the pt had CAR T 2nd line most clinicians would not then do an auto 3rd line (it is ineffective in the majority of pts, >80% even in a 2nd line setting and is extremely toxic). Most pts would have PS 0-2 but it would depend on the cause of the low PS, if due to lymphoma and not other comorbidities then an occasional pt may be considered with PS3 (if within reimbursement criteria) but in general I think most pts will have PS0-2.

○ have ECOG scores of 3 or greater? (%)	3rd line patients who had not had prior auto would have been about 50% but this will increase now that we have 2nd line CAR T on the CDF. 5-10% of pts have a PS 3 or more.
2. Issues associated with the paper used to inform data for SCHOLAR-1 in the matching-adjusted indirect comparisons (MAIC) vs rituximab-based chemoimmunotherapy (R-based CIT)	
3. Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used Questions related to R-based CIT: - What forms of R-based CIT are used most in UK clinical practice? - Is the company's choice of **r**ituximab, gemcitabine and oxaliplatin (R-GEMOX) in their model an appropriate proxy of other types of R-based CIT in terms of a similar clinical effect and cost/resources associated with treatment? - Are you aware of any additional data sources for clinical efficacy data for R-based CIT (other than SCHOLAR-1)?	We consider clinical perspectives may particularly help to address this issue. R chemo in a 3rd line setting is not effective. Rgemox seems a reasonable comparator as the chemo options are very limited in a 3rd line setting. I will not use Rbendapola if I have used pola first line which I now use for most of my pts. I will use R gemox or DECC if a patient has been failed by auto and CAR T It would be unusual for me to use high dose chemo such as GDP or IVE in 3rd line and beyond as that tends to be used 2nd line prior to auto.
4. The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population	
5. Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment - What proportion of people would you expect have epcoritamab as 4th line after CAR-T at 3rd line?	We consider clinical perspectives may particularly help to address this issue. About 60% of pts will relapse post CART and these patients would be considered fit enough for epcoritamab. There will be some patients who

- Do you think that the effectiveness of epcoritamab would differ between people who have received prior CAR-T and people who have not received prior CAR-T?	progress too quickly and drop PS and therefore maybe 30-40% of pts who have had CAR T may then be given epcoritamb
6. It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments	
7. Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons - Would the following factors influence the prognosis of people with relapsed or refractory large B-cell lymphoma? o Refractory to last anti-lymphoma treatment o IPI score ≥3 o ≥3 lines of chemo and ASCT o SCT any time after refractory disease	We consider clinical perspectives may particularly help to address this issue. I would consider the number of prior lines to be the most significant of these with pts having had 4 lines being higher risk than 3 lines. IPI is not validated after first line treatment. Refractory and prior SCT are poor prognostic factors, but number of prior lines is the most impt in my opinion.
8. All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1	
9. Limitations of Sehn *et al.* for the MAIC vs Pola + BR Are the results of pola + BR in relapsed or refractory DLBCL reported in Sehn *et al.* (NCT02257567) reflective of UK clinical practice?	
10. Limitations of ZUMA-1 for the MAIC vs axi-cel	

11. Implementation of when the long-term remission assumption starts in the model
 	
- Is it reasonable to assume that people with relapsed or refractory disease after 2 or more systemic treatments will enter long-term remission (i.e. no further disease progression) if their disease has not progressed after a certain time point?
- At what time point would people enter long-term remission, for example:
  ○ 2 years after treatment initiation?
  ○ 2 years after end of treatment?
  ○ Another time point?
- Would the time point at which long-term remission begins differ for people treated with epcoritamab (vs comparator treatments), noting that epcoritamab does not have a stopping rule and is indicated to be given until progression or unacceptable toxicity?
- Would people in long-term remission require regular follow-up and, if so, how frequent and what would follow-up entail?
- How would you expect quality of life (utility values) for people in long-term remission to compare with:
  ○ people who have not yet progressed at an earlier stage (i.e. 1 year after treatment initiation)?
  ○ age-matched general population?
	We consider clinical perspectives may particularly help to address this issue.
	
	I would consider 2 years from end of treatment (which is when most people obtain a CR) a good assumption of long-term remission if the pt is still in a CR.
	
	After 2 years I will offer pts annual telephone appt and discharge at 3-4 years. If a patient is still on treatment, they will be reviewed by specialist nurse on day of treatment and come to clinic once a year. Pts on bispecs usually feel very well and I have pts back in full time manual employment and majority describe “feeling normal”.
	
	If pts achieve a CR with epcoritamab then the data presented by C Thieblemont at ICML 2023 suggests that if pts achieve a CR then 66% of the patients remain in CR at 15 months. This was in a high-risk population when 70% of pts had had 3 or more prior line, ie not in a 3rd line setting for the majority and 39% prior CAR T. I would therefore expect if epcoritamab is used 3rd line that the durable responses would be higher.
	
	Patients on long term treatment would have follow up but it would be limited. The future may be that we can identify patients who can stop treatment (as with the DESTINY CML trial for CML Clarke et al)
	
	Utility values will depend on response to treatment as well as prior treatment. Pts who have just had polarCHP and then Rgem ox or CAR T second line and achieve a CR will have minimal drop in utility value because most pts have minimal toxicity to these treatments. For those pts who have needed a BEAM auto 2nd line then I would expect a bigger drop because this is one of the most toxic treatments, we subject

- How would you expect survival for people in long-term remission to compare with age-matched general population?	our pts to. Epcoritamab is well tolerated and has minimal toxicity and most drop in utility value is because of toxic prior treatments or progression of lymphoma. The survival will be slightly worse compared to the general population but as discussed, the difference will be less if epcoritamab is given 3rd line not 4th or 5th and also if 2nd line treatment does not include a BEAM auto. Data from LY12 and LYSA suggest that if pts are still remission free at 5 years then their survival matches the matched population.
12. Estimation of overall survival in the model	
13. Estimation of progression-free survival in the model.	
14. Estimation of time to treatment discontinuation in the model.	
15. The population(s) used to derive utilities used in the model (in relation to eligibility for CAR-T).	
16. Treatment and administration costs of comparators in the model. - How many cycles of R-based CIT are typically used in UK? (company assume 8 cycles but EAG notes several UK centres only allow up to 6)	We consider clinical perspectives may particularly help to address this issue. The optimal 3rd line comparator would be Axicel/Tisacel. If considering R chemo as 3rd line (because the pt had CAR T 2nd line) then usually would give 6 cycles of R chemo

17. Subsequent treatments in the model.
 	
- What subsequent treatments would you expect for people who received 3rd line treatment with:
  o epcoritamab?
  o R-based CIT?
  o pola + BR?
  o axi-cel?
- Would eligibility for subsequent therapies after 3rd line treatment with epcoritamab differ between:
  o those ineligible for or who chose not to take intensive therapies like CAR-T
  o those eligible for intensive therapies like CAR-T?
- What proportion of people who had epcoritamab as 3rd line treatment would go on to have CAR-T?
	We consider clinical perspectives may particularly help to address this issue.
	
	Subsequent treatments would depend on which prior treatments the pt has had
	
	If 3rd line epco (assuming pola RCHP first line and axicel 2nd line) then 4th line would consider Rgemox, RDECC and very occasionally take a patient to allogeneic transplant if they obtained an adequate response to 4th line (unlikely)
	
	If 3rd line epco (assuming RCHOP, RGDP auto 2nd line) then would could CAR T 4th line or Rbenda pola or Rgemox or R DECC
	
	If 3rd line epco (assuming RCHOP, Rgemox 2nd line) then would consider Rbenda pol of RDECC
	
	3rd line polaBR (if RCHOP and RGDP auto 2nd line) would consider 4th line CAR T and 4th or 5 th line epco
	
	3rd line polaBR (if RCHOP and axicel 2nd line) would consider epco 4th line and then regemox, RDECC 5th line
	
	3rd line Axicel (if polaRCHP fist line and GDP 2nd line) would used epco 4th line Rgemo ox or RDECC 5th line
	
	3rd line Axicel if RCHOP first line and Rgemox 2nd line then epco 4th line and Rbendapola 5th line or Rgemox or RDECC
	
	All patients if failed by both T cell engagers I would try to get to allo with R chemo but this is a very rare situation and allo for LBCL is not vey effective and associated with high mortality and so I would be trying to

	use T cell engagers first which are more effective and significantly less toxic. Patients may choose 3rd line epco over CAR T because it is easier to deliver, some pts may then have 4th line CAR T but the fitness required for CAR t and epco are similar, maybe slightly fitter for CAR T. Very fit pts who have epco 3rd line would be considered for CAR T 4th line if they haven't had CAR T 2nd line (which is now the standard approach if relapse <12 months which 75% of pts do) I think few people will have CAR T post epco because most will have CAR T 2nd line and at present we have more FU data for CAR T (not ITT data) and so young fit pts near a CAR T centre will still have CAR T before epco. This may change if follow up of the bispec intention to treat data remains as durable.
18. Disease follow-up costs in the model. - Would the frequency of follow-up of people receiving epcoritamab change depending on how long they had been receiving epcoritamab for?	We consider clinical perspectives may particularly help to address this issue. The frequency will reduce once they have obtained a CR and after 2 yrs this will be nurse led when they attend for subcut injection.
Additional question: The company considers pola + BR not to be one of the main comparators. This is because they considered pola + BR would no longer be used for those who previously had polatuzumab as part of pola + R-CHP (following February 2023 guidance on pola + R-CHP in untreated patients). - What proportion of people would you expect to be eligible for pola + BR as 3rd line treatment in current practice?	In current practice about 20 % of pts would receive polaBR 3rd line or beyond but this will drop as more and more pts will have had pola first ine.
Are there any important issues that have been missed in EAR?	Not that I am aware of

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Epcoritamab has a novel mode of action allowing “off the shelf” T cell engagement and a has a high CR rate of 40% which appears durable

This data are intention to treat, unlike comparing with CAR T 3rd line which is only patients who reached infusion

Epcoritamab is easy to deliver and can be delivered in most hospitals following training for CRS management. It is possible that this improves equity of access for patients with RR DLBCL

ICANS is very rare and does not require additional costings, patients do not need a carer with them and can drive on treatment.

Patients feel well on this treatment and it less toxic than other relapsed lymphoma treatments.

Thank you for your time.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

EAG response to company technical engagement comments

September 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135903.

1 Introduction

This document provides the Evidence Assessment Group's (EAG's) critique of the company's technical engagement (TE) response to the key issues raised in the EAG report for the appraisal of epcoritamab for treating relapsed or refractory large B-cell lymphoma (R/R LBCL) after 2 or more systemic treatments [ID4045]. Each of the key issues are discussed in detail in Section 2. For a summary of the EAG's judgement on each issue, see Table 1. The company's updated base case analyses are outlined in Section 2.20.1 and the EAG's preferred assumptions are reported in Section 4.

The EAG outlines its preferred matching-adjusted indirect comparisons (MAICs) for each comparator in Section 2.7, where it compares results between these and the company's preferred analyses, which differ in terms of number of factors adjusted for and, for the axicabtagene ciloleucel (axi-cel) comparison in population B, whether the LBCL or diffuse large B-cell lymphoma (DLBCL) population from EPCORE™ NHL-1 is analysed.

EAG comment on approach for generating comparator curves in economic modelling

While not a key issue in the EAG report, the EAG would like to outline the rationale for the approach that has eventually been taken in this appraisal in terms of epcoritamab and comparator curves in the economic modelling and why hazard ratios (HRs) obtained from MAICs have not been used to obtain comparator curves by applying the MAIC HRs to extrapolations of the unadjusted epcoritamab KM curves, which would usually be the approach when MAICs have been performed. Separate MAICs have been performed for each of the three comparators, each using a different comparator study. In addition, there is a difference between population A (rituximab-based chemoimmunotherapy [R-based CIT] and polatuzumab vedotin with rituximab and bendamustine [Pola + BR] comparisons) and population B (axi-cel comparison) in that a different subgroup of the EPCORE™ NHL-1 population has been analysed in different MAICs. This is because the company defines population A and population B as those ineligible for (or who choose not to receive) and eligible for intensive treatments, respectively.

In the original submission, the company followed the approach of obtaining HRs from MAICs and then applying these to extrapolations of the unadjusted epcoritamab KM curves to obtain the comparator curves for use in the economic model. This approach meant that the same epcoritamab curve would be used within each population (i.e., it would be the same for R-based CIT and Pola +

BR, which are both comparators within population A). However, as part of its clarification questions (CQs), the EAG highlighted that proportional hazards (PH) did not hold for Pola + BR and axi-cel comparisons (with some uncertainty as to whether PHs held for the comparison of R-based CIT), and with fitted survival curves for the comparators being considerably underestimated compared with the underlying KM data from the respective studies when the approach of using HRs was used to generate comparator curves (CQ A7a, A8a and A10).

To address this concern about the accuracy of comparator curves generated using this method, the EAG requested that curves used in the model be fit independently for each outcome using the adjusted epcoritamab KM curves from each MAIC and the respective comparator curve from each comparator trial. The EAG acknowledges that this approach means that epcoritamab curves used for Pola + BR and R-based CIT comparisons are different despite them both being within population A but considers the original approach was not appropriate given PH did not hold for the Pola + BR comparison. Given each of the MAICs has limitations, and is adjusted for different factors based on what is reported in the comparator study, it is not possible for the EAG to determine which of the adjusted epcoritamab curves is most appropriate for population A. However, using the EAG's suggested approach, it is important to use adjusted epcoritamab curves to ensure adjustment for baseline characteristics is incorporated, given adjusted HRs could not be used due to concerns already discussed.

In response to TE, the company has performed the EAG's request regarding this and each base case includes independent extrapolations of adjusted epcoritamab and comparator KM curves. The EAG's concerns have been somewhat mitigated by the fact that the company has independently fitted survival curves, nonetheless, the EAG notes it remains concerned that the company's updated approach is still underpredicting survival curves (particularly for Pola + BR), and that the company's estimated curves still lack the flexibility to accurately predict the shape of the underlying KM data to appropriately capture the overlap and the crossing (or convergence) of the KM curves.

Table 1. Issues for TE and current status regarding issue resolution

Key Issue		Status according to the EAG	Company approach	EAG comment
1	The population in the decision problem may be broader than that covered by the trial	Unresolved (unresolvable)	Reiterates advisory board feedback that EPCORE™ NHL-1 is generalisable to all patients with R/R	Considers this issue remains and should be considered in terms of decision-making, but is likely to be a small number in practice not covered by the

			DLBCL after ≥2 prior treatments in the UK	trial, based on feedback from clinical expert stakeholders consulted as part of TE.
2	Issues associated with the paper used to inform data for SCHOLAR-1 in the MAIC vs R-based CIT	Unresolved	Comparison of OS from Neelapu *et al.* with other sources of OS for R-based CIT and further rationale for preferring Neelapu *et al.* paper	While the EAG appreciates OS curve from Neelapu *et al.* is similar to OS estimates from other sources, the EAG still considers it important to assess the impact of including Crump *et al.* 2017 in the MAIC vs R-based CIT. Other rationale provided has not changed the EAG's position that the use of Crump *et al.* 2017 should be explored.[1, 2]
3	Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used	Unresolved (unresolvable limitations of SCHOLAR-1)	Rationale as to why SCHOLAR-1 is the most appropriate source of evidence for R-based CIT reiterated, limitations acknowledged.	The EAG acknowledges that SCHOLAR-1 may be the best available source of evidence for R-based CIT but considers there are potential limitations, even if Crump *et al.* 2017 was to be used. While these may be minor or the impact may be unknown, the EAG considers them important to consider.[1, 2]
4	The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population	Resolved	Highlight [redacted]	Given the [redacted], the EAG agrees that this is no longer an issue.
5	Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment	Unresolved (unresolvable limitation when SCHOLAR-1 and Sehn *et al.* studies used)	Additional MAICs for the group with prior CAR-T use provided for R-based CIT and Pola + BR comparisons provided. Updated data-cut said to show consistent outcomes between prior and no prior CAR-T groups after [redacted].	While the EAG considers the additional MAICs to be useful in showing how epcoritamab may be effective in groups with prior CAR-T use included, differences compared to base case MAICs and limitations mean it is difficult to make comparisons to base case MAICs where this group was excluded. The EAG's concerns about [redacted] between prior CAR-T experience subgroups remain. Whether the base case MAICs and subsequent economic analysis can be considered applicable to the group with

				prior CAR-T use should be considered as part of the decision-making process.
6	It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments	Unresolved	Confirms populations not limited to those ineligible for intensive treatments as this would be inappropriate as could not also be done for comparator studies	On review, the EAG acknowledges that it is unclear if the population used in comparator trials was specific to those ineligible for intensive treatments but maintains that the MAICs and other details requested for this issue in the EAG report would be useful in assessing the impact of using an EPCORE™ NHL-1 population that is in line with that defined as population A in the CS.
7	Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons	Unresolved	While not used in the company's updated base case analyses, the company has provided versions of the MAICs with full adjustment. The company updated its preferred MAIC vs axi-cel to include the DLBCL rather than LBCL population from EPCORE™ NHL-1.	The EAG acknowledges that MAICs with full adjustment have been provided for consideration; the EAG prefers results from fully adjusted MAICs but acknowledges the company's concerns about R-based CIT when 10 vs 9 factors are adjusted for. It also notes that it would prefer to see a fully adjusted MAIC with Crump *et al.* used for R-based CIT, as discussed in Section 2.2.[2] The EAG notes that not all data required to use fully adjusted MAICs in the model have been provided. The EAG does not agree with the company's decision to prefer the DLBCL analysis for the axi-cel comparison given the ZUMA-1 study includes patients with non-DLBCL.[3] While fully adjusted MAICs have been provided, the EAG still has considerable concerns about the robustness of MAICs for each comparator and considers it possible that studies being compared may be too different to one another, which may limit the ability to obtain robust estimates from any of the MAICs.

8	All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1	Resolved	Analyses using the updated data-cut provided at TE	The EAG acknowledges that updated clinical analyses using the most recent data-cut have been provided as part of TE. EOT values for HRQoL outcomes have now been provided.
9	Limitations of Sehn *et al.* for the MAIC vs Pola + BR	Unresolved (unresolvable limitation)	Emphasises that limitations of Sehn *et al.* and difference vs UK RWE likely means bias against epcoritamab introduced. Additional MAIC provided using another RWE source. Considers the impact of unreported important baseline factors should be limited by adjustment for other similar factors. Reiterates its opinion that Pola + BR should not be included as a comparator in this appraisal.	The EAG agrees that there are differences in survival between Sehn *et al.* and RWE sources but maintains a preference for Sehn *et al.* in the MAIC vs Pola + BR, due to limitations of RWE sources.[4-7] It acknowledges that use of this source may overestimate survival for Pola + BR given values are lower in RWE but that the extent of this is unclear, and given RWE for epcoritamab is not available it is unclear if similar differences would be observed for this treatment. There are also limitations associated with the additional MAIC performed. Considers that important prognostic factors unreported in comparator studies further supports the need to adjust for all reported baseline characteristics. Maintains that Pola + BR should be considered a comparator as it may still be an option for some patients.
10	Limitations of ZUMA-1 for the MAIC vs axi-cel	Unresolved (unresolvable limitation)	Agrees with the EAG's concerns about bias which might favour axi-cel. Has not provided the scenario the EAG highlighted may be useful in terms of outcome definition difference. Considers the impact of unreported important baseline factors should be limited by adjustment for other similar factors.	The EAG maintains that the two limitations highlighted may introduce bias against epcoritamab; however, the scenario requested to explore the impact of different outcome definitions was not performed by the company and the EAG cannot be sure of the impact of this difference in terms of size and direction. Clinical expert input on this may be useful. Considers that important prognostic factors unreported in comparator studies further

				supports the need to adjust for all reported baseline characteristics.
11	Implementation of when the LTR assumption starts in the model	Unresolved	No longer considered necessary to apply LTR assumption due to more mature data – removed from model for all treatment arms.	The EAG considers the removal of the LTR assumption in the comparator arms of the model to be unjustified. It considers that its removal reduces the clinical plausibility of the modelled disease pathway for NHS patients given the EAG's clinical experts considered that patients who are progression-free at 2 years after the end of treatment with R-based CIT; Pola + BR; and axi-cel; should be considered to be in LTR. The EAG acknowledges that flexibility has been added to the model allowing the undertaking of scenario analyses around the LTR assumption for comparator treatments.
12 13 14	Estimation of treatment effectiveness in the model (OS, PFS and TTD)	Unresolved	As noted in Sections 2.7 and 2.8, the company used the more mature data cut from EPCORE™ NHL-1 in the MAICs for the 3 comparators and after adjusting the epcoritamab KM curves using the respective MAICs for each comparator, the company independently fitted survival curves to the epcoritamab and comparator KM curves for OS in line with NICE DSU TSD14.	The EAG remains concerned that the company is not using fully adjusted MAICs in the model for the comparison with Pola + BR and axi-cel, and that the 9/10 MAIC for R-based CIT did not use the EAG-preferred source of data for the comparator. The EAG remains concerned that the company's assumption to estimate a PFS curve for R-based CIT is based on the OS gain for epcoritamab being proportionately the same as the PFS gain associated with the treatment. The EAG also remains concerned that the company's approach to modelling TTD for R-based CIT and Pola + BR overestimates the treatment

				costs associated with these treatments. Overall, the EAG disagrees with nearly all of the company's choices of survival curves to independently fit KM data in the model across all outcomes. The fitted curves estimated by the company are generally a poor fit to the underlying KM data across all comparisons, and in some cases, none of the alternative parametric survival curves are flexible enough to accommodate the underlying change in the hazard of the KM curves for both treatments. The EAG conducted an exploratory analysis to explore this issue, although the EAG caveats its preferred curves by the fact that these are still unlikely to be flexible enough to provide an accurate representation of the underlying KM data several outcomes, across both treatment arms. However, the EAG's approach offers advantages compared to the company's base case approach as it relies on the best-fitting and clinically plausible estimates, while providing a more conservative difference between the fitted curves, which is more representative of the underlying KM data than the company's base case approach.
15	Utilities used in the model	Unresolved	Confirmed that the population used to derive utility values for population A was the same as that used in the MAICs for population A. Did not change or comment on its approach for deriving utilities in population B.	The EAG acknowledges that utility values currently used for population A are in line with the EPCORE™ NHL-1 population included in the MAICs for population A (DLBCL, no prior CAR-T, with no requirement to be ineligible for intensive treatments). The EAG maintains its view that it would be useful to assess the potential impact of using the

				population from EPCORE™ NHL-1 that matches the definition of population A in the CS (i.e., patients ineligible to receive CAR-T), both to conduct the MAICs and the utility analysis. Regarding the utility values used in population B, the EAG notes that the company's original approach of deriving utilities using the utility data from the LBCL population might now be less appropriate as the marketing authorisation for epcoritamab is [redacted], Therefore, the EAG advises that the company conducts a utility analysis on the LBCL population before the committee meeting in order to explore the potential uncertainty in using either set of values.
16	Treatment and administration costs of comparators in the model	Partially resolved.	Updated base case so R-based CIT costs were aligned with the approach taken for Pola + BR and received for 6 rather than 8 cycles. Conducted a scenario analysis to remove the one-time monitoring cost for axi-cel but added a one-off cost to capture bridging therapy. Added bridging costs to patients receiving axi-cel. Confirmed correction of errors identified in the model regarding administration costs of subsequent treatments and epcoritamab cost. Noted that costs in the model were inflated to	The EAG is satisfied with the company's updated approach to R-based CIT administration costs and the scenario analysis provided with axi-cel monitoring costs removed. The EAG remains of the opinion that monitoring costs should not be added to axi-cel administration costs. NICE agreed with the company about the inclusion of bridging costs for axi-cel. The EAG conducted a scenario analysis based on proportions of bridging treatment received by patients in the NHS provided by NICE and on the costs provided in the company's model. The EAG's costs are similar to the company's estimated cost of bridging.

			the most recently available cost year.	
17	Subsequent treatments in the model	Unresolved	Performed the EAG-requested scenario for the proportion of patients receiving subsequent treatments in the model, however with inclusion of an additional QALY adjustment for epcoritamab patients receiving subsequent CAR-T. Did not perform the EAG-requested scenario that those previously treated with an R-based combination should receive palliative chemotherapy without rituximab.	The EAG agrees with the company's added QALY adjustment to the epcoritamab arm for patients receiving subsequent CAR-T given that for population A, the EAG-preferred estimate for the modelled proportion of patients receiving CAR-T is [redacted] the proportion of patients receiving CAR-T in the EPCORE™ NHL-1 trial. For population B, even though the EAG-preferred estimate for the modelled proportion of patients receiving CAR-T (30%) [redacted] than that received by patients in the trial, patients received other active, effective treatments in EPCORE™ NHL-1 (for example, [redacted] of patients received subsequent polatuzumab and lenalidomide, respectively), which have not been considered in the cost of subsequent treatments in the model. Therefore, the EAG removed the company's QALY adjustment to the scenario analysis requested by the EAG with regards to CAR-T (in both populations). The EAG maintains its view that those receiving R-based CIT or Pola + BR should receive subsequent palliative chemotherapy based on advice from the EAG's clinical experts.
18	Disease follow-up costs in the model	Unresolved	Corrected an error where PFS on-treatment costs incurred in the model for the initial 2 years in comparator arms instead of decreasing once patients were PFS off treatment. Reiterated its view that resource use for	The EAG agrees with the company's correction in terms of PFS on-treatment costs for R-based CIT in the first 2 years but not for Pola + BR. The EAG made a correction to the company's update for Pola + BR. The EAG's concerns about reducing follow-up costs for

			epcoritamab is anticipated to decrease over time while patients are on treatment and maintained the view that the median PFS for DLBCL patients in EPCORE™ NHL-1 is the most appropriate value to inform this timepoint because the majority of patients with progression-free disease will have CR after this timepoint ([redacted] based on the latest data cut). Did not address EAG concerns around potential double counting of resource use in the model through cost sources used.	epcoritamab based on median PFS in EPCORE™ NHL-1 remain - the EAG's clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued, meaning that the resource use estimated by the company for epcoritamab for the progression-free, on treatment period should be observed for as long as treatment is given in the model. However, in contrast to this, epcoritamab patients in the model are assumed to incur less resource uses after [redacted]. The company's base case remains biased in favour of epcoritamab and underestimates disease management costs associated with the treatment. The EAG conducted an exploratory analysis to explore this. The EAG remains unsure if cost sources used are double counting resources.

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CR, complete response; CS, company submission; DLBCL, diffuse large B-cell lymphoma; DSU, Decision Support Unit; EAG, External Assessment Group; EOT, end of treatment; HRQoL, health-related quality of life; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; LTR, long-term response; LTRs, long-term responders; MAIC, matching-adjusted indirect comparison; NHL, non-Hodgkin lymphoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; R/R, relapsed or refractory; RWE, real-world evidence; TE, Technical Engagement; TSD, Technical Support Document; TTD, time to treatment discontinuation.

2 EAG's critique of company comments to key issues

2.1 Key issue 1: The population in the decision problem may be broader than that covered by the trial

In its report, the External Assessment Group (EAG) highlighted that the population included in EPCORE™ NHL-1 was specific to those that had failed (or were ineligible for) prior autologous stem cell transplant (ASCT) and those with Eastern Cooperative Oncology Group (ECOG) scores 0-2. Given the National Institute for Health and Care Excellence (NICE) final scope and population described in the decision problem do not specify these criteria,[8] the EAG noted that the decision problem

population may be slightly broader than that covered by the trial. This was raised as it may be an important factor to consider in terms of wording of any recommendations made, particularly if important groups are thought to be missing from the trial.

2.1.1 Company's approach at Technical Engagement

The company highlights clinical expert feedback from its advisory board in July 2022, that data from EPCORE™ NHL-1 are generalisable to all patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after at least two prior treatments in the UK.[9] It also notes that the population of interest in its submission is in line with the NICE final scope and full anticipated marketing authorisation.[8]

2.1.2 EAG's critique of the company's approach at Technical Engagement

The EAG acknowledges that the advisory board report concludes that clinical experts, *"agreed that the key inclusion criteria of the EPCORE™ NHL-1 trial were broadly aligned with the patients seen in UK clinical practice".*[9] However, feedback from clinical experts that submitted a stakeholder response as part of technical engagement (TE) supports the EAG's point that there may be a small group in UK clinical practice not captured by the trial but that would be eligible for epcoritamab, as detailed in Table 2.

These comments suggest that it is possible that some patients with ECOG scores >3 (not included in EPCORE™ NHL-1) might be eligible for epcoritamab, but that it is likely to be a small number (~5% of patients). Comments regarding patients with no prior ASCT suggest that the requirement for patients in EPCORE™ NHL-1 to have either failed or been considered ineligible for prior ASCT is reasonable, as both experts conclude that at third-line (3L), patients are generally considered to be ASCT ineligible.

The EAG concludes that while feedback at TE from clinical experts suggest that the differences between the population described in the decision problem and the population included in EPCORE™ NHL-1 may be small, it is worth noting that some patients with ECOG score ≥3 may be considered eligible for epcoritamab but were not included in the study. It may be worth considering whether data obtained from the trial would be impacted had this group been included or whether outcomes are likely to be the same, and whether the wording of any recommendations in terms of population needs to consider this slight difference.

Table 2. Clinical expert stakeholder responses to Key Issue 1 at TE

Stakeholder	Comment
Clinical expert 1	Trial populations are inevitably selected populations and the "real world" population may include some patients that would not have fulfilled the trial inclusion criteria. The GEN-01 study did allow patients to have 2 lines of therapy, and an ASCT did not have to be part of their prior treatment so I don't think that is an issue. Patients at 3rd line treatment would generally be considered "auto-ineligible" as they would have been offered it in prior lines of treatment if it was a good treatment option. Whilst 2nd line CAR-T cells cannot be considered in this appraisal as they are not baseline commissioned the reality is that in UK practice the majority (~70%) of patients who have relapsed high grade B NHL will have 2nd line CAR-T in preference to an ASCT. Some patients with R/R lymphoma will have ECOG ≥3 at the time of relapse, possibly due to the lymphoma, and some of these may be considered eligible for treatment with epcoritamab. This will be a relatively low number though, ~5%.
Clinical expert 2	In a 3rd line setting most patients would be considered auto ineligible because we would only do an auto in a second line setting and even if the patient had CAR-T 2nd line most clinicians would not then do an auto 3rd line (it is ineffective in the majority of patients, >80% even in a 2nd line setting and is extremely toxic). Most patients would have PS 0-2 but it would depend on the cause of the low PS, if due to lymphoma and not other comorbidities then an occasional patient may be considered with PS3 (if within reimbursement criteria) but in general I think most pts will have PS0-2. 3rd line patients who had not had prior auto would have been about 50% but this will increase now that we have 2nd line CAR T on the CDF. 5-10% of pts have a PS3 or more.

Abbreviations: ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin lymphoma; PS, performance score; R/R, relapsed or refractory; TE, Technical Engagement.

2.2 Key issue 2: Issues associated with the paper used to inform data for SCHOLAR-1 in the MAIC vs R-based CIT

In the EAG report, concerns about the use of the Neelapu *et al.* paper to inform SCHOLAR-1 data for the matching-adjusted indirect comparison (MAIC) vs rituximab-based chemoimmunotherapy (R-based CIT) were noted.[1] This was based on the following limitations:

- This paper involves propensity score matching with ZUMA-1, a chimeric antigen receptor T-cell (CAR-T) eligible population, which the EAG does not consider to be representative of the population that the comparison vs R-based CIT is said to be relevant to (population A, ineligible for intensive treatments).[1] This may have excluded or reduced the weighting of patients in SCHOLAR-1 that are relevant to population A, which may subsequently affect the weighting of epcoritamab patients from EPCORE™ NHL-1 patients when the MAIC is

performed using Neelapu *et al.* as the paper for the comparator study and may impact the adjusted Kaplan-Meier (KM) curves obtained for epcoritamab;

- KM curves for overall survival (OS) in this paper do not contain information on censoring and the company had to assume that censoring pattern is the same as that observed in the Crump *et al.* paper,[2] despite population characteristics differing between the two papers. This is an additional area of uncertainty introduced that could be avoided if Crump *et al.* was used;
- Despite matching for this factor, the proportion with disease stage III-IV in the company's preferred analysis with partial adjustment was still fairly imbalanced ([redacted] % vs 64.5% in the adjusted epcoritamab vs SCHOLAR-1 populations; Table 32 of the EAG report);
- The EAG could not confirm that the Neelapu *et al.* paper limited to DLBCL patients;[1] if the population is actually large B-cell lymphoma (LBCL) overall, limiting the EPCORE™ NHL-1 population analysed in this MAIC to DLBCL may add to uncertainties as it will have created a difference between EPCORE™ NHL-1 and SCHOLAR-1 populations analysed; proportions of those with non-DLBCL types of LBCL are available in the Crump *et al.* paper and could be adjusted for if the whole LBCL population for EPCORE™ NHL-1 is also used;[2]
- The EAG could not confirm that the Neelapu *et al.* paper limits to those with at least two prior treatments, which was the company's main argument for using this paper over the Crump *et al.* paper;[1, 2] given this, the EAG considers that the additional uncertainty (described in the points above) introduced by using Neelapu *et al.* may not be necessary given it may not resolve the company's concern in terms of inclusion of patients with only one prior treatment.

The EAG's conclusion in the EAG report was that use of Neelapu *et al.* introduces additional uncertainty,[1] which could impact conclusions in terms of clinical and cost-effectiveness, and is not an appropriate source of SCHOLAR-1 data for this comparator. It may also not have been appropriate to limit the analysed EPCORE™ NHL-1 population in this MAIC to DLBCL. It noted that while some limitations would remain, performing the MAIC using the Crump *et al.* paper instead of Neelapu *et al.* for SCHOLAR-1 would be preferable if alternative studies and/or individual patient data (IPD) for R-based CIT that could address other concerns about SCHOLAR-1 (described in Section 2.3 below) were not identified.[1, 2]

2.2.1 Company's approach at Technical Engagement

In its TE response, the company acknowledges that there are limitations associated with SCHOLAR-1 and Neelapu *et al.* as a source of efficacy data for R-based CIT. However, it maintains its preference for the Neelapu *et al.* paper and has not performed a scenario where the Crump *et al.* paper is instead used in the MAIC.[1, 2]

The company reiterates its argument that Neelapu *et al.* should be preferred as the Crump *et al.* paper includes 28% of patients with only one prior line of treatment, which is not representative of the decision problem population in the company submission (patients with at least two prior treatments).[1, 2] It acknowledges the EAG's comment that it is not clear from the paper that Neelapu *et al.* is exclusively a 3L population but states that it has been cited elsewhere and described as, *"representative for patients who have received two or more prior lines of therapy".*[10]

It also states that the Neelapu *et al.* paper involved matching of ZUMA-1 to SCHOLAR-1, rather than the other way around, meaning the EAG's argument about SCHOLAR-1 being reweighted to represent a CAR-T eligible population is incorrect.[1] Related to this point, the company also highlights that in the NICE evaluation of axicabtagene ciloleucel (axi-cel; TA872), the Neelapu *et al.* population (n=340) was filtered further to ensure SCHOLAR-1 was comparable to the ZUMA-1 population (n=133), suggesting that the population in Neelapu *et al.* (n=340) is not one that is comparable to ZUMA-1.[11]

In terms of the EAG's concern about whether limiting to a DLBCL population for this MAIC was appropriate, the company notes that given the [redacted], focus on the DLBCL population is appropriate for this MAIC. It also notes that DLBCL was the most common diagnosis in the SCHOLAR-1 dataset. The company has provided a scenario where the LBCL population from EPCORE™ NHL-1 is instead used for comparison against SCHOLAR-1 data from Neelapu *et al.* (Table 48 and associated text in the appendix of the company's TE response).

The company did not comment on the other points raised by the EAG, including the assumption of identical censoring to Crump *et al.* given this detail is lacking in Neelapu *et al.* and imbalances remaining for disease stage III-IV between EPCORE™ NHL-1 and Neelapu *et al.* despite adjustment for this factor.[1, 2]

2.2.2 EAG's critique of the company's approach at Technical Engagement

The EAG summarises its original concerns, the company's response and the EAG's comment on this response in Table 3 below. While the noted imbalance in disease score III-IV proportions between the adjusted EPCORE™ NHL-1 population and Neelapu *et al.* no longer stands when more variables are adjusted for (9/10 reported factors; see Section 2.7.2), the EAG's concerns about other limitations of using Neelapu *et al.* remain and the EAG considers the impact of using Crump *et al.* in the MAIC vs R-based CIT should be explored as it may result in a more robust analysis.[1, 2]

The EAG acknowledges that the use of Crump *et al.* would not be without its limitations (including the fact that 28% of only one prior treatment failure), but considers that Neelapu *et al.* does not necessarily resolve this issue and introduces additional uncertainties. Furthermore, concerns raised by the EAG in Section 2.7.2 about the comparability of EPCORE™ NHL-1 and SCHOLAR-1 (based on Neelapu *et al.*) given difficulties when adjusting for all baseline characteristics, and whether any robust estimates can be obtained from these MAICs, may represent another reason to explore the use of Crump *et al.* for the MAIC vs R-based CIT.[1, 2]

Table 3. Company response to the EAG's concerns about Neelapu *et al.* and EAG comment

Concern in EAG report	Company response	EAG comment
SCHOLAR-1 being reweighted in Neelapu *et al.* to be a better match to the ZUMA-1 population	AbbVie would like to highlight that in the Neelapu *et al.* 2021 ITC, it was the ZUMA-1 population that was reweighted to match SCHOLAR-1 (as is common practice for ITCs), rather than the SCHOLAR-1 population that was adjusted	On reviewing the Neelapu *et al.* paper again, the EAG is unsure whether the company's conclusion about ZUMA-1 being matched to SCHOLAR-1 is correct. The EAG consider that there is no clear statement in Neelapu *et al.* that reweighting of patients was only done for ZUMA-1 patients to SCHOLAR-1. Given the same company was involved in ZUMA-1 and SCHOLAR-1, it is equally possible that some reweighting of SCHOLAR-1 patients has been performed. One statement in particular that leads the EAG to consider this is, "*propensity scores were calculated for each patient by combining the ZUMA-1 and SCHOLAR patients into a single dataset and calculating the probability of being in the ZUMA-1 trial based on demographics and disease characteristics*", which suggests SCHOLAR-1 patients may have been reweighted based on how likely they were to have been present in ZUMA-1. Nonetheless, the EAG notes that one difference in particular between Neelapu

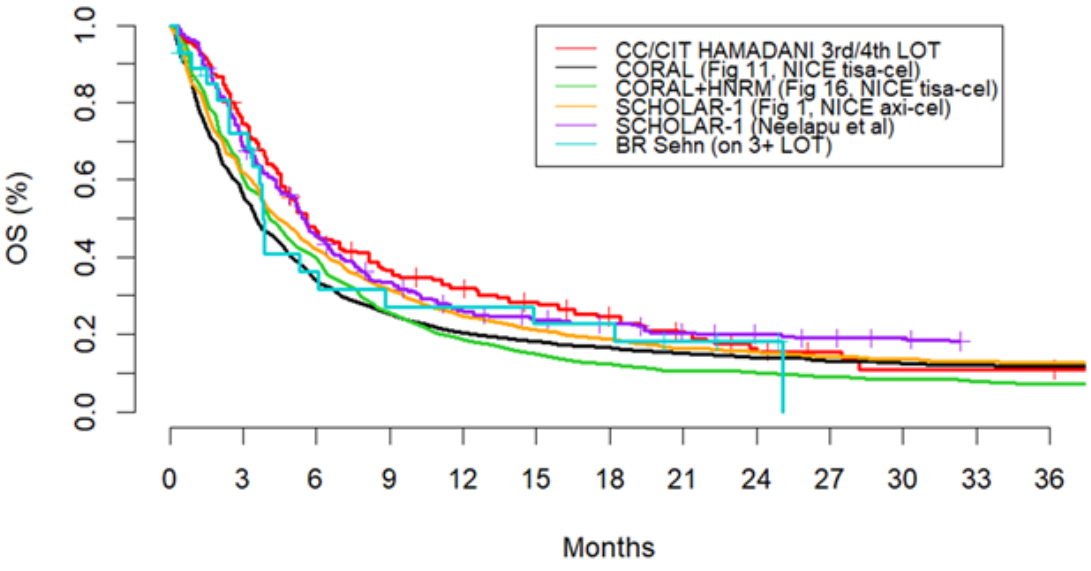
		et al. and Crump *et al.* in terms of baseline characteristics supports the EAG's conclusion that a population more in line with ZUMA-1 has been selected; 100% of patients have ECOG scores 0-1 (as per ZUMA-1) whereas this is 73% in the Crump *et al.* paper. Therefore, the EAG considers that the Neelapu *et al.* paper does involve the selection of a population that is more in line with ZUMA-1 and a CAR-T eligible population, which differs to population A as defined by the company in its submission (unsuitable for intensive treatments). This may mean that some SCHOLAR-1 patients (those with ECOG scores not considered suitable for CAR-T or other intensive treatments) that would be relevant to this comparison have been excluded when Neelapu *et al.* is used.[1, 2]
KM curves for OS in Neelapu *et al.* do not contain information on censoring and assumption had to be made that this was the same as in the Crump *et al.* paper	NA	While the company has not commented on this, the EAG still consider this to be an additional uncertainty introduced as a result of using Neelapu *et al.,* which would not be required if Crump *et al.* was used.[1, 2]
Imbalance in disease stage III-IV proportions between adjusted epcoritamab and Neelapu *et al.* populations despite matching for this factor	NA	While the EAG considers the use of Neelapu *et al.* to be inappropriate and that Crump *et al.* should be explored, of the MAICs available, the EAG's preferred one using Neelapu *et al.* is with 9/10 reported factors adjusted for (see Section 2.7 for further discussion). In this analysis, this imbalance is no longer observed and the EAG no longer consider this to be a factor against using the Neelapu *et al.* paper.[1, 2]
Only including DLBCL patients from the EPCORE™ NHL-1 study in this MAIC, while Neelapu *et al.* likely also includes non-DLBCL types of LBCL	In light of the [redacted] for epcoritamab, AbbVie consider the MAIC using the DLBCL population from EPCORE™ NHL-1 as the most relevant, whilst also noting DLBCL was the most common diagnosis in the SCHOLAR-1 data set. Additionally, AbbVie have conducted a MAIC versus SCHOLAR-1 (based on Neelapu *et al.* 2021) in which the LBCL, no CAR-T population from EPCORE™ NHL-1 is used to inform the efficacy estimates of	The EAG considers that the company's response confirms that it is possible that Neelapu *et al.* includes some with types of LBCL other than DLBCL. This means that the analysed EPCORE™ NHL-1 and Neelapu *et al.* populations potentially differ with regards to LBCL type included, which could introduce bias. While the EAG acknowledges that it would be ideal to use the population in the [redacted] for epcoritamab ([redacted]), if the comparator study used does not also focus on this population it may introduce bias. Given the uncertainties already associated with performing unanchored MAICs, the EAG has a preference for study populations to

	epcoritamab. The results from this MAIC are consistent with the DLBCL population.	be as aligned as possible with matching performed for reported baseline characteristics, even if this deviates slightly from the [redacted]. The EAG considers that the additional MAIC performed by the company (using the LBCL population from EPCORE™ NHL-1 and comparing to Neelapu *et al.*; Table 48 and associated text in the appendix of the company's TE response) does not resolve its concerns as type of LBCL cannot be adjusted for given it is not reported in the Neelapu *et al.* paper. Given that adjustment for LBCL type cannot be performed when Neelapu *et al.* is used, the EAG considers this to be another reason that Crump *et al.* should be explored; the EAG's preferred analysis using Crump *et al.* would involve the LBCL populations from EPCORE™ NHL-1 and SCHOLAR-1 with type of LBCL included as a factor in the matching process (in addition to matching for all other reported baseline characteristics).[1, 2]
Neelapu *et al.* may not actually be limited to those with at least two prior treatments, which is the company's main argument for using this paper over Crump *et al.*	AbbVie maintain that conducting this MAIC using data from Neelapu *et al.* 2021 for SCHOLAR-1 (n=340), as opposed to Crump *et al.* 2017 for SCHOLAR-1 (n=636), is the most suitable approach. This is because, of the 636 patients included in the analysis presented by Crump *et al.* 2017, 28% of patients received only one prior line of therapy, which is not representative of the decision problem in this submission. Whereas, although it is not explicitly stated within the paper to be exclusively a 3L+ population, the data reported in the secondary Neelapu *et al.* 2021 publication have been cited as representative for patients who have received two or more prior lines of therapy.[10] Therefore, it is more appropriate to use this data set compared with the Crump *et*	The company's response confirms the EAG's point that it is unclear whether the Neelapu *et al.* paper is actually limited to those with at least two prior treatments. The EAG does not consider that a citation within the paper cited by the company is sufficient to assume that Neelapu *et al.* is more representative of those with at least two prior treatment failures than the Crump *et al.* population.[1, 2, 10] On review of this paper, other than both Crump *et al.* and Neelapu *et al.* publications being cited in the paper, the EAG could not identify a statement about Neelapu *et al.* being representative of a 3L+ population, nor a comparison of the applicability of the two publications for SCHOLAR-1 to the 3L+ population. The EAG notes that the focus of this paper was comparisons between CAR-T treatments, which is why the Neelapu *et al.* paper may also have been cited (as it involved matching with ZUMA-1, a CAR-T trial). In conclusion, the EAG is not convinced that the Neelapu *et al.* paper necessarily resolves the company's concern about including patients with only one prior

	al. 2017 data to align with the decision problem in this submission as closely as possible.	treatment failure and given the use of this paper introduces additional uncertainties, considers that an alternative version of the MAIC using Crump *et al.* should be explored.
Additional point by the company at TE	A comparison of OS outcomes based on Neelapu *et al.* with historical OS outcomes for R-based CIT (Figure 1 below) demonstrate that survival estimates from Neelapu *et al.* are a reasonable estimate, and potentially optimistic, for the survival of patients receiving R-based CIT.	While the EAG acknowledges that the OS curve for Neelapu *et al.* presented in Figure 1 below is similar to other R-based CIT sources and is one of the most optimistic, this does not change the EAG's position that exploring the impact of using Crump *et al.* instead would be appropriate, given the limitations described above. Even though OS curves for Neelapu *et al.* and Crump *et al.* are similar (see Figures 3A and 2 of Crump *et al.* and Neelapu *et al.* papers, respectively), given certain baseline characteristics differ between the two papers (see Table 4 below), comparing curves from these two papers alone does not give an indication of how adjusted epcoritamab curves obtained from MAICs using the two papers would differ. In addition, longer term follow-up is available in the Crump *et al.* paper.[1, 2]

Abbreviations: 3L+, third-line and beyond; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NA, not applicable; NHL, non-Hodgkin lymphoma; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy; TE, Technical Engagement;

Figure 1. OS in historical controls in R/R DLBCL – reproduced from Figure 1 of the company's TE response



Abbreviations: axi-cel, axicabtagene ciloleucel; CC/CIT, chemotherapy or chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma; LOT, line of treatment; NICE, National Institute for Health and Care Excellence; OS, overall survival; R/R, relapsed or refractory; TE, Technical Engagement; tisa-cel, tisagenlecleucel.

Table 4. Comparison of baseline characteristics between Crump *et al.* and Neelapu *et al.* papers for SCHOLAR-1

Factor	Neelapu *et al.* 2021 (n=340)	Crump *et al.* 2017 (n=636)
Male sex	231 (68%)	407 (64%)
Median age (range), years	NR	55 (19-81)
Age ≥65 years	56 (16%)	NR
Primary diagnosis		
DLBCL	NR	553 (87%)
PMBCL	NR	13 (2%)
TFL	NR	25 (4%)
Indeterminate/missing	NR	45 (7%)
Total lines of chemotherapy and ASCT received		
1	NR	178 (28%)
2-3	NR	312 (49%)
≥3 lines of chemotherapy and ASCT[a]	98 (29%)	NR
≥4	NR	NR (<1%)
Ever primary refractory[b]	126 (37%)	178 (28%)
Refractory to ≥2 consecutive lines of therapy	170 (50%)	318 (50%)
SCT any time after refractory disease	126 (37%)	NR
Relapse within 12 mo of ASCT	74 (22%)	140 (22%)
ECOG PS 0-1[c]	126/126 (100%)	464 (73%)
Disease stage III-IV[c]	80/124 (65%)	458 (72%)
IPI score ≥3[c,d]	33/119 (28%)	210 (33%)

[a]Prior to and including the qualifying line of therapy (i.e., the next-to-last treatment a SCHOLAR-1 patient received that was used to determine the most recent refractory status) in SCHOLAR-1; [b]refractory to initial therapy – patients may or may not have been refractory to subsequent therapies; [c]assessed within 3 months of determination of refractory status and prior to salvage therapy in SCHOLAR-1; [d]defined as high-intermediate to high risk in the Crump *et al.* paper.

Abbreviations: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; NR, not reported; PMBCL, primary mediastinal B-cell lymphoma; PS, performance score; SCT, stem cell transplant; TFL, transformed follicular lymphoma;

2.3 Key issue 3: Limitations of SCHOLAR-1 in the MAIC vs R-based CIT regardless of the paper used

The EAG highlighted a number of additional SCHOLAR-1 limitations that are not specific to Neelapu *et al.* and would also apply if the Crump *et al.* paper was used as the source of data for R-based CIT in SCHOLAR-1.[1, 2] These include the following:

- SCHOLAR-1 is specific to those with refractory disease, which might underestimate survival for R-based CIT compared to if there had not been a requirement for patients to be refractory to at least one prior treatment;
- Types of R-based CIT used in SCHOLAR-1 are not reported – while the Crump *et al.* paper describes one of its advantages as that it represents a large number of patients treated in the *"modern rituximab era"*, it is unclear if all or most patients received R-based CIT.[2] Estimates of survival for R-based CIT in UK clinical practice could be underestimated in this study if a large proportion did not receive R-based CIT;
- SCHOLAR-1 includes 28% of patients with only one prior treatment failure as reported in Crump *et al.* – while Neelapu *et al.* does not report the proportion, this cannot be assumed to mean that none were included and the EAG considers this to be an issue for both papers.[1, 2]

The first two points might introduce bias against R-based CIT, whereas the third may have the opposite effect.

2.3.1 Company's approach at Technical Engagement

The company acknowledges the limitations associated with SCHOLAR-1 but maintains that it is an appropriate source to derive efficacy estimates for R-based CIT for this decision problem. It reiterates the systematic literature review (SLR) process that was followed to identify sources of comparator evidence and outlines reasons that other sources were dismissed (Table 3 of the company's TE response).

With regards to refractory to treatment being a requirement in SCHOLAR-1, the company highlights that the inclusion criterion was that patients had to have been refractory to any line of therapy and they did not have to be refractory to all lines of treatment. It also notes that 21% of patients in Neelapu *et al.* relapsed within 12 months of ASCT, which is said to be comparable to the high proportion of refractory patients in the EPCORE™ NHL-1 trial.[1] It also highlights that after adjustment

in the MAIC, baseline characteristics of Neelapu *et al.* and EPCORE™ NHL-1 patients are well-balanced (Appendix B.1.1.1 of the company's TE response), and that estimates of survival from Neelapu *et al.* are similar to those obtained from other sources and potentially more optimistic (see Figure 1 above).

Discussion of the inclusion of patients with only one prior treatment in SCHOLAR-1 has been discussed above in Section 2.2 and the company has not commented on the EAG's point about the proportions using R-based CIT being unclear for SCHOLAR-1.

2.3.2 EAG's critique of the company's approach at Technical E

The EAG acknowledges that SCHOLAR-1 may be the most appropriate source of data for R-based CIT and accepts that baseline characteristics reported for other studies identified were more limited; however, this does not mean that it is without limitations. The EAG already understood that SCHOLAR-1 did not require patients to have been refractory to all prior treatments, but considers that the requirement for patients to have been refractory to at least one does select a group that may have worse prognosis, given feedback from the EAG's clinical experts that refractory status is an important prognostic factor. While the EAG agrees with the company's point that adjustment via MAICs for factors related to refractoriness could reduce differences in baseline characteristics between EPCORE™ NHL-1 and SCHOLAR-1 populations, it is important to note that this is unlikely to fully account for the fact that EPCORE™ NHL-1 did not have the same requirement for all patients to have been refractory to at least one prior treatment.

The EAG also acknowledges that the OS curve from Neelapu *et al.* in Figure 1 above is similar to others and is one of the more optimistic curves for R-based CIT.[1] While it may not be a major concern and is unresolvable when SCHOLAR-1 is used, the EAG considers it worthy of note that patients who were relapsed to all of their prior treatments (as opposed to being refractory to at least one of them) were not included in SCHOLAR-1, which may limit the applicability of SCHOLAR-1 to the overall R/R DLBCL population.

The EAG considers that uncertainty about the proportion that had R-based CIT in SCHOLAR-1 remains but that it is likely that a substantial proportion were using these treatments patients being treated in the *"modern rituximab era"* is described as one of the advantages of SCHOLAR-1 in the Crump *et al.* paper.[2] The EAG has discussed the inclusion of patients with only one prior treatment failure in SCHOLAR-1 in Section 2.2 above.

2.4 Key issue 4: The MAIC for epcoritamab vs Pola + BR is limited to the DLBCL population

As part of the EAG's report, the EAG highlighted that when Sehn *et al.* is used as the comparator study for the polatuzumab vedotin with rituximab and bendamustine (Pola + BR) comparison, the analysis population has to be limited to DLBCL (rather than the larger LBCL population) given Sehn *et al.* focuses on DLBCL.[4-6] This was considered to be an unresolvable limitation by the EAG given that in its original submission, the company positioned epcoritamab for use in the whole LBCL population and not specifically the DLBCL subgroup. Limiting the analysis for this comparison to DLBCL therefore meant it may be limited in terms of applicability to the full LBCL population.

2.4.1 Company's approach at Technical Engagement

At TE, the company highlighted that there has been [redacted]. The company also notes that the DLBCL population in the MAIC vs Pola + BR is in line with the population for which Pola + BR is recommended by NICE in TA649.[12]

2.4.2 EAG's critique of the company's approach at Technical Engagement

The EAG considers that, given the focus of the submission [redacted], this issue can be considered to be resolved as the analysis population in the MAIC vs Pola + BR [redacted] with that described in the decision problem with regards to types of LBCL included.

2.5 Key issue 5: Results from the MAICs, and therefore the economic model, may not be applicable to groups with prior CAR-T treatment

In its report, the EAG highlighted that the MAICs for all comparators required those with prior CAR-T use to be removed from the analysed EPCORE™ NHL-1 population, given comparator trials did not include these patients. While this was not considered to be an issue for the comparison vs axi-cel, the EAG highlighted it as a potential issue for R-based CIT and Pola + BR comparisons. This was because results from EPCORE™ NHL-1 indicated that survival may be [redacted] for those with prior CAR-T use compared to those without it. Therefore, had these been included in MAICs, results might have differed and incremental cost-effectiveness ratios (ICERs) might [redacted]. The EAG, therefore, considered that the results of these MAICs and the economic model may not be applicable to the group with prior CAR-T use.

2.5.1 Company's approach at Technical Engagement

To address uncertainty associated with the generalisability of MAICs for R-based CIT and Pola + BR to patients that have received prior CAR-T, the company conducted a number of additional MAICs, including one for Pola + BR using Northend *et al.* (real-world evidence [RWE] study described in Section 2.9) that includes patients that have received prior CAR-T treatment and a number of MAICs vs R-based CIT using data from Tomas *et al.*, which is specific to the group with prior CAR-T use and focuses on this population from EPCORE™ NHL-1.[7, 13] The company concludes that results of these MAICs for R-based CIT are consistent with those for their base case analysis which limits to those with no prior CAR-T use. For the Pola + BR additional MAICs, the company concludes in Appendix B.2.1.1 that [redacted] benefits of epcoritamab vs Pola + BR are observed for OS and progression-free survival (PFS).

The company notes that while the EAG highlights that survival results from EPCORE™ NHL-1 [redacted] with and without prior CAR-T use based on the [redacted], additional follow-up up to [redacted] suggests survival outcomes are consistent between these groups after [redacted].

The company reiterates that those with prior CAR-T use in EPCORE™ NHL-1 had to be excluded given comparator studies used for R-based CIT and Pola + BR (SCHOLAR-1 and Sehn *et al.,* respectively) did not include these patients as CAR-T treatment was only introduced after data for these studies had been collected.[1, 2, 4-6] The company emphasises that it would be inappropriate to conduct analyses where epcoritamab populations included those with prior CAR-T use but the comparator populations do not as a high degree of uncertainty would be introduced.

The company notes that feedback from clinical experts and literature indicates that outcomes for patients post-CAR-T are poorer than those without prior CAR-T.[9, 13] While it acknowledges that epcoritamab may initially have [redacted] in patients with prior CAR-T experience compared with patients that have not received prior CAR-T treatment (median OS [redacted] months vs [redacted] months in EPCORE™ NHL-1), this decrement is expected to be larger for R-based CIT. The company cites a comparison between Tomas *et al.* (those with prior CAR-T use) and SCHOLAR-1 (no prior CAR-T use), with complete response (CR) rates being 0.0% vs 12.1% in these two studies, respectively.[1, 13] The company acknowledges that the populations may not be comparable and this naïve comparison is subject to uncertainty but considers this demonstrates that there may be a substantial difference in response to R-based CIT for those with and without prior CAR-T treatment.

2.5.2 EAG's critique of the company's approach at Technical Engagement

Additional MAICs vs R-based CIT

The EAG acknowledges the additional MAICs that have been performed for the R-based CIT comparison. This involves the Tomas *et al.* study and specifically analyses the group with prior CAR-T use from EPCORE™ NHL-1.[13] Baseline characteristics and results of the MAICs can be found in Section B.2, with analyses outlined in Table 46 of the company's TE response appendix. The company provides separate MAICs for those in EPCORE™ NHL-1 receiving epcoritamab as the first treatment following CAR-T and those receiving epcoritamab at any point after CAR-T, with the latter having a larger sample size. Each of these MAICs are performed for the DLBCL and LBCL population separately, meaning four additional MAICs in total have been performed.

Given Tomas *et al.* includes LBCL overall and the EAG considers any use of prior CAR-T to be more important than whether they received epcoritamab as the first treatment after CAR-T, the EAG considers the MAIC in the LBCL population with any prior use of CAR-T to be the most relevant.[13] Baseline characteristics for this MAIC are presented in Table 53 of the company's TE appendix. While only six variables in this table appear to be reported for both studies, all of which have been adjusted for in the MAIC, the EAG notes that the Tomas *et al.* paper does report the proportion with DLBCL (77%), which has not been included in this table and has not been adjusted for.[13] Therefore, the EAG has concerns that differences between the adjusted epcoritamab population and Tomas *et al.* population may remain that could limit the reliability of this MAIC. The same issue in terms of potential difference in LBCL type between the two studies also applies to the other three additional MAICs performed for this comparison (while DLBCL analyses limit to DLBCL in EPCORE™ NHL-1, Tomas *et al.* does not limit to DLBCL meaning this introduces a difference between studies).

In terms of results, the EAG notes that the company compares additional analyses in the DLBCL population to their base case analysis for R-based CIT, given DLBCL is the population used in that analysis vs SCHOLAR-1. The company concludes that given results obtained are similar to the base case analysis using SCHOLAR-1 and excluding those with prior CAR-T, the generalisability of this base case analysis to those with prior CAR-T should not be considered a significant source of uncertainty. Results of the base case analysis and additional MAICs are presented in Table 5 below.

While the EAG acknowledges that adjusted hazard ratios (HRs) for epcoritamab vs R-based CIT are fairly similar, with better survival observed for epcoritamab based on point estimates, it does not

consider it possible to make robust comparisons between the SCHOLAR-1 MAIC and MAICs based on Tomas *et al.*. This is because the MAICs used different studies, adjust for different factors and are all associated with limitations. The EAG accepts that the MAICs using Tomas *et al.* as they may suggest that epcoritamab would be beneficial over R-based CIT in a prior CAR-T group; however, these results cannot be compared to a completely different MAIC to conclude CAR-T inclusion would not impact the outcomes of the MAIC vs SCHOLAR-1 had they been included and adjusted for in both studies. The EAG also reiterates limitations that remain with the Tomas *et al.* MAICs, including the difference in DLBCL type and lack of adjustment for this in LBCL analyses, and the fact that there is uncertainty for these analyses based on 95% confidence intervals [redacted].

Table 5. Comparison of adjusted MAIC results for epcoritamab vs R-based CIT (no prior CAR-T vs prior CAR-T analyses) – adapted from Table 4 of the company's response to TE and Tables 63 and 65 of the appendix of the company's TE response

Epcoritamab population	Comparator data source	Adjusted OS HR (95% CI); p-value
DLBCL, no prior CAR-T	SCHOLAR-1	[redacted]
DLBCL, prior CAR-T, epcoritamab 1L after CAR-T	Tomas *et al.*	[redacted]
DLBCL, no prior CAR-T, epcoritamab any-line after CAR-T		[redacted]
LBCL, prior CAR-T, epcoritamab 1L after CAR-T		[redacted]
LBCL, no prior CAR-T, epcoritamab any-line after CAR-T		[redacted]

[a]The EAG notes that a piecewise HR approach was explored for the MAICs vs Tomas *et al.* but these are not presented here.

Abbreviations: 1L, first line; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; HR, hazard ratio; LBCL, large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy; TE, Technical Engagement.

Additional MAICs vs Pola + BR

The additional MAICs for Pola + BR involve the Northend *et al.* study, which is also discussed in Section 2.9.[7] These MAICs were primarily performed by the company to address the point made in Section 2.9 that Sehn *et al.* as a source of data for Pola + BR may overestimate survival outcomes compared to RWE, which is reflected in Northend *et al.*[4-7] As this population included patients with prior CAR-T use, the analysis did not have to limit the EPCORE™ NHL-1 population to no prior CAR-T use unlike the company's preferred analysis for this comparator using Sehn *et al.* (scenario A.1). The

analysed population is instead focused on those with DLBCL and no prior ASCT. The EAG assumes this is because the Northend *et al.* population obtained is limited to this group but cannot confirm this as it does not have the data for the specific subgroup with ≥2 prior treatment failures requested and obtained by the company. Various versions of this MAIC with different levels of adjustment have been provided.

The company concludes that these MAICs demonstrate [redacted] benefits of epcoritamab compared to Pola + BR (see Section 2.9). Given that there are large differences in the MAIC performed using Sehn *et al.* and those using Northend *et al.*, including population analysed, factors adjusted for and type of study (trial-based vs RWE), the EAG does not consider that these additional MAICs provide any insight into how including or excluding those with prior CAR-T from MAICs would impact adjusted survival estimates for epcoritamab as there are too many differences in the analyses.[4-7] Limitations of these additional MAICs are described in more detail in Section 2.9.

Differences in survival between those with and without prior CAR-T

In terms of differences in survival in EPCORE™ NHL-1 for those with and without prior CAR-T treatment outlined in Section 3.3.4.2 of the EAG report, the company argue that with additional follow-up included as part of the [redacted] data cut-off, survival outcomes appear to be consistent after [redacted]. On review of the updated curves provided in Figures 8 to 11 of the appendix of the company's TE response, the EAG does not consider its concerns to be resolved. This is because while separation of curves [redacted] for OS, as already acknowledged in the EAG report, there is a [redacted] for PFS curves ([redacted] in those with no prior CAR-T), which [redacted]. Nonetheless, the EAG still considers differences in outcome between these groups [redacted] to be important in terms of how important their inclusion or exclusion from MAICs is and applicability of MAICs and economic model to the group with prior CAR-T use. Survival curves for the DLBCL population based on the [redacted] data-cut are provided below in Figure 2 and Figure 3.

Figure 2. KM plot of OS by prior CAR-T status – DLBCL patients (FAS, XXXXXXXX data cut-off) – reproduced from Figure 8 of the appendix of the company's TE response

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TE, Technical Engagement.

Figure 3. KM plot of PFS by prior CAR-T status – DLBCL patients (FAS, XXXXXXXX data cut-off) – reproduced from Figure 10 of the appendix of the company's TE response

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; TE, Technical Engagement.

The EAG acknowledges that median OS within the DLBCL population is [redacted] months vs [redacted] months for those without and with prior CAR-T use in EPCORE™ NHL-1, which is more limited than the difference in complete response (CR) rates the company highlights between Tomas *et al.* and SCHOLAR-1 (0.0% vs 12.1%).[1, 13] Based on this, the company suggests that the impact of prior CAR-T failure on outcomes would be larger for R-based CIT compared with epcoritamab (there would be a bigger decrement associated with prior CAR-T failure for those having R-based CIT). The EAG considers this conclusion to be based on a large number of assumptions and does not consider there is robust evidence to support this; in addition to there being differences in populations between Tomas *et al.* and SCHOLAR-1, comparing OS for those with and without prior CAR-T for EPCORE™ NHL-1 is not the same as comparing CR rates as has been done for the two R-based CIT studies. Furthermore, the EAG's largest concern in terms of differences between those with and without prior CAR-T use was for the PFS outcome, which has not been discussed given PFS was not reported for SCHOLAR-1.

Conclusion

The EAG considers the additional MAICs performed for R-based CIT and Pola + BR comparisons with inclusion of those with prior CAR-T are flawed and cannot be used to confirm that epcoritamab estimates obtained from original MAICs for each comparator would not be different had it been possible to include those with prior CAR-T use in them. The EAG acknowledges that MAICs vs SCHOLAR-1 and Sehn *et al.* cannot include EPCORE™ NHL-1 patients with prior CAR-T use given these patients were not included in the comparator studies and excluding from EPCORE™ NHL-1 avoids introducing bias related to differences in this population factor. The EAG is unsure what the impact on MAIC outcomes would be if comparator trials had included those with prior CAR-T use and matching could be performed, without the need to exclude them to bring populations in line. It has no reason to believe that prior CAR-T failure would have more of a detrimental effect on one treatment than another and is not convinced by the company's suggestion that a bigger impact would be observed for R-based CIT compared to epcoritamab, as the evidence put forward to support this was not robust. The EAG considers that this remains an unresolvable uncertainty associated with MAICs for R-based CIT and Pola + BR, which are limited to the group with no prior CAR-T use, and this should be considered in terms of whether original MAICs and subsequent economic model are applicable to those with prior CAR-T use.

2.6 Key issue 6: It is unclear if the population analysed from EPCORE™ NHL-1 in the MAICs vs R-based CIT and Pola + BR was specific to those ineligible for intensive treatments

The EAG highlighted that for MAICs vs R-based CIT and Pola + BR within population A (defined as those ineligible for intensive treatments, or who choose not to have them, in the company submission), it was unclear whether the EPCORE™ NHL-1 population analysed was specific to those ineligible for intensive treatments. It was unclear, therefore, how well the analysed population matches that set out for population A in the company submission (CS). The EAG concluded that, if the population from EPCORE™ NHL-1 analysed in these MAICs differed substantially from that of a population ineligible to intensive treatments, it had the potential to affect results of the MAICs and economic model and would be less applicable to population A as described in the CS. The EAG requested further information be provided regarding the population analysed and criteria used to conclude an individual would be eligible for intensive treatments, as well as baseline characteristics and outcomes for the group that was ineligible for intensive treatments. It also suggested that exploring the potential impact of including only those ineligible for intensive treatments be performed if this was not already part of these MAIC analyses.

2.6.1 Company's approach at Technical Engagement

The company confirmed at TE that the population analysed for R-based CIT and Pola + BR MAICs is those with DLBCL and no prior CAR-T treatment, with it not being specific to those that were ineligible for intensive treatments. It notes that it would not be appropriate to limit the EPCORE™ NHL-1 population analysed in these MAICs to those ineligible for intensive treatments, as doing so would introduce an imbalance between EPCORE™ NHL-1 and comparator studies given the company do not have access to the individual patient data (IPD) for comparator studies and the same adjustment could not be made. Therefore, the company have not explored this as suggested by the EAG. It has also not provided baseline characteristics and outcomes separately for the subgroup ineligible for intensive treatments in EPCORE™ NHL-1 or the criteria that would be required for someone to have been considered ineligible for intensive treatments in this study.

2.6.2 EAG's critique of the company's approach at Technical Engagement

The EAG acknowledges the company's argument that if the EPCORE™ NHL-1 population were to be further limited to those ineligible to intensive treatments, the same would have to be done in comparator trials to avoid the introduction of bias into the MAIC due to differences between studies for this population factor. While the EAG had initially assumed patients in studies receiving treatments such as Pola + BR and R-based CIT might be ineligible for intensive treatments, as it may be unlikely for them to receive these treatments as opposed to an intensive treatment if they were eligible for it, the EAG accepts that it is not clear from the comparator studies whether this assumption is valid. While the EAG accepts that this is an uncertainty, it maintains that its request for MAICs using the no prior CAR-T, ineligible for intensive treatments subgroup from EPCORE™ NHL-1 would be useful in assessing the impact on results, given the uncertainty that already exists with the MAICs. The EAG notes that for the comparison vs SCHOLAR-1, if the Crump *et al.* paper is subsequently used for the main analysis in response to issues described in Section 2.2, the scenario should be performed using this study and in the LBCL population with adjustment for LBCL type included. For both comparisons, full adjustment should be included. Furthermore, providing baseline characteristics and outcomes separately for the group in EPCORE™ NHL-1 that were ineligible for intensive treatments with no prior CAR-T use would be useful, as well as information on the criteria used to conclude that an individual was not eligible for intensive treatments in EPCORE™ NHL-1 (as also requested in Table 7 of the EAG report).

In conclusion, the EAG considers that uncertainty surrounding the analysis population in the MAICs for R-based CIT and Pola + BR and how well it represents a group that is ineligible for intensive treatments (definition of population A in the CS) remains. It considers this to be an unresolvable limitation of the MAICs when SCHOLAR-1 and Sehn *et al.* are used but considers MAICs and other details requested in the EAG's report (Table 7) would be useful in assessing the potential impact of this on MAIC results.[1, 2, 4-6]

2.7 Key issue 7: Not all factors reported, including some in imbalance, have been adjusted for in the MAICs for the three comparisons

The EAG raised concerns that MAICs included for all three comparators did not adjust for all baseline characteristics reported in comparator studies, despite some remaining in imbalance between arms and the importance of adjustment particularly for unanchored MAICs regardless of the impact on effective sample size (ESS). The EAG requested that MAICs be updated to adjust for all baseline

characteristics reported in the comparator studies, with specific factors thought to be important prognostically listed for each comparison (Table 8 of the EAG report).

2.7.1 Company's approach at Technical Engagement

The company has provided results of the three MAICs with adjustment for all reported baseline characteristics in comparator studies. However, it maintains that the factors adjusted for in its original MAICs for each comparator are appropriate and fully adjusted MAICs are not used in any of its base case analyses. In addition, the company did not provide fitted curves for the fully adjusted MAICs for Pola + BR or axi-cel meaning the EAG could not implement them in the economic model for these comparisons (see Section 2.12.1).

The company does not prefer the fully adjusted MAICs as it reiterates points it outlined in response to clarification, that feedback from clinical experts suggests that some variables are correlated, such as disease stage and International Prognostic Index (IPI) score, so adjusting for both will result in issues associated with collinearity and over-adjustment. It notes that its preferred analyses provide the most robust estimates of comparative efficacy, maximising larger sample sizes to inform the adjusted HRs.

It concludes that fully adjusted MAICs have the potential to introduce bias into the analyses, given that a [redacted] for epcoritamab at ~[redacted] was observed when the fully adjusted R-based CIT MAIC was performed and that UK clinical experts considered the fully adjusted MAICs for axi-cel to be implausible in terms of the extent that [redacted] epcoritamab. It also notes that the clinical experts consulted questioned the plausibility of the results for Pola + BR vs epcoritamab when fully adjusted, which [redacted] Pola + BR. It notes that when the MAIC with adjustment for 9/10 reported variables in SCHOLAR-1 is implemented in the economic model for the comparison vs R-based CIT, the ICER is reduced vs its base case analysis for this comparison; however, it did not provide similar comment for comparisons against Pola + BR or axi-cel (see Section 2.12.1).

Epcoritamab vs R-based CIT

Two additional MAICs were performed, one with adjustment for all variables reported in the Neelapu *et al.* SCHOLAR-1 paper (10 variables; ESS [redacted]) and one with adjustment for 9/10 variables reported in this SCHOLAR-1 paper (ESS [redacted]).[1] The latter was performed as clinical experts consulted

by the company considered the results with 10 variables adjusted for to be clinically implausible, as there was a [redacted]. This is shown in Figure 4 below.

Figure 4. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T epcoritamab population adjusted to SCHOLAR-1 (all reported variables, with truncation) – reproduced from Figure 46 of the appendix of the company's TE response

[a]Truncation of weights at 1% and 99% of their distribution was performed given the version without truncation would not converge.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy; TE, Technical Engagement.

The company concludes, based on results presented in Table 6 below, that the results of all MAICs are consistent and suggest that informing base case A is a conservative estimate of the comparative efficacy of epcoritamab vs R-based CIT. Associated KM curves are presented below in Figure 5.

Table 6. Comparison of MAIC results for epcoritamab vs R-based CIT, based on SCHOLAR-1 (Neelapu *et al.*), for OS – adapted from Table 5 of the company's TE response

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted OS HR (95% CI); p-value
DLBCL, no prior CAR-T	SCHOLAR-1 (Neelapu *et al.*)	7; with truncation[a]; N_{eff} = [redacted]	[redacted]
		9; no truncation[b]; N_{eff} = [redacted]	[redacted]
		10; with truncation; N_{eff} = [redacted]	[redacted]

[a]MAIC analysis used to inform base case analysis A; [b]MAIC analysis used to inform scenario analysis A.4.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; N_{eff}, effective sample size; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy; TE, Technical Engagement.

Figure 5. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) – DLBCL, no prior CAR-T epcoritamab population adjusted to SCHOLAR-1– reproduced from Figures 24, 31 and 46 of the appendix of the company's TE response

[redacted]

Top image = 7 adjusted factors used in base case, middle image = 9/10 adjusted factors and bottom image = 10/10 adjusted factors.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy; TE, Technical Engagement.

Epcoritamab vs Pola + BR

The same discussion of fully adjusted MAICs for Pola + BR and how they compare to the original MAIC for this comparator is not provided in the company's TE response document but a version with full adjustment has been performed (Section B.2 of the appendix of the company's TE response). This includes adjustment for 10 reported variables in Sehn *et al.* compared with 6 adjusted for in the original MAIC described in scenario A.1. A comparison of fully adjusted results to the original MAIC is provided in Table 7, Figure 6 and Figure 7 below.

Table 7. Comparison of MAIC results for epcoritamab vs Pola + BR, based on Sehn *et al.*, for OS and PFS – adapted from Tables 39 and 60 of the appendix of the company's TE response

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted HR (95% CI); p-value	
DLBCL, no prior CAR-T	Sehn *et al.*	6; no truncation[a]; N_{eff} = [redacted]	Up to [redacted]	After [redacted]
			OS: [redacted] PFS: [redacted]	OS: [redacted] PFS: [redacted]
		10; with truncation; N_{eff} = [redacted]	OS: [redacted] PFS: [redacted]	

[a]MAIC analysis used to inform scenario analysis A.1.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; N_{eff}, effective sample size; NR, not reported; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; TE, Technical Engagement.

Figure 6. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.*) – DLBCL, no prior CAR-T epcoritamab population adjusted to Sehn *et al.* – reproduced from Figures 25 and 47 of the appendix of the company's TE response

Top image = 6/10 adjusted factors used in scenario analysis A.1 and bottom image = 10/10 adjusted factors.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; OS, overall survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; TE, Technical Engagement.

Figure 7. Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.*) – DLBCL, no prior CAR-T epcoritamab population adjusted to Sehn *et al.* – reproduced from Figures 26 and 48 of the appendix of the company's TE response

Top image = 6/10 adjusted factors used in scenario analysis A.1 and bottom image = 10/10 adjusted factors.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; IRC, independent review committee; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; TE, Technical Engagement.

Epcoritamab vs axi-cel

One additional MAIC was performed to include adjustment for all variables reported in ZUMA-1 for the analysis in the DLBCL,[3, 14] no prior CAR-T and CAR-T eligible population. This included 10 variables; while the company state that the original MAIC in this population included 8 variables, the

EAG considers this may actually be 7, as for the DLBCL analysis, adjustment for type of LBCL could not be performed given only DLBCL were included in the analysed EPCORE™ NHL-1 population. The EAG confirms that 8 variables appear to have been adjusted for in the company's original MAIC for this comparison where the LBCL population from EPCORE™ NHL-1 is instead included.

The company concludes that the results of the fully adjusted MAIC in DLBCL are consistent with that informing the updated base case analysis (updated data-cut for EPCORE™ NHL-1 and ZUMA-1, and switch from LBCL to DLBCL based [redacted]) of epcoritamab vs axi-cel, noting that the analysis with further adjustment suggests a slightly greater treatment benefit for epcoritamab vs axi-cel compared to its preferred analysis, although the difference [redacted]. The company adds that the same was true when full adjustment was applied to the analysis in the LBCL (scenario B.1), no prior CAR-T and CAR-T eligible population. Results are presented in Table 8 and Figure 8 to Figure 11 below.

Table 8. Comparison of MAIC results for epcoritamab vs axi-cel, based on ZUMA-1 for OS and PFS – adapted from Table 6 of the company's TE response and Tables 45 and 70 of the appendix of the company's TE response

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted HR (95% CI); p-value
DLBCL, no prior CAR-T, CAR-T eligible	ZUMA-1	7[a,b,c]; (N_{eff} = [redacted])	OS: [redacted] PFS: [redacted]
		10; (N_{eff} = [redacted])	OS: [redacted] PFS: [redacted]
LBCL, no prior CAR-T, CAR-T eligible		8; (N_{eff} = [redacted])[d]	OS: [redacted] PFS: [redacted]
		11; (N_{eff} = [redacted])	OS: [redacted] PFS: [redacted]

[a]MAIC analysis used to inform the company's updated base case analysis B; [b]the EAG notes that the company suggested this was 8 rather than 7, but the EAG considers DLBCL was not adjusted for in this MAIC given the analysed population from EPCORE™ in this analysis did not include other types of LBCL; [c]the EAG notes there is a discrepancy between Table 6 of the company's TE response and Table 44 of the appendix of the company's TE response with regards to the results and N_{eff} for the original MAIC in the DLBCL population. Results presented here are based on Table 44 of the appendix of the company's TE response, given the N_{eff} matches the N_{eff} for this population in company's original submission (Table 30 of the original CS). The EAG notes that the erroneous results in Table 6 are for the LBCL population instead. The EAG considers that 8 were adjusted for in the original MAIC for this comparison when the LBCL population was included; [d]MAIC analysis described as scenario analysis B.1.

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; LBCL, large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; N_{eff}, effective sample size; OS, overall survival; PFS, progression-free survival; TE, Technical Engagement.

Figure 8. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, no prior CAR-T, CAR-T eligible epcoritamab population adjusted to ZUMA-1 – reproduced from Figures 34 and 60 of the appendix of the company's TE response

Top image = 7/10 adjusted factors used in updated base case analysis B and bottom image = 10/10 adjusted factors.

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; OS, overall survival; TE, Technical Engagement.

Figure 9. Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – DLBCL, no prior CAR-T, CAR-T eligible epcoritamab population adjusted to ZUMA-1 – reproduced from Figures 35 and 61 of the appendix of the company's TE response

Top image = 7/10 adjusted factors used in updated base case analysis B and bottom image = 10/10 adjusted factors.
Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; TE, Technical Engagement.

Figure 10. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, no prior CAR-T, CAR-T eligible epcoritamab population adjusted to ZUMA-1 – reproduced from Figures 36 and 62 of the appendix of the company's TE response

Top image = 8/11 adjusted factors used in scenario analysis B.1 and bottom image = 11/11 adjusted factors.
Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; OS, overall survival; TE, Technical Engagement.

Figure 11. Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – LBCL, no prior CAR-T, CAR-T eligible epcoritamab population adjusted to ZUMA-1 – reproduced from Figures 37 and 63 of the appendix of the company's TE response

Top image = 9/11 adjusted factors used in scenario analysis B.1 and bottom image = 11/11 adjusted factors.

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; TE, Technical Engagement.

2.7.2 EAG critique of the company's approach at Technical Engagement

The EAG acknowledges that the company has now provided fully adjusted versions of the MAICs included for each of the three comparators. However, it does not agree with the company's decision to maintain a preference for MAICs with only partial adjustment. While the EAG acknowledges difficulties associated with similar characteristics that may overlap, the EAG reiterates its point that unanchored MAICs are associated with considerable uncertainty. Furthermore, MAICs are limited by the variables reported in the comparator studies and examples of potentially important prognostic factors not reported in certain comparator studies have been highlighted by the EAG, as well as other differences or uncertainties in terms of patients included (see Sections 2.3, 2.8.1 and 2.10).

Adjusting for all reported baseline characteristics in comparator studies is, therefore, the EAG's preference for all MAICs and it does not consider the maintenance of ESS and increased precision when adjusting for fewer factors to represent a more robust analysis than one which adjusts for all reported variables. While it acknowledges that a balance between factors adjusted for and ESS may be important for anchored MAICs, the increased uncertainty associated with unanchored MAICs means adjustment for all reported baseline characteristics is critical. The EAG considers that a substantially reduced ESS indicates a lack of overlap (or comparability) of the studies being compared. If this results in an unstable estimate, this is a direct reflection of the lack of comparability between trials included in the analysis; making an arbitrary decision to limit the number of factors adjusted for does not make the trials more comparable – it only obscures their lack of comparability. The EAG is concerned that the partially adjusted MAIC results preferred by the company ignore this underlying issue of the lack of comparability of the trials and that the company is inappropriately emphasising the ESS to indicate that a partially adjusted analysis is more robust than a fully adjusted analysis.

The EAG comments on each MAIC separately in the sections that follow; given fitted curves were not provided for some comparators meaning fully adjusted MAIC results could not be implemented in the economic model, the EAG has commented on the similarity of KM curves between partially adjusted MAICs and MAICs with full adjustment or adjustment for most reported factors (the company and EAG-preferred MAICs, respectively).

Epcoritamab vs R-based CIT

The EAG acknowledges the company's concern about the MAIC with 10/10 reported factors adjusted for and agrees that the KM curve for OS may not be clinically plausible, with the [redacted]. However, while the company suggests that this is because full adjustment introduces bias into the MAIC and reduced ESS, the EAG considers it likely that this is instead caused by the lack of comparability between SCHOLAR-1 (Neelapu *et al.*) and EPCORE™ NHL-1 populations.[1] It is important that unanchored MAICs adjust for all reported baseline characteristics and implausible patterns arising as more adjustments are made suggest that the two studies are not comparable and that it may not be possible for robust estimates to be obtained from any MAIC involving the two studies.

In this case, the EAG accepts that using the 10/10 adjusted MAIC would not be appropriate and considers the 9/10 adjusted MAIC gives more clinically plausible results. However, the EAG considers this MAIC remains flawed given it does not adjust for all reported baseline characteristics and using the 9/10 MAIC merely gives the illusion that the two trials are more comparable than they actually are. In particular, the variable that had to be removed was "SCT any time after refractory disease" which is considerably imbalanced between the adjusted EPCORE™ NHL-1 and SCHOLAR-1 populations ([redacted] in EPCORE™ NHL-1 and 37.1% in SCHOLAR-1) and could bias results of the MAIC. The EAG is unsure as to which direction bias might introduced due as a result of this imbalance (i.e., whether the lower proportion with this factor in EPCORE™ NHL-1 might be an advantage or disadvantage for epcoritamab); clinical expert input on this may be useful. While the 9/10 adjusted MAIC is the EAG's preferred of those available for the current MAIC vs R-based CIT, the EAG considers using Crump *et al.* rather than Neelapu *et al.*, with full adjustment performed, may be more appropriate as discussed in Section 2.2.[1, 2]

While the EAG agrees that adjusted HR obtained for the 9/10 adjusted MAIC is similar to that in the company's preferred MAIC with partial adjustment, and that the company's preference may represent a conservative estimate, for reasons already described the EAG considers it important that results from MAICs with more factors adjusted for, regardless of whether they are more or less favourable for epcoritamab, are preferred. The EAG notes that when 9/10 factors are adjusted for, it resolved the issue the EAG raised in Section 2.2 about the imbalance remaining between studies for disease stage III-IV proportions when the Neelapu *et al.* study is used and baseline characteristics overall appear more well-balanced compared to the original adjustment performed (Table 34 vs Table 30 in the appendix of the company's TE response),[1] other than "SCT any time after refractory disease" which remained in imbalance as described above.

The EAG concludes that it has considerable concerns about the MAICs including SCHOLAR-1 and whether robust estimates could be obtained from any MAIC containing these two studies. The EAG considers that this may be another reason to explore how use of Crump *et al.* for SCHOLAR-1 would impact MAIC results (see Section 2.2) as it considers that this paper may result in a more robust analysis.[2] This is because of factors already discussed in Section 2.2.2, including that Crump *et al.* would allow for LBCL type to be adjusted for rather than remaining an uncertain difference between EPCORE™ NHL-1 and SCHOLAR-1 and that there are differences in baseline characteristics between Crump *et al.* and Neelapu *et al.*, with the latter more in line with a CAR-T eligible population given 100% of patients had ECOG score 0-1, which was 73% in the Crump *et al.* paper.[1, 2]

Epcoritamab vs Pola + BR

The EAG confirms that a fully adjusted version of the MAIC vs Pola + BR (using Sehn *et al.*) has been provided. It notes that populations are fairly well balanced, although some larger imbalances remain, some of which may bias against epcoritamab and some which may bias against Pola + BR. While some variables are less well-balanced in the fully adjusted MAIC compared to the partially adjusted MAIC (Table 48 vs Table 31 in the appendix of the company's TE response), the EAG notes that more extreme differences between groups are reduced in the fully adjusted MAICs (for example, refractory to last prior anti-lymphoma therapy initially differed by ~[redacted]% between studies and was a factor that the EAG's clinical experts considered to be important in terms of prognosis; there are no factors with this level of difference in the fully adjusted MAIC). The EAG considers that the remaining slight imbalances between studies after matching for all reported variables highlights the potential lack of comparability between EPCORE™ NHL-1 and Sehn *et al.* and highlights remaining uncertainty in the results of the MAICs for this comparison.[4-6]

The EAG considers a comparison of HRs for OS and PFS outcomes to be difficult, given the original MAIC presents HRs for up to and following [redacted] months separately in a piecewise approach but only single HRs are provided for the fully adjusted MAIC (Table 7 above). However, on review of the KM curves presented in Figure 6 and Figure 7 above, the EAG notes that the fully adjusted MAIC appears to be [redacted] for epcoritamab compared to the partially adjusted MAIC; survival estimates for OS and PFS appear to be [redacted] at time-points of 6, 18 and 24 months, for example, in the fully adjusted MAIC. For reasons described earlier in terms of uncertainty associated with unanchored MAICs, the EAG's preference is for the MAIC with full adjustment of baseline characteristics. While the company notes that clinical experts considered that the results of the fully adjusted MAIC vs Pola + BR may not be clinically plausible, the EAG considers that this raises concerns about whether there are important unknown differences between the studies that are not appropriately adjusted for, but is not a reason to prefer an analysis that is partially adjusted.

Epcoritamab vs axi-cel

The EAG acknowledges the company's statement that for fully adjusted MAICs in DLBCL and LBCL populations vs ZUMA-1,[3, 14] results suggest slightly [redacted] results for epcoritamab compared to partially adjusted results. While the company notes that clinical experts consulted do not consider the results from the fully adjusted MAIC to be clinically plausible in terms of the benefit

of epcoritamab over axi-cel, the EAG notes that substantial imbalances observed in the partially adjusted MAICs have been resolved by full adjustment (Tables 57 and 58 vs 36 and 37, for DLBCL and LBCL, respectively, in the appendix of the company's TE response).

In the absence of direct comparative data observed in an appropriately-powered double-blind randomised controlled trial, the EAG considers the balancing of population characteristics between studies being compared within the MAIC to be a priority and does not consider it reasonable to prefer an analysis with partial adjustment. If these fully adjusted curves are clinically implausible, the EAG considers this to be due to unreported differences between the trials that have not been appropriately adjusted for. Given this point highlighted by the company, while the EAG prefers analyses with full adjustment, the EAG has concerns about how robust and accurate any of the MAICs vs axi-cel are.

While in its TE response the company has changed its preference for the MAIC vs axi-cel to the one in which the DLBCL population from EPCORE™ NHL-1 is used (given the [redacted] for epcoritamab), the EAG does not consider this to be appropriate and maintains a preference for the analysis in which the LBCL population from this study is used. This is because the ZUMA-1 study focuses on a LBCL population and when the DLBCL population from EPCORE™ NHL-1 is selected for comparison in the MAIC,[3, 14] this introduces a population difference between the studies that could introduce bias and cannot be adjusted for. Therefore, while it may slightly deviate from the [redacted] for epcoritamab, the EAG prefers that the MAIC vs ZUMA-1 include LBCL with adjustment for type of LBCL between the two studies performed. On comparing the company's preferred MAIC (DLBCL partially adjusted) with the EAG's preferred MAIC (LBCL fully adjusted), the EAG notes that the latter demonstrates [redacted] estimates for epcoritamab for both OS and PFS and the company's preferred MAIC may, therefore, be conservative. The same difference appears to apply between partially and fully adjusted versions of the analysis including DLBCL and inclusion of LBCL overall appears to have limited impact on the results, although it may be slightly more noticeable for the LBCL analysis. However, given the EAG's preference for fully adjusted MAICs throughout, the EAG considers fully adjusted MAICs most appropriate and favours the LBCL analysis as this means adjustment for LBCL type can be included.

Conclusion

The EAG concludes that it has considerable concerns about the robustness of MAICs for each comparator, even with all or most reported baseline characteristics adjusted for, and questions whether robust results can be obtained from any of these analyses, particularly given the company concludes that fully adjusted results are clinically implausible based on clinical expert feedback. The EAG considers that the studies being compared may be too different meaning adjustment for further characteristics leads to unexpected observations and/or that there are important unreported factors that have not been appropriately adjusted for. For axi-cel, the EAG retains a preference for the LBCL analysis given this avoids introducing a population difference between EPCORE™ NHL-1 and ZUMA-1 in this MAIC and that it is adjusted for.[3, 14]

2.8 Key issue 8: All clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1

The EAG highlighted in its report that all clinical and economic analyses should be based on the most recent data-cut available for EPCORE™ NHL-1, as a different data-cut was mentioned in response to some clarification questions (CQs; Table 9 of the EAG report).

2.8.1 Company's approach at Technical Engagement

In response to TE, the company highlights that a more recent data-cut ([redacted]) is available from EPCORE™ NHL-1 and that all MAICs and economic analyses have been updated based on this new data-cut. Clinical data from this data-cut are presented, updated MAICs using this data and updated economic analyses are presented in Appendices A, B and C, respectively, of the company's response to TE.

2.8.2 EAG's critique of the company's approach at Technical Engagement

The EAG confirms that updated clinical results from the EPCORE™ NHL-1 have been provided by the company and that updated MAICs are now based on longer term data available up to [redacted].

In terms of the clinical outcomes from EPCORE™ NHL-1 covered in Section 3.3 of the EAG report, the EAG has not provided an updated section with results as of [redacted] in this report given this section in the EAG report simply reported the results in the CS with no further conclusions drawn for most outcomes. Instead, the EAG highlights that the most up to date data from EPCORE™ NHL-1 is presented in Appendix A of the company's TE response, where a comparison vs the last included data-cut has also been presented by the company for response outcomes. The EAG notes that Appendix A focuses on the DLBCL population (whereas Section 3.3 of the EAG report included all

LBCL patients in the trial) given the [redacted] since the original CS.

The EAG has included Table 9 below to highlight where in Appendix A of the company's TE response updated data in the EAG's report can be found for each subsection, albeit for some outcomes the DLBCL rather than LBCL population included in EPCORE™ NHL-1 is focused on. The EAG notes that data for health-related quality of life (HRQoL) outcomes in the DLBCL population is identical in the new data-cut to the last one provided (up to cycle 9) given minimum follow-up in the last data-cut was [redacted]. Data for following cycles have not been provided but end of treatment (EOT) scores are provided in the updated CSR for Functional Assessment of Cancer Therapy (FACT-Lym) scales, including the lymphoma subscale (FACT-LymS), and EQ-5D-3L utility scores. EOT FACT-Lym scores show that while up to cycle 9 scores [redacted] as described in Section 3.3.2 of the EAG report, [redacted] the end of treatment (mean change from baseline EOT scores [redacted] for FACT-Lym total score and [redacted] for FACT-LymS, with [redacted] analysed for both change from baseline outcomes; Table 14.2.3.5.5 of CSR tables for [redacted]). The same applied for EQ-5D-3L EOT scores (change from baseline value of [redacted], with [redacted] analysed).

The EAG notes that the company has also provided data for certain subgroup analyses presented in Section 3.3.4 of the EAG report updated with data from the most recent data-cut in its TE response (Appendix A.8):

- The company did not provide full updated data for "type of LBCL" subgroup analyses (section 3.3.4.1 of the EAG report) and the EAG could not assess whether conclusions in the EAG report for overall response rate (ORR) or CR outcomes for this subgroup analysis still apply. For other outcomes within this subgroup, while the exact values may have changed, the EAG's conclusions regarding potential differences between these subgroups have not changed (Appendices A.4 and A.7 of the company's TE response, and Tables 14.2.3.5.5 and 14.2.3.5.6 of the CSR tables updated for [redacted] for HRQoL outcomes);
- The company did not provide updated data for ORR, CR, duration of response (DOR) or HRQoL outcomes for the subgroup comparing those with and without prior CAR-T treatment and the EAG could not assess whether conclusions in the EAG report for these outcomes still apply (Section 3.3.4.2 of the EAG report). However, conclusions made for other outcomes still apply in terms of potential differences between these two subgroups (Appendix A.8.2 of

the company's TE response) for both the DLBCL and LBCL populations. The EAG considers there may be an error in the labelling of Figures 8 and 9 of the appendix of the company's TE response as median survival values are [redacted] in the no prior CAR-T group but discussed elsewhere as being [redacted] in the no prior CAR-T group;

- The company did not provide updated data for ORR, CR, DOR or HRQoL outcomes for the subgroup analysis comparing between numbers of prior anti-lymphoma treatments and the EAG could not assess whether conclusions in the EAG report for these outcomes still apply (Section 3.3.4.3 of the EAG report). However, conclusions made for most other outcomes still apply in terms of potential differences between these two subgroups (Appendix A.8.3 of the company's TE response) for DLBCL and LBCL populations.

Table 9. Sections of Appendix A of company's TE response that contains updated data for outcomes covered in Section 3.3 of the EAG report

Outcome	Section in EAG report	Section in Appendix A of company's TE response	EAG comment
Survival and response outcomes	3.3.1	Appendices A.1, A.3 and A.4	NA
Health-related quality of life	3.3.2	Appendix A.6	The EAG notes that data provided here for DLBCL as part of the [redacted] data-cut is identical to that provided in the original CS as part of the [redacted] data-cut (Table 20 of the original CS). EOT values have been provided which show that [redacted] observed up to cycle 9 of treatment [redacted] by EOT.
Adverse events	3.3.3	Appendix A.7	The EAG considers there are no major differences between the data-cut included in the EAG report and the updated data-cut presented as part of TE; proportions with certain types of adverse events have increased with the new data-cut as may be expected with longer follow-up. Results for DLBCL and LBCL populations were concluded to be similar in the EAG report and the same applies for the new data-cut.

Abbreviations: CS, company submission; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; EOT, end of treatment; LBCL, large B-cell lymphoma; NA, not applicable; TE, Technical Engagement.

2.9 Key issue 9: Limitations of Sehn *et al.* for the MAIC vs Pola + BR

In the EAG report, the EAG highlighted two limitations of Sehn *et al.* for the MAIC vs Pola + BR, which it considers are potentially important. This included acknowledgement of the company's point that survival estimates for Pola + BR in Sehn *et al.* are not in line with those from a UK RWE source (with more favourable results observed in Sehn *et al.* compared to the RWE source)..[4-7] In addition, the proportion of patients refractory to primary treatment was not reported meaning it could not be adjusted for in the MAICs; given this was noted by the EAG's clinical experts to be an important prognostic factor, and it is unclear how proportions differ vs EPCORE™ NHL-1, this could be an important limitation of this MAIC.

2.9.1 Company's approach at Technical Engagement

The company reiterates its position in the original submission that Sehn *et al.* likely overestimates survival for Pola + BR, compared to UK RWE from Northend *et al.* 2022, and biases against epcoritamab as a result in this MAIC.[4-7] The company did not originally perform a MAIC using this study as a scenario but has provided this in response to TE (scenario analysis A.5 in Appendix B.1 of the company's TE response and additional scenarios in Appendix B.2, as outlined in Table 46 of the TE appendix), as data from this RWE study for the group that received at least two prior lines of treatment was requested and obtained. The company concludes that results presented in Table 10 below indicate that use of Sehn *et al.* biases against epcoritamab as estimates obtained from MAICs when Northend *et al.* data is instead used are more favourable for epcoritamab, with [redacted] benefits of epcoritamab vs Pola + BR identified. KM curves comparing these two analyses are presented below in Figure 12 and Figure 13.

In response to the fact that primary refractoriness could not be adjusted for in the MAIC using Sehn *et al.*, the company agrees that this is a source of uncertainty that is unresolvable when Sehn *et al.* is used.[4-6] It notes that adjustment for other related factors (such as refractory to last prior anti-CD20 agent) may limit differences observed between Sehn *et al.* and EPCORE™ NHL-1 in terms of primary refractoriness.

It also maintains that it does not consider Pola + BR to be a relevant comparator in this appraisal given it would only be used for a minority of patients with R/R LBCL after two or more lines of treatment.

Table 10. Comparison of MAIC results for epcoritamab vs Pola + BR based on Sehn *et al.* 3L+ and Northend *et al.* 3L+ - adapted from Tables 39, 43 and 145 of the appendix of the company's TE response

Epcoritamab population	Comparator data source	Number of variables adjusted for (N_{eff})	Adjusted HR (95% CI); p-value	
DLBCL, no prior CAR-T	Sehn *et al.* 3L+	6; no truncation[a]; N_{eff} = [redacted]	Up to [redacted] OS: [redacted] PFS: [redacted]	After [redacted] OS: [redacted] PFS: [redacted]
DLBCL, no prior ASCT	Northend *et al.* RW data 3L+	11; with truncation[b]; N_{eff} = [redacted]	OS: [redacted] PFS: [redacted]	

[a]MAIC analysis used to inform scenario analysis A.1; [b]MAIC analysis informing scenario A.5.

Abbreviations: 3L+, third-line and beyond; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; N_{eff}, effective sample size; NR, not reported; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; RW, real-world; TE, Technical Engagement.

Figure 12. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (or) – DLBCL, no prior CAR-T (Sehn *et al.* 3L+) or DLBCL, no prior ASCT (Northend *et al.* 3L+) epcoritamab population adjusted to comparator studies – reproduced from Figures 25 and 32 of the appendix of the company's TE response

[redacted]

Top image = 6/10 adjusted factors used scenario analysis A.1 and bottom image = 11/16 adjusted factors used in scenario analysis A.5.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; OS, overall survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; TE, Technical Engagement.

Figure 13. Unadjusted and adjusted PFS KM curve for epcoritamab (EPCORE™ NHL-1) and Pola + BR (or) – DLBCL, no prior CAR-T (Sehn *et al.* 3L+) or DLBCL, no prior ASCT (Northend *et al.* 3L+) epcoritamab population adjusted to comparator studies – reproduced from Figures 26 and 33 of the appendix of the company's TE response

[redacted]

Top image = 6/10 adjusted factors used in scenario analysis A.1 and bottom image = 11/16 adjusted factors used in scenario analysis A.5.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; TE, Technical Engagement.

2.9.2 EAG's critique of the company's approach at Technical Engagement

The EAG acknowledges the large difference in survival estimates from Sehn *et al.* and Northend *et al.* 3L+ DLBCL populations, which is shown in Figure 12 and Figure 13 above, suggesting that Sehn *et al.* may not be a reflection of outcomes with Pola + BR in UK clinical practice, given Northend *et al.* is a UK RWE source[4-7] It also acknowledges that this leads to different results in terms of the benefit of epcoritamab compared to Pola + BR from the MAICs. However, differences in outcome between trial-based results such as Sehn *et al.* and RWE sources such as Northend *et al.* may not be surprising and other differences that may affect outcomes also differ between these two studies; for example, there is a large difference between those with ECOG scores 0-1 ([redacted]% vs 89% in Northend *et al.* and Sehn *et al.*, respectively) and the proportion with international prognostic index (IPI) scores ≥3 ([redacted]% vs 55.2% in Northend *et al.* and Sehn *et al.*, respectively) suggesting that the RWE source may represent a population with a poorer prognosis, as might be expected compared to a trial.[4-7]

Furthermore, given that EPCORE™ NHL-1 is itself a clinical trial rather than an RWE source, the EAG considers that the MAICs using Northend *et al.* introduce additional bias given outcomes from trial-based and RWE sources are likely to differ and RWE for epcoritamab when available may similarly

differ to outcomes obtained from EPCORE™ NHL-1. While the EAG acknowledges the differences observed between Sehn *et al.* and RWE sources for Pola + BR and that Sehn *et al.* may overestimate Pola + BR outcomes compared to UK clinical practice, it considers the same is likely to apply to RWE for epcoritamab.[4-7]

The EAG notes that the MAIC presented by the company for Northend *et al.* is not adjusted for all reported baseline characteristics and while others with further adjustment are also provided (Section B.2), these also do not include all reported baseline characteristics.

In terms of primary refractoriness not being reported and, therefore, not adjusted for in any MAICs using Sehn *et al.*, the EAG acknowledges the company's point that adjustment for other similar characteristics such as refractory to last prior anti-CD20 agent as performed in the company's preferred analysis for this comparator (scenario A.1) may limit the impact of this.[4-6] However, it notes that important factors such as this that are unreported is a reason why all reported baseline characteristics should be adjusted for, as discussed in Section 2.7. With regards to this comparison specifically, the EAG notes that the fully adjusted version of the MAIC vs Pola + BR also adjusts for *"refractory to last prior anti-lymphoma therapy"*, which remains in large imbalance in the company's preferred analysis for this comparison (scenario A.1). The EAG considers that the concern about unreported baseline characteristics supports the EAG's preference for a fully adjusted MAIC for this and other comparisons (Section 2.7).

The EAG acknowledges that Pola + BR may be a treatment that is not used as often at 3L+ than others included in this appraisal but considers its inclusion relevant given it will still be an option for some patients based on feedback from the EAG's clinical experts, as stated in the EAG report. Clinical experts that submitted stakeholder responses also noted that while it may not be a large population and it may continue to reduce, Pola + BR may be an option for some patients at 3L+.

2.10 Key issue 10: Limitations of ZUMA-1 for the MAIC vs axi-cel

A number of limitations associated with using ZUMA-1 as the source of comparator data for the comparison with axi-cel were highlighted in the EAG's report.[3, 14] This included:

- Differences in the definition used for PFS, which the EAG considered may be more sensitive in EPCORE™ NHL-1 compared to ZUMA-1, potentially introducing bias against epcoritamab;

- The fact that the ZUMA-1 study focuses on those that were infused with axi-cel, excluding those that may become ineligible by the time the infusion is ready (treatment has to be manufactured for each patient after cells are taken) and potentially introducing bias against epcoritamab;
- At least one potentially important prognostic factor highlighted by the EAG's clinical experts was not reported in ZUMA-1 and could not be adjusted for (refractory to last anti-lymphoma treatment). It is, therefore, unclear whether there were any important differences compared to the EPCORE™ NHL-1 population in the MAIC.

The EAG considers that these factors could impact the clinical and cost-effectiveness outcomes, particularly the first two which may introduce bias against epcoritamab. The EAG concluded that the latter two points were unresolvable limitations when ZUMA-1 is used in the MAIC but that the first point could be explored by applying the criteria for PFS used in ZUMA-1 to IPD from EPCORE™ NHL-1 and assessing the impact.

2.10.1 Company's approach at Technical Engagement

The company acknowledges that some limitations of ZUMA-1 exist and notes the fully adjusted MAIC provided as a scenario for this comparison may address concerns about factors that were not reported and could not be adjusted for (see Section 2.7 for further discussion). In addition, it notes that adjusting for related factors such as primary refractoriness, resistance to two consecutive lines and refractory to second-line treatment is likely to mean proportions refractory to last anti-lymphoma treatment in EPCORE™ NHL-1 and ZUMA-1 studies are similar.[3, 14]

The company agrees that use of the infused population in ZUMA-1 and differences in PFS definition between the trials are likely to introduce bias against epcoritamab in the MAIC.[3, 14] For the former, the company are not aware of published data for the intention to treat (ITT) population of ZUMA-1 that could be used instead of the modified ITT (mITT) population which is specific to those infused and is currently used in the MAIC. The company highlights UK RWE demonstrating that ~17% of R/R LBCL patients approved for treatment with CAR-T treatment were unable to receive the infusion due to either disease progression or death due to disease progression, with 35% of those approved for treatment not receiving the infusion[15]. The company highlights that this paper also supports the idea that results of the mITT population will overestimate the clinical benefit of CAR-T. The company notes that were ITT data from ZUMA-1 available, it anticipates that the cost-effectiveness of epcoritamab vs this comparator would improve.

A comparison of the definitions for PFS is provided in Table 7 of the company's response to TE but it the company has not performed the scenario suggested by the EAG, where the definition from ZUMA-1 could be applied to EPCORE™ NHL-1 IPD.

It also highlights that at TE, 5-year data for ZUMA-1 was incorporated into this MAIC, as requested by the EAG at the clarification stage.[14]

2.10.2 EAG's critique of the company's approach at Technical Engagement

The EAG acknowledges the company's point that when some important baseline characteristics are not reported and cannot be adjusted for in MAICs, adjusting for other, similar factors may reduce the difference for the unreported factor; however, it is not possible to confirm to what extent the difference remains unresolved. Furthermore, the EAG highlights that unreported factors that are particularly important in terms of prognosis is one reason why fully adjusted MAICs should be preferred, as discussed in Section 2.7; the EAG notes that the fully adjusted MAIC vs axi-cel includes an additional factor related to refractory status (*"refractory to second-line or subsequent therapy"*) compared to the company's preferred MAIC for this comparison. Given the concerns about not being able to adjust for refractory to last anti-lymphoma treatment as it is not reported in ZUMA-1, the EAG considers the fully adjusted MAIC reduces concerns about this issue compared to the partially adjusted MAIC.

In terms of the infused population (mITT) being used in ZUMA-1, the EAG notes that one of the clinical experts that submitted a stakeholder response agreed with the EAG and company's point about this potentially overestimating outcomes for CAR-T treatments such as axi-cel. The EAG agrees that the paper cited by the company also supports this idea, but could not validate the value of 35% cited above for percentage recommended for CAR-T but not receiving the infusion; the EAG considers this may instead be ~26% (104/404 not receiving infusion).[15] The EAG considers that this remains an unresolvable limitation of using ZUMA-1 given ITT data is not available for this study and that bias may be introduced against epcoritamab in the MAIC, although it is not possible to quantify the extent of this.

For the different definitions of PFS between EPCORE™ NHL-1 and ZUMA-1, the EAG does not consider Table 7 in the company's TE response to clearly confirm that the EAG's suggestion that Lugano criteria used in EPCORE™ NHL-1 may be more sensitive to International Working Group (IWG) criteria used in ZUMA-1. On review of the papers cited for each of these criteria by the

company,[16, 17] the EAG notes that one paper reports that the use of positron emission tomography computed tomography (PET-CT) for staging in FDG-avid lymphomas increases sensitivity compared to CT and notes that the Lugano criteria includes this while suggesting that the IWG at the time (2007, as cited in the paper for ZUMA-1) does not as it notes it as a departure from IWG criteria.[3, 16] While the EAG, therefore, considers it likely that any difference in definitions used for PFS may bias the MAIC results against epcoritamab, the EAG remains unsure about the extent this may change results and the EAG's suggestion that the company performs a MAIC where the IWG criteria are instead applied to the PFS outcome in EPCORE™ NHL-1 may make any impact clearer. It may also be useful to hear from clinical experts about the potential difference in sensitivity of these different PFD definitions.

2.11 Key issue 11: Implementation of the long-term remission assumption in the model

The company's original model assumed that all patients in the progression-free state 2 years after the beginning of the model entered long-term remission (LTR) in all treatment arms. This assumption meant that after 2 years in the model:

1. Patients experienced no further progression events.
2. Patients experienced an adjusted background mortality rate, where a standardised mortality ratio (SMR) of 1.41 was applied to the general population mortality matched for age and sex.
3. Patients did not use any healthcare resources associated with treatment follow-up.
4. Patients experienced the utility value associated with being in the PFS state while alive.

The EAG originally noted that the company's LTR assumption did not imply that patients' survival returned to that observed in the general population after 2 years, nor that patients' quality of life returned to that of the general population. Therefore, the company's assumption was not the equivalent of a "structural cure" in the model. The EAG noted that it was mainly satisfied with the company's LTR assumption as:

1. Its clinical experts explained that R/R LBCL patients who have not progressed 2 years after the end of their treatment would be considered to be in LTR (i.e., further disease progression events were unlikely to occur).

2. Clinical experts would discharge patients from follow-up when these were considered to have entered LTR.
3. The KM PFS data for comparator treatments mainly showed a plateau in disease progression at around 2 years.

Notwithstanding, the EAG had two main issues with the implementation of the LTR assumption in the model:

1. For comparator treatments – the company assumed that progression-free patients 2 years after treatment initiation (not treatment end) were in LTR. For axi-cel (where treatment consisted of a one-off treatment at the beginning of the model) the EAG did not have concerns; however, treatment duration in the company's base case with R-based CIT in the model was 7 months and 4 months with Pola + BR, therefore the model should have accounted for LTR beginning at 2 years and 7 months for progression-free R-based CIT patients and 2 years and 4 months for progression-free Pola + BR patients.
2. For epcoritamab – the company applied the same assumption that progression-free patients were in LTR 2 years after treatment initiation. The EAG's clinical experts advised that patients on epcoritamab would not be considered to enter LTR while on treatment, nor would they be discharged from follow-up in the NHS while on treatment. The company's approach, which assumed that epcoritamab patients entered LTR and were discharged from any follow-up while still on treatment (although still incurring the costs of treatment) was, therefore, considered clinically implausible by the EAG. The EAG noted that epcoritamab does not have a stopping rule and is indicated to be given until progression or unacceptable toxicity. In the company's base case, patients stayed on treatment for much longer than 2 years, with patients in the population B (for example) having a mean duration of treatment of 10 years, even though they entered LTR at 2 years in the model.

The EAG noted that the LTR assumption mainly effected follow-up costs in the model and survival, as patients in LTR were assumed to not be followed up anymore (as well as having an increase in their probability of survival). The EAG, therefore, concluded that the company's approach underestimated the costs of follow up associated with epcoritamab treatment in the NHS and overestimated survival.

The EAG recommended that during TE, the company included a scenario analysis allowing the model to have a flexible option whereby the time at which patients entered the LTR assumption could be varied by the user and crucially, could be selected for different points in time for each comparator and for epcoritamab in each comparison. The EAG noted that this scenario should have also allowed for the removal of the LTR assumption in the model for epcoritamab only.

Finally, the EAG noted some implementation errors in the mortality rates used to adjust the OS curves in the model (see Section 4.2.2.1 of the EAG report for more details).

2.11.1 Company's approach at Technical Engagement

In their response to TE, the company reported that following the availability of more mature data for both epcoritamab and axi-cel, it was no longer considered necessary to apply the LTR assumption in the economic model. Instead, the company removed the LTR assumption from the model for all treatment arms and stated that patients entering LTR were assumed to be implicitly captured within the modelled survival curves.

The company also reported that the error identified in the model related to the estimation of OS during the LTR period was corrected.

2.11.2 EAG's critique of the company's approach at Technical Engagement

The EAG disagrees with the unjustified removal of the LTR assumption in the comparator arms of the model. Even though this is not explicitly stated in the company's response to TE, by removing the LTR assumption in all arms of arms of the model the company assumed that progression-free patients at 2 years after finalising their treatment, patients:

1. Could experience further progression events.
2. Do not experience an adjusted background mortality rate (SMR of 1.41 as originally applied).
3. Used the same healthcare resource use associated with the PFS-off treatment while in the PFS state (i.e., patients were not discharged from follow-up).
4. Experienced the utility value associated with being in the PFS state while in the PFS state.

This represents a major change in the company's fundamental assumption in the R/R LBCL disease pathway and in the management of patients in the NHS, with no justification provided. The company

stated that, "*LTR was assumed to be implicitly captured within the modelled survival curves*" however, this is not accurate as the company made changes not only to the assumptions around survival but also around how follow-up costs apply for patients who have been in the PFS state for 2 years after the end of treatment. Crucially, the EAG's clinical experts' opinion did not change with regards to the clinical plausibility of assuming that patients who are progression-free 2 years after the end of their treatment should be considered LTRs.

Therefore, by removing the LTR from the model for all treatments, the company decreased the clinical plausibility of the modelled disease pathway for NHS patients. The EAG discusses in detail the clinical plausibility of the PFS curves for each treatment individually in Section 2.13, and the company's updated assumption around follow-up costs in Section 2.18.

Finally, the EAG notes that the company included a flexible option whereby the time at which patients entered the LTR assumption could be varied by the user and could be selected for different points in time for each comparator and for epcoritamab, as per the EAG request before TE. This addition increased the model flexibility and transparency and allowed the EAG to conduct alternative scenario analysis around the LTR assumption.

In Section 4, the EAG presents the impact of switching on the LTR assumption in the model for each comparator, 2 years after the end of treatment. The EAG could not conduct the same analysis for epcoritamab as the company's model did not directly track which patients stopped treatment with epcoritamab (as opposed to the comparator treatments which have a fixed duration). The EAG recommends that the company conducts this analysis before the first committee meeting.

2.12 Key issue 12, 13 and 14: Overview of estimation of treatment effectiveness in the model

As discussed in Key issues 2, 3, 6, 7, 9, and 10, the EAG was originally concerned with the MAICs undertaken to estimate the relative treatment effect of epcoritamab on OS and PFS outcomes compared to other treatments. Furthermore, the EAG considered the company's original approach of jointly fitting survival curves (and thus relying on the use of HRs to estimate survival curves) unfit for purpose, particularly for the comparison of epcoritamab with Pola + BR and axi-cel, where the underlying OS and PFS KM curves crossed for both outcomes, between each comparator and epcoritamab.

Therefore, the EAG recommended that at TE the company undertook a fully adjusted MAIC on OS and PFS outcomes for all comparators in the model and that the company independently fitted OS and PFS curves for each comparator and epcoritamab in the model. The EAG also anticipated that the more mature OS and PFS data cut would help inform the curve fitting exercise.

2.12.1 Company's approach at Technical Engagement

As discussed in Section 2.7, and as a result of TE, the company undertook the following approach for each population and comparator, respectively, for their updated base case:

- Population A, for the comparison of epcoritamab vs R-based CIT: The company conducted a MAIC to adjust the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 (latest data-cut) to a subgroup of patients from the SCHOLAR-1 trial that was more aligned and may have been matched to patients in the ZUMA-1 trial (and who were described in a publication by Neelapu *et al.*). The company's base case MAIC was not based on a fully adjusted analysis and the details of this MAIC are described in detail Section 2.7.
- Population A, for the comparison of epcoritamab vs Pola + BR: The company conducted a MAIC to adjust the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 (latest data-cut) to the Sehn *et al.* 3L+ population. The company's base case MAIC was not based on a fully adjusted analysis and the details of this MAIC are described in detail Section 2.7.
- Population B, for the comparison of epcoritamab vs axi-cel: The company conducted a MAIC to adjust the DBCL, no prior CAR-T population from EPCORE™ NHL-1 (eligible to receive CAR-T and using the latest data-cut) to the ZUMA-1 trial population. The company's base case MAIC was not based on a fully adjusted analysis and the details of this MAIC are described in detail Section 2.7. The company also included an update data-cut for the ZUMA-1 trial compared to the original submission (5-year data).

After adjusting the epcoritamab KM curves using the respective MAICs for each comparator, the company independently fitted survival curves to the epcoritamab and comparator KM curves for OS in line with NICE DSU TSD14.[18]

The EAG notes that all the MAIC-adjusted epcoritamab curves included in the company's base case model were only partially adjusted and therefore not based on the fully-adjusted MAIC curves preferred by the EAG. The only exception was for the comparison of epcoritamab with R-based CIT,

where the company included the option in the model to use the 9/10 adjusted MAIC-adjusted epcoritamab curves.

Despite the EAG's reservations (see Section 2.7) around the 9/10 adjusted MAIC for epcoritamab with R-based CIT (scenario A4 in the company's model), the EAG prefers this analysis to the company's partially adjusted base-case MAIC. Therefore, the EAG focused its critique on the company's approach using scenario A.4 for the comparison of epcoritamab with R-based CIT.

Similarly (and as discussed in Section 2.7) the EAG-preferred clinical data to be used in the comparison of epcoritamab with axi-cel has been provided by the company in scenario B.1 (LBCL, no prior CAR-T, CAR-T eligible population, as opposed to the DLBCL population favoured by the company in its revised base case), therefore the EAG focused its critique on the company's approach using scenario B.1 in the model. Nonetheless, the EAG notes that this analysis is not based on a fully adjusted MAIC, therefore, the EAG notes that this analysis is based on fundamentally flawed data.

In the next sections, the EAG describes its original concerns with regards to OS, PFS and TTD, separately; the company's approach at TE with regards to each outcome; and finally, the EAG's view of the company's updated approach. In Section 2.16, the EAG summarises its discussion around the appropriateness of the company's approach after TE, together with the robustness of the EAG's alternative analysis.

2.13 Key issue 12: Estimation of overall survival in the model

The EAG was originally concerned that the relative effect of epcoritamab on OS was overestimated for every comparison in the model:

1. The OS curve for R-based CIT underpredicted OS in the long-term model for this treatment when compared to the long-term SCHOLAR-1 data (see Table 46 in the original EAG report). This directly impacted the estimated PFS curve for R-based CIT, given the company's approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve.
2. The OS curve estimated for Pola + BR was likely to considerably underpredict OS in the long-term model for this treatment, when compared to the observed data in Sehn *et al.* (see Table 47 in the EAG report).

3. The OS curve estimated for axi-cel was likely to underpredict OS in the long-term model for this treatment when compared to the long-term ZUMA-1 data (see Table 48 in the EAG report).
4. The OS curve for epcoritamab in all compassions was likely to be overestimated, particularly for the comparison with R-based CIT and axi-cel, where there was approximately an average of [redacted] of epcoritamab patients alive at the age of 90.

2.13.1 Company's approach at Technical Engagement

The curves used by the company are reported in Table 11 and critiqued in Section 2.13.2.

Table 11. Distributions used to fit OS KM curves in company's base case model

OS curve	Distribution	Ranking according to AIC and BIC	Table in company's TE appendix reporting AIC and BIC
Epcoritamab, population A, comparison with R-based CIT (scenario A4)	Lognormal	Second best-fitting	Table 95
R-based CIT	Lognormal	Second best-fitting	Table 127
Epcoritamab, population A, comparison with Pola + BR	Generalised gamma	Fourth best-fitting (AIC) and worst-fitting (BIC)	Table 77
Pola + BR	Log-logistic	Second best-fitting (AIC) and third best-fitting (BIC)	Table 129
Epcoritamab, population B (scenario B1)	Gompertz	Third best-fitting	Table 113
Axi-cel	Gompertz	Best-fitting	Table 141
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion			

2.13.2 EAG's critique of the company's approach at Technical Engagement

2.13.2.1 Population A – comparison to R-based CIT

The company chose a lognormal curve to model the 9/10 adjusted MAIC KM OS data for epcoritamab. Based on the AIC and BIC criteria (Table 95 of the company's TE appendix) provided for the 9/10 MAIC-adjusted KM OS data from EPCORE™ NHL-1 (latest data cut), the exponential distribution was the best-fitting one; however, with very little difference between the AIC and BIC statistics for the latter and the lognormal; log-logistic or the Gompertz curves. The EAG is concerned with the long-term predictions of survival in the epcoritamab curve – at 35 years in the model, when

patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population A, particularly given that patients in population A are ineligible to receive CAR-T therapy.

As discussed in Section 2.2, the EAG maintains its view that the Crump *et al.* publication of the observed KM OS data for R-based CIT from SCHOLAR-1 should have been used instead of the Neelapu *et al.* source. Furthermore, the EAG's original concern that the OS curve for R-based CIT underpredicted OS in the long-term model for this treatment when compared to the long-term SCHOLAR-1 data was only exacerbated in the company's updated base case model, where the lognormal curve used by the company starts to underpredict survival comparatively to Neelapu *et al.* from month 24, with long-term predictions considerably and consistently underestimating survival in the model for over 5 years when compared to the observed data in Crump *et al.* (Table 12).

Overall, the EAG notes that the alternative parametric survival models explored by the company might not be flexible enough to accommodate the underlying change in the hazard of the KM OS curves for both treatments. When the EAG used the best-fitting exponential curve in the epcoritamab arm, and the best-fitting generalised gamma curve for R-based CIT, the long-term survival predictions became more clinically plausible for epcoritamab, with [redacted] patients being alive at 35 years in the model; however, the tail of the epcoritamab OS curve is likely to be underestimated by the exponential curve when compared to the underlying KM data (Figure 14) and the R-based CIT curve still considerably underpredicts survival when compared to the underlying KM data and the Crump data (Figure 15 and Table 12).

The EAG could not find a more satisfactory combination of estimated curves which provided a good fit and long-term plausible predictions (for example, the third-best fitting Gompertz curve to the OS R-based CIT data provided a more accurate reflection of the Crump *et al.* data but estimated that [redacted] of R-based CIT patients would be alive at 35 years in the model, which is likely to be implausible with this treatment [Table 12]). Therefore, the EAG-preferred approach is to use the best-fitting curves for epcoritamab, and the second-best fitting generalised gamma curve for R-based CIT (which still underpredicts OS for R-based CIT but less so than the Weibull curve. However, it caveats the analysis by the fact that this results in an underprediction of survival for R-based CIT when compared to the 15-year Crump *et al.* data and (where 15% of patients are reported to be alive with R-based CIT in contrast to [redacted] in the model), and might also result in an underestimation of survival for epcoritamab

given the difference in the trajectory of the tail of the OS KM curve and the estimated exponential curve (Figure 16). This approach was deemed preferable to the company's base case which considerably underestimated survival for R-based CIT while likely overestimating survival for epcoritamab (Figure 17).

In the EAG-preferred analysis, the epcoritamab OS curve [redacted], after which the EAG took the maximum between the two curves, implying that the epcoritamab curve [redacted] to the R-based CIT OS curve. Given the EAG has not seen any evidence to suggest that survival with epcoritamab would be worse than survival with R-based CIT, the EAG assumed that at 12 years survival converges between treatment arms (Figure 16).

The results of the EAG scenario are reported in Section 4.

Table 12. Landmark OS estimates for R-based CIT compared with SCHOLAR-1 OS data and for epcoritamab in company's analysis post-TE

Treatment	Data source	Month						
		12	24	30	60	120	180	35 years
R-based CIT	Subgroup of patients in SCHOLAR-1 matched to Neelapu *et al.*	26%	20%	19%	NR	NR	NR	NR
	SCHOLAR-1 (Crump *et al.)**	25%	21%	20%	18%	15%	15%	NR
	Company's updated base case model (lognormal)	[redacted]						
	Weibull (best fitting)	[redacted]						
	Generalised gamma (second best fitting)	[redacted]						
	Gompertz (3rd best fitting)	[redacted]						
Epcoritamab	EPCORE™ NHL-1	[redacted]						
	Company's updated model with 9/10 adjusted MAIC	[redacted]						
	Company's updated model with 9/10 adjusted MAIC –	[redacted]						

	exponential (best fitting)							
[redacted]								

Abbreviations: KM, Kaplan-Meier; OS, overall survival; R-based CIT, rituximab-based chemoimmunotherapy.

Figure 14. Best-fitting epcoritamab (light blue) and R-based CIT (dark blue) OS curves

[redacted]

Figure 15. Unadjusted and adjusted OS KM curve for epcoritamab (EPCORE™ NHL-1) and R-based CIT (SCHOLAR-1) scenario A4 – Figure 31, company's TE appendix

[redacted]

Figure 16. Best-fitting epcoritamab (light blue) and R-based CIT (dark blue) OS curves (capped)

[redacted]

Figure 17. Company's base case for epcoritamab (light blue) and R-based CIT (dark blue) OS curves

[redacted]

2.13.2.2 Population A – comparison to Pola + BR

As discussed in Section 2.7, the fully adjusted MAIC OS analysis shows that the fully adjusted epcoritamab OS curve converges to the Pola + BR OS curve at approximately 15 months (Figure 6), in contrast to the company's base case KM curves, which never fully converge (Figure 18). Therefore, even in a hypothetical scenario where the company's fitting exercise to the epcoritamab and Pola + BR OS curves was "perfect", this would still translate an overestimation of the survival benefit associated with epcoritamab when compared to using the fully adjusted MAIC curves.

The generalised gamma chosen by the company to fit OS for epcoritamab was the fourth best-fitting curve according to AIC and BIC statistics, with the lognormal curve being the best-fitting distribution. The company's experts also noted that, "*the long-term OS estimates provided by the generalised gamma model represent clinically plausible estimates, with the loglogistic and lognormal models also producing plausible long-term estimates.*" Therefore, the EAG does not see a reason why the generalised gamma curve should be used instead of best-fitting, clinically plausible lognormal curve. Nonetheless, the EAG notes that the short- and long-term survival predictions with the generalised gamma and the lognormal curves are very similar and the EAG reports the results of using the lognormal curve in Section 4.

The EAG also notes that at 35 years in the model, when patients would be 90 years old, there are [redacted] of patients alive in the epcoritamab arm when the lognormal curve is used, which contrasts with the company's base case [redacted] estimated for the same population in the epcoritamab curve vs R-based CIT, but is in accordance with the EAG's preferred best-fitting exponential curve used for epcoritamab in the comparison with R-based CIT. This reinforces the EAG's view that using the exponential curve in the former analysis is a more robust approach, as it creates some consistency in the long-term survival predictions for epcoritamab patients in population A.

The log-logistic curve used by the company to fit OS for POLA + BR was the second best-fitting curve according to the AIC and BIC criteria, with the lognormal providing the best statistical fit. The EAG notes that the survival predictions in the two curves are similar (Table 13) and likely to underpredict survival for Pola + BR from month 24 onwards.

When compared to the underlying OS KM data for epcoritamab and Pola + BR (Figure 18), the EAG-preferred (best-fitting) curves (Figure 19) [redacted] although, are still likely to underpredict the survival trend overserved in the Pola + BR curve from 18 months onwards. Of note, is that the curves used by the EAG provide very similar survival predictions to those used in the company's base case and that none of the curves provided by the company for Pola + BR were particularly good at replicating the possible plateau observed in the OS curve from month 18 to month 27 in Sehn *et al*. Therefore, the EAG caveats its preferred analysis by the fact that the survival benefit for epcoritamab in comparison with Pola + BR is likely to be overestimated.

Table 13: Landmark OS estimates for R-based CIT compared with Sehn *et al.* OS data

Treatment	Data source	Month					
		3	6	12	24	60	120
	Pola + BR (Sehn *et al.)**	90%	78%	50%	32%	NR	NR
	Company's base case model post-TE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's model post-TE – best fitting curve (lognormal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: KM, Kaplan-Meier; OS, overall survival; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine.

Figure 18. Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – Figure 25, company's TE appendix

[redacted]

Figure 19. EAG-preferred fitted curves for epcoritamab (blue) and Pola + BR (pink)

[redacted]

2.13.2.3 Population B – comparison to axi-cel

As discussed in Section 2.7, the fully adjusted KM OS curve for epcoritamab in scenario B.1 shows a slight survival advantage compared to the company's used KM OS curve (Figure 8, Figure 10 and Figure 20), therefore, the EAG's concerns around the company not using fully adjusted MAIC OS curves is somewhat mitigated in this comparison. The EAG also notes that the company's preferred base case analysis differs to the EAG's preferred analysis in terms of DLBCL/LBCL inclusion as well as level of adjustment.

The company chose the Gompertz curve to fit the MAIC-adjusted KM OS data in scenario B.1. The EAG notes that Gompertz curve was the third best-fitting curve according to the AIC and BIC criteria, although the difference in AIC and BIC criteria between the three best-fitting curves was minimal. The best fitting curve was the generalised gamma, followed by the lognormal.

The company chose a Gompertz curve to fit the 5-year unadjusted OS KM data from ZUMA-1, based on it providing the best statistical fit and the company's experts view that at 5 years 40–45% was the most likely survival estimate for axi-cel patients (Table 14).

Table 14: Landmark OS estimates for axi-cel compared with ZUMA-1 OS data

Treatment	Data source	Month					
		6	12	24	30	60	120
Axi-cel	ZUMA-1[3]	79%	61%	NR	NR	NR	NR
	ZUMA-1, 5-year data cut*	79%	61%	50%	48%	45%	NR
	Company's base case model post-TE (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; NR, not reported; OS, overall survival.

The KM OS data for the epcoritamab MAIC-adjusted DLBCL and the ZUMA-1 unadjusted curves are reported in Figure 20. The three best fitting OS curves for epcoritamab and the best-fitting curve OS curve for axi-cel are reported in Figure 21. Even though the axi-cel OS curve provides a generally good fit to the ZUMA-1 data, the EAG is concerned that none of the best-fitting curves available for epcoritamab provide the needed flexibility to accurately predict the shape of the underlying KM OS data, therefore overestimating the survival benefit associated with epcoritamab. The KM OS curves show a survival advantage with axi-cel for the initial 8 months of the observed period, which is not translated into the fitted curves. Furthermore, it is possible that the [redacted]. In contrast, the company's base case Gompertz OS epcoritamab and axi-cel curves only converge at [redacted]. This slightly negates the purpose of the EAG's request to have independently fitted curves to epcoritamab and axi-cel, respectively, in order to appropriately capture the overlap and the crossing (or convergence) of the KM curves.

Therefore, the EAG decided to use the second-best fitting OS epcoritamab lognormal curve (Figure 22), which provided a more conservative scenario compared to the company's base case. In the EAG's exploratory analyses the epcoritamab and axi-cel OS curves [redacted], after which, the EAG opted to present a scenario where the maximum between the curves was taken from the point of the curves crossing, therefore, implying that the epcoritamab OS curve would converge to the axi-cel OS (instead of becoming worse).

The EAG remains concerned with the long-term predictions of survival in the epcoritamab curve, even when the EAG-preferred curves are used. At 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population B (Figure 22).

Figure 20. Unadjusted and adjusted OS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – Figure 34, company's TE appendix

[redacted]

Figure 21. Three best-fitting OS curves for epcoritamab (green and blue curves) and best-fitting curve for axi-cel (brown dotted curve)

[redacted]

Figure 22. EAG-preferred estimated OS for epcoritamab (blue curve) and axi-cel (brown curve) (long-term)

[redacted]

2.14 Key issue 13: Estimation of progression-free survival in the model

Given that SCHOLAR-1 did not report PFS data, the company originally used the OS HR derived from the MAIC comparing epcoritamab versus R-based CIT and applied it to the epcoritamab PFS curve in order to generate a PFS curve for R-based CIT. The EAG was concerned with the company's approach of assuming that the HR derived for OS outcomes was the same as the HR for PFS outcomes between epcoritamab and R-based CIT as the company's assumption relied on the OS gain for epcoritamab being proportionately the same as the PFS gain associated with the treatment when the company did not provide any evidence to justify this assumption.

The EAG was also concerned with the company's estimated PFS survival curves for epcoritamab given these provide a considerably bad visual fit to the end of the KM PFS data. Given the immaturity of the data at the time, the EAG was concerned with the lack of evidence presented to substantiate the company's long-term PFS assumptions.

The EAG considered that the relative effect of epcoritamab on PFS was overestimated for every comparison in the model:

1. The proportion of patients on R-based CIT entering LTR at 2 years was likely to be underestimated based on the underestimated OS curve when compared to the observed SCHOLAR-1 OS data; and the proportion of epcoritamab patients entering LTR

in this comparison was overestimated (and above what was deemed plausible by the company's clinical experts).

2. The proportion of patients on Pola + BR entering LTR at 2 years was considerably underestimated when compared to the observed PFS data from Sehn *et al*; even though the proportion of epcoritamab patients entering LTR in this comparison was plausible according to the company's clinical experts.
3. The proportion of patients on axi-cel entering LTR at 2 years could be a reasonable prediction of PFS for this treatment when compared to the underlying observed ZUMA-1 PFS data; with the main problem in this comparison being the overestimation of the PFS epcoritamab curve, according to the proportion deemed plausible by the company's clinical experts.

The EAG noted that the issues originally raised could be (at least partially) mitigated by the following actions, which the EAG recommended the company undertook at TE:

1. Using the more mature PFS data which was likely to help inform the plausible probability of patients in the epcoritamab PFS curves at later stages past 20 months in the model.
2. Independently fitting OS and PFS curves for each comparator in the model for each comparator.
3. Allowing the model to have a flexible option, whereby the time at which patients entered the LTR assumption could be varied by the user and crucially, could be selected for different points in time for each comparator and for epcoritamab in each comparison.
4. Allowing for the removal of the LTR assumption in the model for epcoritamab only.
5. Including a scenario analysis where the HR between the OS and PFS KM curves for epcoritamab for the unadjusted, DLBCL population, no prior CAR-T from EPCORE™ NHL-1 is used to estimate a PFS curve for R-based CIT, as requested by the EAG at the clarification stage.

2.14.1 Company's approach at Technical Engagement

Given that SCHOLAR-1 did not report PFS data, the company used the OS HR derived from the 9/10 adjusted MAIC of epcoritamab versus R-based CIT in Scenario A.4. (discussed in Section 2.7) of [redacted] to the PFS epcoritamab curve to generate the R-based CIT PFS curve.

The PFS curves fitted by the company at TE are reported in Table 15 and critiqued in Section 2.14.2.

As also noted in Section 2.11, the company removed the LTR assumption from the model for all treatments and stated that patients entering LTR were assumed to be implicitly captured within the modelled survival curves.

Table 15. Distributions used to fit PFS KM curves in company's base case model

PFS curve	Distribution	Ranking according to AIC and BIC	Table in company's TE appendix reporting AIC and BIC
Epcoritamab, population A, comparison with R-based CIT (scenario A4)	Gompertz	Fourth best-fitting	Table 97
Epcoritamab, population A, comparison with Pola + BR	Generalised gamma	Second best-fitting (AIC) and third best-fitting (BIC)	Table 79
Pola + BR	Gamma	Worst-fitting	Table 131
Epcoritamab, population B (scenario B1)	Gompertz	Third best-fitting	Table 115
Axi-cel	Gompertz	Second best-fitting	Table 143
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion			

2.14.2 EAG's critique of the company's approach at Technical Engagement

2.14.2.1 Population A – comparison to R-based CIT

The company chose the fourth-best fitting Gompertz curve to fit the 9/10 MAIC adjusted PFS epcoritamab curve, based on "*feedback from UK clinical experts*". However, the Gompertz curve provides a considerably worst AIC and BIC values than the 2-top best fitting curves (the generalised gamma and the lognormal). Given the lack of details around the company's experts inputs and the fact that the company's experts expected a range of "*20–30% of patients to be progression-free at five years*" with epcoritamab, the EAG preference is to use the best fitting curve, which according to the AIC and BIC statistics is the generalised gamma curve. The EAG also notes that using the Gompertz and the generalised gamma curve provides similar PFS predictions at 5 years (Figure 23).

Figure 23. Long-term PFS extrapolations for epcoritamab (pink) vs R-based CIT (dark yellow)

[redacted]

As discussed in the EAG's original report, there is uncertainty around the validity of the PH assumption for OS outcomes between EPCORE™ NHL-1 and SCHOLAR-1. Therefore, the EAG remains concerned with the appropriateness of assuming PHs for PFS. Nonetheless, the EAG acknowledges that SCHOLAR-1 did not report PFS data, therefore making it impossible to validate the PFS predictions in the model for R-based CIT. However, given the EAG's concerns around the underestimation of the OS curve for R-based CIT compared to the observed data in SCHOLAR-1, it is likely that the same concerns would apply for PFS.

The EAG also remains concerned with the company's assumption that the OS gain for epcoritamab is proportionately the same as the PFS gain associated with the treatment. Therefore, during TE (and clarification), the EAG asked that the company used the HR between the OS and PFS KM curves for epcoritamab for the unadjusted, DLBCL population, no prior CAR-T from EPCORE™ NHL-1 – by applying this HR to the OS SCHOLAR-1 curve derived for R-based CIT the company could estimate a PFS curve for R-based CIT. This method still relied on the assumption that the relationship between OS and PFS outcomes for epcoritamab is the same as that for OS and PFS for R-based CIT; however, it wouldn't assume that the proportional gain observed for epcoritamab for OS is the same as the PFS gain in relation to R-based CIT. The company did not conduct the scenario as it deemed inappropriate to assume that, "*the relationship between OS and PFS for epcoritamab is the same as that for R-based CIT*", given that, "*epcoritamab is considerably more effective at inducing complete response than R-based CIT*". The EAG acknowledges the company's point; however, notes that both

options are based on strong, unverifiable assumptions, with the company's assumption potentially favouring epcoritamab and the EAG's assumption being more conservative.

Even though the EAG's experts agreed that progression-free R/R LBCL patients at 2 years after the end of treatment with R-based CIT could be considered to enter LTR, it was noted that the proportion of patients who would reach this status would be low with R-based CIT – one expert suggested that virtually no patients would reach the 2-year mark without a progression event, while the second expert indicated this proportion to be closer to 10% or 15% of patients. A study by Mounier *et al*. 2013, reported in TA883, showed that approximately 20% of patients receiving R-based CIT were progression-free at 2 years, with 15% of patients potentially plateauing from 4 years to 6 years.[19] Nonetheless, the EAG caveats the results in the Mounier *et al*. study by the fact that only 50% of patients in the study received previous rituximab treatment and that most patients were on their second-line treatment. Overall, given the lack of a robust source of data to estimate PFS for R-based CIT in third line R/R LBCL, the EAG considers that the company's extrapolation (Figure 24), which predicts that approximately 3% of patients on R-based CIT enter LTR at 2 years, might be underestimated.

Figure 24. Long-term PFS extrapolations for epcoritamab (pink) R-based CIT (blue)

2.14.2.2 Population A – comparison to Pola + BR

As discussed in Section 2.7, the fully adjusted KM PFS curves show that the epcoritamab PFS curve [redacted] (Figure 7) and continues to considerably [redacted]. However, the KM epcoritamab curve used by the company shows a much [redacted] (Figure 25). Therefore, even in the hypothetical scenario where the company's fitting exercise to the epcoritamab and Pola + BR PFS curves was "perfect", this would still translate an overestimation of the PFS benefit associated with epcoritamab when compared to using the fully adjusted MAIC curves.

Figure 25. Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and Pola + BR (Sehn *et al.* 3L+) – Figure 26, company's TE appendix

[redacted]

The EAG notes that the generalised gamma curve chosen by the company to estimate PFS for epcoritamab was the fourth best-fitting curve (with the lognormal being the best-fitting curve followed by the log-logistic). Figure 26 shows that neither the lognormal nor the generalised gamma curves are particularly good at providing a visual fit to the end of the MAIC-adjusted KM PFS curve for epcoritamab. A more flexible modelling approach to accommodate the underlying change in the hazard of the KM PFS curve would have been more appropriate. Given the lack of more flexible modelling options, the EAG's preference is to use the best-fitting and clinically plausible lognormal curve to fit to the epcoritamab KM data. Results of this analysis are reported in Section 4.

Figure 26. Long-term PFS extrapolations for epcoritamab (pink) vs Pola + BR (yellow)

[redacted]

The company chose a gamma curve to fit the unadjusted PFS KM data from Sehn *et al*., which was the worst-fitting curve according to the AIC and BIC statistics. The best-fitting curve was the generalised gamma, followed by the lognormal and the log-logistic. The company reported that "*all the distributions overestimate the observed median PFS (7.4 months) except the generalised gamma distribution*" and that "*during interviews with UK clinical experts, the experts stated that the gamma, exponential, lognormal or loglogistic distributions provide the most plausible estimates based on their experience in UK clinical practice*." Therefore, the EAG cannot see a plausible reason why the best-fitting, clinically plausible PFS curve was not chosen, instead of the worst-fitting curve for the analysis. Furthermore, Table 16 shows that the company's base case gamma curve considerably underestimates PFS when compared to Sehn *et al*. at 24 months, while overestimating PFS for the initial period of the KM curve. The best-fitting generalised gamma provides a much closer fit to the observed values reported in Sehn *et al*. The EAG's preference is, therefore, to use the best-fitting and clinically plausible generalised gamma curve to fit to the Pola + BR KM data. Results of this analysis are reported in Section 4.

Table 16. Landmark PFS estimates for Pola + BR compared with Sehn *et al.* PFS data

	Data source	Month					
		3	6	12	18	24	60
Pola + BR	Pola + BR (Sehn *et al.)**	70%	58%	36%	30%	30%	NR
	Company's base case model post-TE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's model post-TE – best fitting curve (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: EAG, External Assessment Group; KM, Kaplan-Meier; NR, not reported; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine.

Finally, the EAG notes that the KM data in Figure 25 show that PFS for Pola + BR is likely to be [redacted] to the MAIC-adjusted PFS data for epcoritamab (and [redacted] when the fully adjusted MAIC results are considered). Of note, is that the Pola + BR curve shows a potential plateau for the last 12 months of data available from Sehn *et al*., with the epcoritamab PFS curve [redacted]. In stark contrast, the company's base case curves (Figure 27 and Figure 28) do not capture a [redacted] in the Pola + BR curve, but instead show a declining PFS curve throughout the model's time horizon, with [redacted].

The best-fitting lognormal and generalised gamma PFS curves for epcoritamab and Pola + BR, respectively, show a much more [redacted] trajectory in PFS curves for both treatments, with Pola + BR having a [redacted] (Figure 29 and Figure 30). The EAG notes that the "odd" shape of the PFS Pola + BR curve is due to the PFS curve being capped by the OS curve for the same treatment. The EAG caveats its preferred curves by the fact that these are still unlikely to be flexible enough to provide an accurate representation of the underlying KM data for both treatment arms. However, the EAG's approach offers advantages compared to the company's base case approach as it relies on the best-fitting and clinically plausible (according to the company's own experts) PFS fitted curves, while providing a more conservative difference between the PFS curves between the two treatments, which is more representative of the underlying KM data than the company's base case approach.

Figure 27. Company's base case PFS curves for epcoritamab (pink) and Pola + BR (red)

Figure 28. Company's base case PFS curves for epcoritamab (pink) and Pola + BR (red) (long-term extrapolations)

Figure 29. EAG's preferred PFS curves for epcoritamab (pink) and Pola + BR (red)

[redacted]

Figure 30. EAG's preferred PFS curves for epcoritamab (pink) and Pola + BR (red) (long-term extrapolations)

[redacted]

2.14.2.3 Population B – comparison to axi-cel

As discussed in Section 2.7, the fully adjusted KM PFS curves do not show much of a difference in trajectory to the KM curves used by the company (Figure 9, Figure 11 and Figure 31) and may be slightly more favourable for epcoritamab, therefore, the EAG's concerns around the company not using fully adjusted MAIC PFS curves is somewhat mitigated in this comparison.

Figure 31. Unadjusted and adjusted PFS KM curves for epcoritamab (EPCORE™ NHL-1) and axi-cel (ZUMA-1) – Figure 35, company's appendix to TE response

[redacted]

The company chose the Gompertz curve to fit the MAIC-adjusted KM OS data from EPCORE™ NHL-1 (LBCL population, latest data cut) in scenario B1. The EAG notes that the Gompertz curve was the third best-fitting curve, with the generalised gamma being the best-fitting curve followed by the lognormal. The EAG notes that the Gompertz curve is likely to provide an implausible [redacted], which is not substantiated by the epcoritamab KM data (Figure 32). Therefore, the EAG preference is to use the second-best fitting lognormal PFS epcoritamab curve, which provided a more plausible long-term prediction of PFS, in line with the company's experts of an expected range of "*20–30% of patients progression-free at five years*" than the company's base case Gompertz curve or the generalised gamma curve (Figure 32).

Figure 32. Long-term PFS extrapolations for epcoritamab curves (all three curves are for epcoritamab)

[redacted]

The company chose a Gompertz curve to fit the 5-year unadjusted PFS KM data from ZUMA-1, which was the second best-fitting curve after the generalised gamma. The EAG notes that there is not much difference between the estimated Gompertz and generalised gamma PFS curves when compared to the underlying PFS ZUMA-1 KM data (Table 17), with the curves starting to diverge after 60 months in the model. Nonetheless, the EAG prefers using the best-fitting curve in its analysis.

Table 17: Landmark PFS estimates for axi-cel compared with ZUMA-1 PFS data

Treatment	Data source	Month					
		6	12	24	30	60	120
Axi-cel	ZUMA-1, 5-year data cut*	51%	42%	40%	40%	32%	NR
	Company's base case model post-TE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Company's model post-TE – best fitting curve (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; NR, not reported; PFS, progression-free survival.

The EAG notes that when the KM PFS data for the epcoritamab MAIC-adjusted and the ZUMA-1 unadjusted curves are considered (Figure 31) in comparison with the company's base case curves (Figure 33 and Figure 34), the lack of appropriateness in the company's approach to modelling PFS curves for population B is noticeable. The KM PFS curves [redacted]

[redacted]. In contrast, the company's estimated curves are [redacted]. The lack of flexibility of the estimated curves to accurately predict the shape of the underlying KM PFS data slightly negates the purpose of the EAG's request to have independently fitted curves to epcoritamab and axi-cel, respectively, in order to appropriately capture the overlap and the crossing (or convergence) of the KM curves.

When the EAG used the lognormal curve to fit the epcoritamab data and the generalised gamma to fit the axi-cel PFS data, the epcoritamab curve [redacted] (Figure 52 in the Appendix), therefore, providing a much better alignment with the underlying KM PFS data observed for both treatments. The EAG notes that [redacted], therefore indicating that epcoritamab is associated with [redacted] rates of progression than axi-cel. The EAG notes that the 5-year axi-cel PFS data and the approximately 2-year epcoritamab data available (Figure 31) do not provide a robust insight into which treatment might be better at keeping patients in a progression-free state after 2 years - the curves [redacted], where the numbers at risk in the epcoritamab curves are low (about 8 patients out of the initial 32) making it impossible to robustly assess whether the curves are showing [redacted] without a paramount level of uncertainty.

The EAG presented a more optimistic scenario, where the maximum between the epcoritamab and the axi-cel PFS curves was taken from the point of the curves crossing, therefore, implying that the epcoritamab PFS curve would [redacted] (Figure 35 and Figure 36). However, the EAG cannot discard the possibility that the crossing of the KM curves seen in Figure 31 indicates that epcoritamab patients start progressing (or dying) faster than axi-cel patients at after 2 years, therefore, the EAG has conducted a scenario analysis where the curves are not capped in the model. Results of the EAG's analyses are reported in Section 4.

Figure 33. Company's base case PFS curves for epcoritamab (pink) and axi-cel (green)

[redacted]

Figure 34. Company's base case PFS curves for epcoritamab (pink) and axi-cel (green) (long-term)

[redacted]

Figure 35. EAG-preferred PFS curves for epcoritamab (pink curve, lognormal) and for axi-cel (green curve, generalised gamma) capped

[redacted]

Figure 36. EAG-preferred PFS curves for epcoritamab (pink curve, lognormal) and for axi-cel (green curve, generalised gamma) capped (long-term)

[redacted]

2.15 Key issue 14: Estimation of time to treatment discontinuation in the model

The EAG was originally concerned with the company's choice of models to fit the TTD KM data for epcoritamab, particularly with the discrepancy in the rationale for choosing the TTD distributions for population A and population B. The EAG accepted that as a result of conducting 3 different MAICs and adjusting the epcoritamab outcomes to 3 different studies for each comparator, all epcoritamab

PFS curves would be different. Nonetheless, the EAG noted a lack of consistency in the company's approach in accepting that the shape of TTD and PFS curves for epcoritamab should (or should not) be the same; therefore, implicitly assuming different levels of toxicity for epcoritamab in each of the comparator analysis. The EAG anticipated that the more mature TTD and PFS data available during TE would help to better inform the relationship between PFS and TTD fitted curves.

The EAG noted that the company's assumption for R-based CIT and Pola + BR of assuming that patients never discontinue due to toxicity was highly unlikely to be plausible, considering the toxicity of these treatments. The EAG noted that the company's assumption biased the cost-effectiveness results in favour of epcoritamab. The EAG also recommended that the company reconsidered the assumption that TTD for R-based CIT and Pola + BR was the same as PFS.

2.15.1 Company's approach at Technical Engagement

The curves used by the company are reported in Table 18 and critiqued in Section 2.15.2.

Table 18. Distributions used to fit TTD KM curves in company's base case model

TTD curve	Distribution	Ranking according to AIC and BIC	Table in company's TE appendix reporting AIC and BIC	Justification provided by the company
Epcoritamab, population A, comparison with R-based CIT (scenario A4)	Exponential	Worst-fitting (AIC) and third-best fitting (BIC)	Table 99	Company's clinical experts' opinion provided during TE that, "*they would expect very few patients to remain on treatment with epcoritamab beyond 5 years*".
Epcoritamab, population A, comparison with Pola + BR	Exponential	Worst-fitting	Table 81	
Epcoritamab, population B (scenario B1)	Exponential	Fourth best fitting (AIC) and best fitting (BIC)	Table 117	

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; R-based CIT, rituximab-based chemoimmunotherapy; Pola + BR, polatuzamab vedotin + bendamustine + rituximab; TE, technical engagement

The company did not change its original approach of assuming that TTD for R-based CIT and Pola + BR would be the same as PFS for the treatment. In their response to TE, the company reported that, "*this assumption was adopted in response to feedback from UK clinical experts*" and that the company was, "*unable to identify any suitable data on the proportion and timing of patients*

discontinuing treatment with R-based CIT or Pola + BR due to reasons other than progression, and as a result, no scenario analyses have been performed varying this assumption."

As the recommended treatment regimen for axi-cel is a single dose administered via IV, no TTD curve for this treatment was modelled.

2.15.2 EAG's critique of the company's approach at Technical Engagement

The EAG disagrees with the company's approach to modelling the TTD epcoritamab curves after TE and is concerned with the drastic change in the company's clinical experts' view before and after TE – in the original CS, the company's experts stated, "*they would expect the TTD curve to be similar in shape but repressed compared to PFS curves, as patients would be likely to remain on treatment until they progress; the clinical experts stated that it was possible for patients to discontinue treatment due to toxicity rather than progression, but the available data suggests that epcoritamab is well-tolerated with only* [redacted] *of patients with DLBCL from EPCORE™ NHL-1 discontinuing due to AEs*." Therefore, the company's approach to choosing the distributions used to fit the TTD data was justified based on the original choice of curves made for PFS.

The company's original clinical experts' view that patients are mostly likely to stay on epcoritamab until they progress is therefore, highly inconsistent with the company's clinical experts' view at TE that patients are, "*unlikely to remain on treatment after 5 years*".

Figure 37, Figure 39, and Figure 41 show that the in latest data-cut, PFS and TTD curves are similar for the initial 6 months of treatment, with some curve separation thereafter. However, the company's estimated [redacted] in TTD curves is unsubstantiated by the underlying KM TTD data. The more mature discontinuation data from EPCORE™ NHL-1 shows that [redacted] of BLBCL patients discontinued epcoritamab due to toxicity in the trial.

Figure 38, Figure 40, and Figure 42 show that when the best-fitting lognormal curves are used to estimate TTD for epcoritamab vs all comparators, the fit to the underlying TTD KM curves improves (particularly for epcoritamab in the comparison with Pola + BR). However, the EAG remains concerned that none of the best-fitting TTD curves (with the exception of epcoritamab vs Pola + BR) reflect clinically plausible scenarios, with the epcoritamab TTD curve vs axi-cel being highly implausible:

1. In the comparison to R-based CIT , when using the best-fitting curve to estimate TTD for epcoritamab, the mean TTD and mean PFS in the model is [redacted], respectively. Considering the company's original expectation (and the EPCORE™ NHL-1 TTD and PFS data) that epcoritamab is well tolerated and very few patients discontinue due to AEs or toxicity, the EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation is high likely to underestimate the treatment costs for epcoritamab and that they remain underestimated while the treatment costs for R-based CIT remain overestimated.
2. In the comparison to Pola + BR, when using the best-fitting curve to estimate TTD for epcoritamab, the mean TTD and mean PFS in the model is [redacted], respectively. The EAG considers that a difference of [redacted] is a more realistic difference in mean time to progression and mean time to discontinuation than the one estimated epcoritamab (vs R-based CIT).
3. In population B, when using the best-fitting curve to estimate TTD for epcoritamab, the mean TTD and mean PFS in the model is [redacted], respectively. The EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation is extremely high and unsubstantiated, and unlikely to be clinically plausible (as it implies that [redacted] of PFS benefit) therefore, the treatment costs for epcoritamab remain underestimated in the EAG's exploratory analysis.

Therefore, the EAG recommends that the company considers fitting more flexible survival curves to the TTD KM data. Of note is that in the company's base case, the difference in mean PFS and mean TTD in the model is [redacted] for epcoritamab for the comparison with R-based CIT; Pola + BR; and axi-cel, respectively.

Finally, the EAG notes that the assumption that R-based CIT and Pola + BR patients do not discontinue treatment for reasons other than progression remains a concern, as it likely overestimates the treatment costs with these therapies. The EAG reinforces its original view that the findings by Cazelles *et al*.[20] suggest that 10% of patients discontinued treatment with R-based CIT due to toxicity. The EAG also noted that this estimate was [redacted] with the discontinuation rate for epcoritamab reported in the EPCORE™ NHL trial of [redacted].

Figure 37. Population A, epcoritamab TTD and PFS fitted curves, together with epcoritamab TTD and PFS KM data (vs R-based CIT)

Figure 38. Population A, epcoritamab TTD and PFS EAG -prefered fitted curves, together with epcoritamab TTD and PFS KM data (vs R-based CIT)

Figure 39. Population A, epcoriatmab TTD and PFS fitted curves, together with epcoriatmab TTD and PFS KM data (vs Pola + BR)

Figure 40. Population A, epcoritamab TTD and PFS EAG -prefered fitted curves, together with epcoritamab TTD and PFS KM data (vs Pola + BR)

Figure 41. Population B, epcoriatmab TTD and PFS fitted curves, together with epcoritamab TTD and PFS KM data

Figure 42. Population B, epcoritamab TTD and PFS EAG -prefered fitted curves, together with epcoritamab TTD and PFS KM data

2.16 Key issue 12, 13 and 14: Conclusions on the estimation of treatment effectiveness in the model

2.16.1 Population A – comparison to R-based CIT

The EAG's concerns for the comparison of epcoritamab vs R-based CIT have been somewhat mitigated by the fact that the company has provided the results for the 9/10 adjusted MAIC for epcoritamab vs R-based CIT (scenario A4 in the company's model), and the company's approach to independently fitting survival curves. Nonetheless, the EAG remains concerned with the following:

1. The EAG maintains its view that the Crump *et al.* publication of the observed KM OS data for R-based CIT from SCHOLAR-1 should have been used instead of the Neelapu *et al.* source.
2. The OS curve for R-based CIT is likely to considerably underpredict OS in the long-term model for this treatment. This directly impacts the estimated PFS curve for R-based CIT, given the company's approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve.
3. The EAG also remains concerned with the company's assumption that the OS gain for epcoritamab is proportionately the same as the PFS gain associated with the treatment.
4. The OS predictions for epcoritamab are likely to be overestimated – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population A, particularly given that patients in population A are ineligible to receive CAR-T therapy.
5. The company's approach to modelling TTD after TE underestimates the treatment costs associated with epcoritamab.
6. The company's approach to modelling TTD for R-based CIT overestimates the treatment costs associated with R-based CIT.

The EAG conducted exploratory analysis to help mitigate some of the concerns around the estimation of treatment effectiveness for this comparison in the model. However, the EAG caveats its exploratory analysis by the following:

1. The alternative parametric survival models included in the model are unlikely to be flexible enough to accommodate the underlying change in the hazard of the KM OS curves for both treatments. When the EAG used the best-fitting exponential curve in the epcoritamab arm, and the second best-fitting generalised gamma curve for R-based CIT, the long-term survival

predictions become more clinically plausible for epcoritamab, with [redacted] patients being alive at 35 years in the model; however, the tail of the epcoritamab OS curve is likely to be underestimated by the exponential curve when compared to the underlying KM data (Figure 14) and the R-based CIT curve still underpredicts survival considerably when compared to the underlying KM data and the Crump *et al.* data (Figure 15 and Table 12). Therefore, survival is likely to be underpredicted in both arms, attenuating the underestimation in the incremental survival, however, the EAG cannot predict to what extent.

2. When using the best-fitting curve to estimate TTD for epcoritamab, the mean TTD and mean PFS in the model is [redacted], respectively. Considering the company's original expectation (and the EPCORE™ NHL-1 TTD and PFS data) that epcoritamab is well tolerated and very few patients discontinue due to AEs or toxicity, the EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation might be slightly high, therefore, it is likely that the treatment costs for epcoritamab remain underestimated while the treatment costs for R-based CIT remain overestimated.
3. The company did not undertake the scenario analysis requested by the EAG to assume that a proportion of R-based CIT patients discontinue treatment due to toxicity, and the EAG did not have sufficient time at TE to conduct such analysis.

The EAG-preferred curves for population A (compared to R-based CIT) are summarised in Table 19 and reported in Figure 43, while the results of the analysis are reported in Section 4.

Table 19. Distributions used in EAG's exploratory analysis

Outcome	Treatment	Distribution	Ranking according to AIC and BIC	Table in company's TE appendix reporting AIC and BIC
Overall survival	Epcoritamab, population A, comparison with R-based CIT, scenario A4 (capped)	Exponential	Best-fitting	Table 95
	R-based CIT	Generalised gamma	Second best-fitting	Table 127
Progression-free survival	Epcoritamab, population A, comparison with R-based CIT, scenario A4	Generalised gamma	Best-fitting	Table 97
Time to treatment discontinuation	Epcoritamab, population A, comparison with R-based CIT, scenario A4	Lognormal	Best-fitting	Table 117

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Figure 43. EAG-prefered OS and PFS curves for epcoritamab (pink and dark blue dotted curves) and R-based CIT (dark pink and light blue solid curves)

2.16.2 Population A – comparison to Pola + BR

The EAG's concerns for the comparison of epcoritamab vs Pola + BR have been somewhat mitigated by the fact that the company has independently fitted survival curves. Nonetheless, the EAG notes that this analysis is not based on the fully adjusted MAIC epcoritamab curves, therefore, the EAG remains concerned that this analysis is based on fundamentally flawed data. Furthermore, the EAG remains concerned with the following:

1. The OS curve estimated for Pola + BR underpredicts OS in the long-term model for this treatment, when compared to the observed data in Sehn *et al*.
2. The company's approach to modelling TTD after TE underestimates the treatment costs associated with epcoritamab.
3. The company's approach to modelling TTD for R-based CIT overestimates the treatment costs associated with Pola + BR.

The EAG conducted exploratory analysis to help mitigate some of the concerns around the estimation of treatment effectiveness for this comparison in the model. However, the EAG caveats its exploratory analysis by the following:

- As discussed in Section 2.7, the fully adjusted MAIC OS analysis shows that the adjusted epcoritamab OS curve converges to the Pola + BR OS curve at approximately 15 months, in contrast to the company's base case KM curves, which never fully converge. Therefore, even in a hypothetical scenario where the curve fitting exercise to the epcoritamab and Pola + BR OS curves was "perfect", this would still translate an overestimation of the survival benefit associated with epcoritamab when compared to using the fully adjusted MAIC curves.
- When compared to the underlying OS KM data for epcoritamab and Pola + BR (Figure 18), the EAG-preferred curves (Figure 19) are still likely to underpredict the survival trend observed in the Pola + BR curve from 18 months onwards. Of note, is that the curves used by the EAG (the best-fitting curves) provide very similar survival predictions to those used in the company's base case and that none of the curves provided by the company for Pola + BR were particularly good at replicating the possible plateau observed in the Pola + BR curve from month 18 to month 27 in Sehn *et al*. Therefore, the survival benefit for epcoritamab in comparison with Pola + BR for the partially adjusted MAIC is also overestimated.
- As discussed in Section 2.7, the fully adjusted KM PFS curves show that the epcoritamab PFS curve [redacted] and continues to considerably [redacted]. However, the partially-adjusted KM epcoritamab curve used by the company shows a much [redacted]. Therefore, even in a hypothetical scenario where the curve fitting exercise to the epcoritamab and Pola + BR PFS curves was "perfect", this would still translate an overestimation of the survival benefit associated with epcoritamab when compared to using the fully adjusted MAIC curves.

The curves for population A (compared to Pola + BR) are summarised in Table 20 and reported in Figure 44, while the results of the analysis are reported in Section 4.

When the EAG reintroduced the LTR assumption for axi-cel in the model (as discussed in Section 2.11), this created a discrepancy in the Pola + BR curves (creating an "LTR-based plateau" in the PFS Pola + BR curve) and the epcoritamab curve. Therefore, the EAG had to assume that Pola + BR and epcoritamab curves became the same after the crossing of the curves in the scenario where LTR is considered in the model, therefore, artificially creating the same LTR plateau in the epcoritamab curve. The EAG caveats this by the fact that the EAG's clinical experts explicitly stated that a LTR should not be assumed while patients are on treatment (which is the case for epcoritamab patients),

therefore the epcoritamab PFS curves are likely to be considerably overestimated in the EAG's exploratory analysis (Figure 45).

Table 20. Distributions used in EAG's exploratory analysis

Outcome	Treatment	Distribution	Ranking according to AIC and BIC	Table in company's TE appendix reporting AIC and BIC
Overall survival	Epcoritamab, population A, comparison with Pola + BR	Lognormal	Best-fitting	Table 77
	Pola + BR	Lognormal	Best-fitting (AIC) and second best-fitting (BIC)	Table 129
Progression-free survival	Epcoritamab, population A, comparison with Pola + BR	Lognormal	Best-fitting	Table 79
	Pola + BR	Generalised gamma	Best-fitting	Table 131
Time to treatment discontinuation	Epcoritamab, population A, comparison with R-based CIT, scenario A4	Lognormal	Best-fitting	Table 81

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Figure 44. EAG-prefered OS and PFS curves for epcoritamab (dotted lines) and Pola + BR (solid lines)

Figure 45. EAG-prefered OS and PFS curves for epcoritamab (dotted lines) and Pola + BR (solid lines) when LTR is assumed for Pola + BR.

[redacted]

2.16.3 Population B – comparison to axi-cel

The EAG notes that the company did not provide fully adjusted MAIC epcoritamab curves; however, the fully adjusted KM OS and PFS curves do not show much of a difference in trajectory to the KM curves used by the company, therefore, the EAG's concerns around the company not using fully adjusted MAIC PFS curves is somewhat mitigated in this comparison. Nonetheless, the EAG remains concerned with the following:

1. The KM OS curves show [redacted]. Furthermore, it is possible that the [redacted].
2. The company's fitted PFS curves do not accurately reflect the underlying KM PFS data for the epcoritamab MAIC-adjusted and the ZUMA-1 unadjusted PFS curves. The KM PFS curves [redacted]. The lack of flexibility of the estimated curves to accurately predict the shape of the underlying

KM PFS data slightly defeats the purpose of the EAG's request to have independently fitted curves to epcoritamab and axi-cel, respectively, in order to appropriately capture the overlap and the crossing (or convergence) of the KM curves.

3. The company's approach to modelling TTD after TE underestimates the treatment costs associated with epcoritamab.

The EAG conducted exploratory analysis to help mitigate some of the concerns around the estimation of treatment effectiveness for this comparison in the model. However, the EAG caveats its exploratory analysis by the following issues, which when combined, still result in a fundamentally flawed analysis for this comparison:

1. Even though the axi-cel OS curves provide a generally reasonable fit, the EAG is concerned that none of the best-fitting curves available for epcoritamab provide the needed flexibility to accurately predict the shape of the underlying KM OS data, therefore overestimating the survival benefit associated with epcoritamab. [redacted] after which, the EAG opted to present a scenario where the maximum between the curves was taken from the point of the curves crossing, therefore, implying that the epcoritamab OS curve would converge to the axi-cel OS (instead of becoming worse).
2. The EAG remains concerned with the long-term predictions of survival in the epcoritamab curve even when the EAG-preferred curves are used – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population B (Figure 22).
3. When the EAG used the lognormal curve to fit the epcoritamab PFS data and the generalised gamma to fit the axi-cel PFS data, the epcoritamab curve [redacted] therefore, providing a much better alignment with the underlying KM PFS data observed for both treatments. The EAG opted to present an optimistic scenario, where the maximum between the epcoritamab and the axi-cel PFS curves was taken from the point of the curves crossing, therefore, implying

that the epcoritamab PFS curve would converge to the axi-cel PFS curve from month 29 onwards (Figure 35 and Figure 36). However, the EAG cannot discard the possibility that the crossing of the KM curves seen in Figure 31 indicates that epcoritamab patients start progressing (or dying) faster than axi-cel patients at after 2 years, therefore, the EAG has conducted a scenario analysis where the curves are not capped in the model.

4. Given the EAG's assumption that the epcoritamab and axi-cel curves become the same in the model after crossing, when the EAG reintroduced the LTR assumption for axi-cel in the model (as discussed in Section 2.11), this indirectly applied the LTR assumption to the PFS epcoritamab curves. As originally noted by the EAG, clinical experts explicitly stated that a LTR should not be assumed while patients are on treatment (which is the case for epcoritamab patients), therefore the epcoritamab PFS (and OS) curves are likely to be considerably overestimated in the EAG's exploratory analysis.
5. When using the best-fitting curve to estimate TTD for epcoritamab, the mean TTD and mean PFS in the model is [redacted], respectively. Considering the company's original expectation (and the EPCORE™ NHL-1 TTD and PFS data) that epcoritamab is well tolerated and very few patients discontinue due to AEs or toxicity, the EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation is an alarming discrepancy, therefore, the treatment costs for epcoritamab remain underestimated in the EAG's exploratory analysis.

The curves for population B are summarised in Table 21 while the results of the analysis are reported in Section 4.

Table 21. Distributions used in EAG's exploratory analysis

Outcome	Treatment	Distribution	Ranking according to AIC and BIC	Table in company's TE appendix reporting AIC and BIC
Overall survival	Epcoritamab, population B	Lognormal	Second best-fitting	Table 113
	Axi-cel	Gompertz	Best-fitting	Table 141
Progression-free survival	Epcoritamab, population B	Lognormal	Second best-fitting	Table 115
	Axi-cel	Generalised gamma	Best-fitting	Table 143
Time to treatment discontinuation	Epcoritamab, population B	Lognormal	Best-fitting	Table 117

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Figure 46. EAG-prefered OS and PFS curves for epcoritamab (pink and blue) and axi-cel (green and brown)

2.17 Key issue 15: Utilities used in the model

As discussed in Issue 6, the EAG was unsure whether the data used in the original MAICs for population A were reflective of a group ineligible for intensive treatments. Therefore, the EAG noted that the population used to derive utilities for population A might not have been limited in the same way as the subgroup of patients used in the effectiveness analysis, given that the company had not mention future CAR-T eligibility for this population in the utility analysis.

For population B, the EAG was originally satisfied with the use of the LBCL population (instead of the DBCL population); however, noted that it would have preferred to have restricted the population further to no prior CAR-T, and eligible to receive future CAR-T.

2.17.1 Company's approach at Technical Engagement

The company stated that the population used to derive the utility values for population A was aligned with the epcoritamab population informing the efficacy estimates (DLBCL, no prior CAR-T population). As discussed in Key Issue 6, the company did not consider it appropriate to conduct a MAIC in which the epcoritamab population A was restricted specifically to those ineligible to receive future intensive therapies (therefore the company did not conduct the analysis originally requested

by the EAG) and noted that the utility analysis was also not restricted to patients ineligible to receive intensive therapies.

The company did not change, or comment, on its approach to derive utilities for population B.

2.17.2 EAG's critique of the company's approach at Technical Engagement

The EAG acknowledges that utility values currently used for population A are in line with the EPCORE™ NHL-1 population currently analysed in MAICs for population A (DLBCL, no prior CAR-T , with no requirement to be ineligible for intensive treatments). As discussed in Section 2.6, the EAG acknowledges that for population A, it is not clear from the comparator papers for R-based CIT and Pola + BR if they were specific to populations ineligible for intensive treatments. However, the EAG maintains its view that it would be useful to assess the potential impact of using the population from EPCORE™ NHL-1 that matches the definition of population A in the CS (i.e., patients ineligible to receive CAR-T), both to conduct the MAICs and the utility analysis.

Regarding the utility values used in population B, the EAG notes that the company's original approach of deriving utilities using the utility data from [redacted] instead of the original marketing authorisation for the treatment R/R LBCL after 2 or more systemic treatments.

Nonetheless, as discussed in Section 2.5 the EAG preference is to use the LBCL population from EPCORE™ NHL-1 in order to match the population in ZUMA-1. Therefore, the company's approach might be appropriate; however, the EAG notes that it cannot anticipate the impact of conducting the utility analysis in the DLBCL population and therefore, advises that the company conducts this analysis before the committee meeting in order to explore the potential uncertainty in using either set of values.

2.18 Key issue 16: Treatment and administration costs of comparators in the model

The EAG considered the company's original approach to costing the administration of chemotherapies in the R-based CIT and the Pola + BR treatment combinations inconsistent. For Pola + BR, the company used the SB14Z and the SB15Z codes to reflect the delivery of first and subsequent chemotherapies (£502.74 and £358.62, respectively); however, the company applied an

administration cost of £5,660 (£5,063 updated with inflation) for R-based CIT. In TA559, where the company stated the administration cost for R-based CIT was originally taken from, the cost of administrating a basket to BSC treatments (of which R-based CIT was part) was £5,063, based on the hospital admission of nonelective long-stay HRGs for malignant lymphoma. The EAG in TA559 criticised the company's approach and noted this cost should be replaced with the SB14Z and the SB15Z code to reflect the delivery of first and subsequent chemotherapies.

Therefore, for the current submission, the EAG originally recommended that the company used the SB14Z and the SB15Z codes to cost the administration of R-based CIT in the model.

The EAG also noted that the company assumed 8 cycles of treatment with R-based CIT in the model. Nonetheless, the EAG's clinical experts explained that several centres in the UK only allowed a maximum of 6 cycles of treatment with R-based CIT. Therefore, the EAG conducted a scenario analysis in the model where a maximum of 6 cycles of R-based CIT was given. The impact on the ICER was minimal.

The EAG also disagreed with the company's addition of monitoring costs to the axi-cel administration cost. The final appraisal determination document and the committee slides in TA872 (where the company originally sourced the administration costs for axi-cel) stated that, "*NHSE have accepted this* [£41,101] *as a total cost for the first 100 days and recommend NICE consider this in all ongoing CAR-T appraisals*". Therefore, the EAG conducted a scenario analysis where a total cost of £40,638 for the administration of axi-cel was used in the model ([£41,101 excluding the costs of cytokine release syndrome [CRS]). This scenario reduced the total costs associated with axi-cel by approximately £1,500.

Finally, the EAG noted that it was unsure why all costs in the model were inflated to the 2021 cost year and recommended that the company inflated all relevant costs to the most recent cost year (as per the list of recommendations in Section 1.4 of the EAG original report).

2.18.1 Company's approach at Technical Engagement

The company updated their base case so that the administration costs for R-based CIT were aligned with the approach adopted for Pola + BR, using cost codes SB14Z and SB15Z.

The company also noted that the SmPC for rituximab states the treatment can be used for up to 8 cycles, however, acknowledged that chemotherapy protocols for R-GemOx in the UK NHS suggests 6

cycles are also common. In response to this, the company updated their base to assume that patients receive R-based CIT for a total of 6 cycles.

In response to the EAG's concern regarding the monitoring cost applied to axi-cel, a scenario analysis was conducted where the one-time monitoring cost was removed for axi-cel. However, the company reported that in reviewing the costs included in the administration costs for axi-cel in TA872, "[it] *became apparent that these costs do not capture the costs of bridging therapy, which is an essential component of treatment for a substantial proportion of patients with axi-cel to provide them with interim treatment whilst waiting to receive their infusion*". Therefore, the company added a one-off cost of £24,368 to their base case cost for axi-cel, based on the assumption that 85% of axi-cel patients would incur a bridging cost, where 60%, 18% and 8% of patients received the cost of one cycle of Pola + BR; one cycle of radiotherapy; or one cycle of steroids, respectively.

The company highlighted that the errors identified in the model related to the administration costs applied to subsequent treatments were corrected. These corrections included removing intravenous costs for axi-cel as a subsequent treatment and aligning the administration costs for chemotherapy with those used for R-based CIT as a comparator.

In addition, the company states that a further related to the cost of epcoritamab had also been updated in the model so that the cost of epcoritamab was incurred in line with the modelled TTD curve.

The company also noted that all costs in the model were inflated to the most recent available cost year (2022).

2.18.2 EAG's critique of the company's approach at Technical Engagement

The EAG is broadly satisfied with the company's updated approach to estimating the administration costs for R-based CIT, and with the company's updated assumption of a duration of 6 cycles of treatment for the drug.

As discussed in Section 4.2.6 of the EAG's report, the company's original approach to estimating the administration costs for axi-cel (£41,101) was based on Slide 4 of the Public Committee Slides from the third appraisal committee meeting for TA872 (confirmed by the budget impact template from NHS England).[11] The company reported that it understood this to be the agreed NHSE cost for the

first 100 days following CAR-T use, and that this cost should be used in all ongoing and future appraisals that included CAR-T therapies. The company understood that this cost included:

- Axi-cel leukapheresis costs;
- Hospitalisation costs for conditional chemotherapy;
- Weighted average cost of CRS;
- Hospitalisation costs for axi-cel administration;
- Axi-cel costs for weighted average cost of allogenic SCT;
- Training costs;
- Medical resource use costs for the first three months (~100 days);
- Hypogammaglobulinemia costs for the first three months (~100 days).

The EAG disagreed with the company's original addition of monitoring costs to the axi-cel administration cost. The company provided a scenario analysis after TE in the model removing the monitoring costs, which the EAG is satisfied with.

Even though the company did not specify this in their response to TE, the EAG assumes that the costs of chemotherapy or radiotherapy (with a small percentage of patients getting steroids) added as bridging costs refer to bridging patients to CAR-T (instead of bridging patients from CAR-T to SCT). In TA872 it was stated that, "*Bridging therapy is used to hold progression of disease during CAR-T manufacture and delivery. However, ZUMA-1 did not allow bridging chemotherapy in the trial so no patients in the trial received it. In the real-world scenario careful patient selection should continue with evaluation of the pace of disease progression to ensure it is appropriate for the use of axi-cel therapy with appropriate allowance for the time of manufacturing and delivery*. […] *However, for many patients eligibility for CAR-T is considered because of poor response/refractoriness to chemotherapy and so bridging chemotherapy would be unlikely to be of great benefi*t."

However, the EAG has requested advice on this matter from NICE, which resulted in a recommendation to include bridging costs. The NICE recommendation was that approximately 92% of patients in the UK receive bridging treatment to be able to receive CAR-T, of which 40% receive Pola + BR; 30% receive radiotherapy; 5% receive corticosteroids; and 17% receive chemotherapy (of which 11% receive a rituximab-based treatment). Therefore, the EAG estimated the weighted costs of bridging therapy based on NICE's proportions of treatments and on the costs provided in the company's model, which assumed one full cycle of each treatment. The EAG's costs amounted to

£23,850, not too dissimilar to the company's estimated £24,368 cost of bridging. The results of the EAG analysis are reported in Section 4.

2.19 Key issue 17: Subsequent treatments in the model

The EAG's clinical experts originally explained that 3rd line treatments influence patents' eligibility to receive subsequent treatments, therefore rendering the company's original assumption of the same subsequent treatments being received in both populations A and B implausible (Table 22). For example, patients previously treated with a rituximab-based combination should receive subsequent palliative chemotherapy (and not a subsequent rituximab combination as assumed by the company). Additionally, patients previously treated with epcoritamab would have differing future treatments depending on if they were eligible to receive CAR-T therapy (i.e., if patients were part of population A or B).

Therefore, the EAG recommended that the company included a scenario analysis in the model where subsequent treatments were informed by the proportion of patients suggested by the EAG's clinical experts (and outlined in Table 59 of the EAG report, replicated in Table 23 for clarity) at clarification, however, the company did not conduct the analysis.

After clarification, the EAG conducted a simplified version of the requested scenario analysis where for R-based CIT and Pola + BR patients receiving subsequent palliative chemotherapy, the EAG removed the costs of rituximab from the R-based CIT combination used in the model as a subsequent treatment, leaving patients only to receive GemOx as subsequent treatments in the model. However, the EAG noted that it is likely that these patients would get different chemotherapies from GemOx. The EAG, therefore, recommended that the company conducted the appropriate scenario analysis at TE. The EAG's scenario analysis led to a large increase in the final ICER for epcoritamab vs R-based CIT and Pola + BR, and a large decrease in the total costs associated with axi-cel in the analysis (even though the ICER for this comparison remained dominant in favour of epcoritamab).

Table 22. Proportion of patients receiving subsequent treatments in company's base case

Treatment at entry	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	No active treatment
Epcoritamab	52.5%	5%	25%	0.5%	3%	13.5%

R-based CIT	46%	10%	26%	1.5%	1.5%	15%
Pola + BR	49%	7%	26%	1.0%	2.5%	0%
Axi-cel	52%	0%	32%	1%	5%	10%
Reference	Company's clinical expert interviews					

Abbreviations: Allo, allogenic; auto, autologous; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; R, rituximab; SCT, stem cell transplant.

Table 23. EAG preferred subsequent treatment proportions.

Treatment at entry	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	Alloy-SCT	No active treatment
Epcoritamab (population A)	30%	11%	25%	1%	3%	30%
Epcoritamab (population B)	30%	30%	25%	1%	3%	12%
R-based CIT	30%*	8%	30%	0%	2%	30%
Pola + BR	30%	8%	30%	0%	2%	30%
Axi-cel	9%	0%	32%	1%	5%	53%

*Additional chemotherapy following treatment with R-based CIT would be palliative and not R-based.

Abbreviations: Allo, allogenic; auto, autologous; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; R, rituximab; SCT, stem cell transplant.

2.19.1 Company's approach at Technical Engagement

The company noted that the EAG's preferred subsequent treatment proportions reflected a substantially higher proportion of patients receiving CAR-T therapy after treatment with epcoritamab (11% [population A] and 30% [population B]) compared with the assumptions used in the company's original base case (5%; based on UK clinical expert opinion for both populations) and the proportion of patients who received subsequent CAR-T therapy in EPCORE™ NHL-1 ([redacted]%).

The company stated that if the proportion of patients receiving CAR-T therapy after epcoritamab was assumed to be higher in the model than the proportion who received CAR-T therapy after

epcoritamab in EPCORE™ NHL-1, the increased CAR-T usage would only increase costs in the model without reflecting the clinical benefit for epcoritamab patients in the model. Therefore, in order to conduct the scenario suggested by the EAG and reflect the increased efficacy associated with the increased subsequent CAR-T use for the epcoritamab arm, the company added "*an additional QALY adjustment for the epcoritamab arm*". In the absence of suitable published data, the additional QALYs added were based on the difference in total QALYs estimated for R-based CIT and axi-cel in base case analysis A and B, respectively, multiplied by the increased proportion of patients that receive subsequent CAR-T in the model. This results in a total QALY adjustment of [redacted] and [redacted] when applied to population A and population B, respectively.

The company reported that for population A, this scenario analysis resulted in both increased incremental costs and QALYs, compared to the base case analysis, with an ICER of £30,650; however, noted a high degree of uncertainty associated with this scenario. For population B, epcoritamab remained dominant over axi-cel.

With regards to the EAG request that patients previously treated with a rituximab-based combination should receive subsequent palliative chemotherapy (and not a subsequent rituximab combination), the company stated that they did not consider this was relevant to UK clinical practice and so the company did not conduct the analysis.

2.19.2 EAG's critique of the company's approach at Technical Engagement

The EAG investigated the proportion of patients in EPCORE™ NHL-1 with disease progression (95 patients) who got subsequent treatments ([redacted]) in the latest trial data cut and which treatments were given in the trial. These are reported in Table 24. Out of the patients with disease progression in the trial, [redacted] of patients did not receive any subsequent treatment, which is higher than the company's cost analysis but broadly in accordance with the EAG's clinical experts' expectations for population A. Importantly, in their response to TE, the company states that [redacted]% of patients received CAR-T in EPCORE™ NHL-1; however, this is calculated as the number of patients who received CAR-T out of the total of LBCL patients enrolled in the trial, which is the wrong estimation for the comparison with the model estimates, where only progressed patients received subsequent treatment. In EPCORE™ NHL-1, out of the 95 progressed patients, [redacted] of patients received subsequent CAR-T, which is the [redacted] by the EAG's clinical experts for population A. Compared to the company's analysis and the EAG's experts, the proportion of patients who received subsequent R-based CIT in EPCORE™ NHL-1 was [redacted]; however, the EAG notes that [redacted]

and [redacted] of patients in EPCORE™ NHL-1 received subsequent polatuzumab and lenalidomide, respectively, and that none of these active treatments were included in the model as possible subsequent treatments. Furthermore, [redacted] of patients received other treatments in the trial [redacted], although the total number of patients receiving each of these therapies was low ([redacted]).

Therefore, the EAG does not agree with the company's assessment that, "*if the proportion of patients receiving CAR-T therapy after epcoritamab was assumed to be higher in the model than the proportion who received CAR-T therapy after epcoritamab in EPCORE™ NHL-1, the increased CAR-T usage would only increase costs in the model without reflecting the clinical benefit for epcoritamab patients in the model*" given that:

- for population A, the EAG-preferred estimate for the modelled proportion of patients receiving CAR-T (11%) is [redacted] as the proportion of patients receiving CAR-T in the trial.
- for population B, even though the EAG-preferred estimate for the modelled proportion of patients receiving CAR-T ([redacted]) is higher than that received by patients in the trial, patients received other active, effective treatments in EPCORE™ NHL-1 ([redacted] and [redacted] of patients received subsequent polatuzumab and lenalidomide, for example), which have not been considered in the cost of subsequent treatments in the model. Therefore, it is unknown how the treatment effectiveness of CAR-T compares to that of lenalidomide or Pola + BR (among the other treatments received in the trial), and thus, not possible to ascertain in which direction an adjustment in effectiveness would have to be made in order to reflect the clinical benefit in modelled patients when the proportion of subsequent CAR-T is increased.

Therefore, the EAG removed the company's QALY adjustment to the scenario analysis requested by the EAG with regards to CAR-T (in both populations).

The EAG caveats its analysis by the fact that the data provided for subsequent treatments in EPCORE™ NHL-1 does not differentiate between populations A and B, therefore, it is possible that the estimates provided by the EAG in Table 24 would look different if data were analysed by population.

Finally, the EAG maintains its view that patients receiving R-based CIT or Pola + BR, should receive subsequent palliative chemotherapy (and not a subsequent rituximab combination as assumed by the company), as per the EAG's clinical experts' advice. Given that the company did not conduct this analysis, the EAG conducted the same simplified version of this analysis where for R-based CIT and Pola + BR patients receiving subsequent palliative chemotherapy, the costs of rituximab were removed from the R-based CIT combination used in the model as a subsequent treatment.

Results of the EAG analysis are reported in Section 4.

Table 24. Proportion of patients receiving subsequent treatments

Treatment at entry	Percentage of patients receiving subsequent treatments									
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	Pola	No active treatment	Lenalidomide	Other	Corticosteroids
Epcoritamab company's base case	52.5%	5%	25%	0.5%	3%	0%	13.5%	0%	0%	0%
Epcoritamab (population A) EAG- preferred	30%	11%	25%	1%	3%	0%	30%	0%	0%	0%
Epcoritamab (population B) EAG-preferred	30%	30%	25%	1%	3%	0%	12%	0%	0%	0%
Epcoritamab - EPCORE™ NHL-1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Allo, allogenic; auto, autologous; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; R, rituximab; SCT, stem cell transplant.

[redacted]

2.20 Key issue 18: Disease follow-up costs in the model

The EAG had several concerns with the company's implementation of follow-up costs in the original model. Firstly, investigations of the company's model led the EAG to the conclusion that for R-based CIT; Pola + BR; and axi-cel; all patients incurred the "PFS on-treatment" costs for the initial 2 years of the model, after which progression-free patients started incurring no costs as these were considered to be in LTR. However, this was inconsistent with the company's approach to estimating follow-up costs for epcoritamab, where patients incurred a "PFS off-treatment" follow-up cost after [redacted] months in the model. The EAG noted that patients were on treatment with R-based CIT and Pola + BR for 7 and 4 months, respectively and therefore, the company's approach was biased in favour of epcoritamab and was unjustified. The EAG, therefore, recommended that the company allowed R-based CIT; Pola + BR and axi-cel patients in the model to switch from the "PFS on-treatment" to the "PFS off-treatment" resource use in the model after finishing their treatment.

Furthermore, the EAG disagreed with the company's assumption that after [redacted] months in the PFS state, epcoritamab patients would move to the off-treatment resource use cost. The company justified this approach based on it reflecting median PFS in the trial. The EAG highlighted that median PFS in the model was [redacted] months in population A and [redacted] months in population B and that, crucially, the EAG did not understand how median PFS from the trial should dictate resource use for patients on epcoritamab treatment in the model. The EAG noted that its clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued, meaning that the resource use estimated by the company for epcoritamab for the progression-free, on treatment period, should be incurred for as long as treatment was given in the model. However, in contrast to this, epcoritamab patients in the model were assumed to incur less resource uses after what seemed a poorly-defined threshold of [redacted] months. The EAG noted that the company's base case approach was biased in favour of epcoritamab and artificially underestimated the disease management costs associated with the treatment, without a plausible clinical explanation.

The EAG, therefore, requested that the company included a scenario analysis where patients on treatment with epcoritamab experienced the same resource use (that of the "PFS on-treatment" state) from cycle 0 to end of treatment in the model.

The EAG also conducted an exploratory analysis where the follow-up costs ("PFS on-treatment") were incurred for epcoritamab while patients were on treatment.

Finally, the EAG was also concerned that some resources lacked clarity around what had been included in their costs, leading to potentially double counting of some services. This was the case for residential care, day care, home care and hospice care. For example, the PSSRU22 source used by the company to cost day care, included 1 working hour of a band 7 nurse. However, the company also included time with a specialist nurse; district nurse; and nurse time separately. During clarification, the company stated that the district nurse resource use was considered to be community-based health care, while the specialist nurse and nurse resource use are hospital-based health care. However, the cost associated with the district nurse, specialist nurse and nurse time are all based on the National Schedule of Reference Costs 2019-20 (N02AF), in line with previous NICE TAs in R/R LBCL. The EAG was unclear how this avoided double counting of resources in the model. The company's justification for other queries about double counting of resources in the model at clarification was generally that, "*all cost categories and cost sources used in the model are aligned with previous NICE appraisals in R/R LBCL (such as TA649, TA306 and TA559).*" and, "*TA649 does not include a detailed explanation of what is included in these two resource use categories, but they are both part of professional and social services*.". The EAG was not satisfied that the cost sources used to cost resource use in the model were not double counting resources.

2.20.1 Company's approach at Technical Engagement

The company clarified that patients in the comparator arms of the model incurring the PFS on-treatment resource use for the initial 2 years was an error in the model, thus, corrected this in the updated base case to ensure that PFS on-treatment resource use costs were applied only while patients received treatment. The company noted that for axi-cel, the PFS on-treatment resource use estimates were incurred for one cycle, in line with the time when patients receive bridging therapy before axi-cel treatment. The EAG notes that this represents a change in the follow-up costs for axi-cel, where previously there was no cost incurred for this one-off treatment.

The company restated its view that, while epcoritamab is given until progression or unacceptable toxicity, the resource use for patients receiving epcoritamab is anticipated to decrease over time once patients have achieved a complete response (CR). The company acknowledged that the timepoint of reducing the intensity of resource use (i.e., decreasing follow-up costs) for patients receiving treatment with epcoritamab is uncertain. Furthermore, the company explained that during

validation with the company's UK clinical experts, the experts stated that the timepoint by which most patients are in CR represents an appropriate timepoint for the resource use associated with epcoritamab to decrease. This is because patients are unlikely to require resource use beyond injection service, blood tests, interpretation of blood tests by nurse or pharmacist, and occasional consultant lead contacts after this stage following this timepoint.

The company considered the EAG's requested scenario analysis in which patients receiving epcoritamab continue to incur the resource use associated with the PFS on-treatment health state for their duration of treatment to be an overestimation of the healthcare resource use and clinically implausible. The company maintained that the median PFS for DLBCL patients in EPCORE™ NHL-1 is the most appropriate value to inform this timepoint because the majority of patients with progression-free disease will have CR after this timepoint. Based on the [redacted] data cut, patients on epcoritamab incur the PFS on-treatment resource use estimates for [redacted] in the model, after which they switch to the less intense PFS resource use estimates.

The company did not address the EAG's concerns around the potential double counting of resource use in the model through the cost sources used.

2.20.2 EAG's critique of the company's approach at Technical Engagement

The EAG agrees with the implementation of the company's correction to the on- and off-treatment PFS costs in the R-based CIT arm of the model; however, disagrees with the implementation in the Pola + BR arm – the company assumed that Pola + BR patients are on treatment for 6 cycles in the model, when patients receive a fixed duration of 4 cycles of treatment. Therefore, the EAG corrected this in the model and reports the results in Section 4.

Given NICE's recommendation that bridging costs should be included for axi-cel in the model, the EAG considers that the inclusion of a one cycle of follow-up costs for axi-cel, might be reasonable.

The EAG notes that the company's removal of the LTR assumption from the model means that patients carry on incurring the associated PFS-off treatment costs after 2 years of ending treatment in the model. However, as discussed in the EAG's report, the clinical experts advising the EAG noted that progression-free patients 2 years after the end of treatment would be discharged, therefore, not incurring any subsequent follow-up costs. Therefore, when the EAG reintroduced the LTR assumption in the model, this automatically assumed no follow-up costs thereafter for the comparator treatments.

The EAG's original concerns around the assumption of decreasing the follow-up costs for epcoritamab based on median PFS in the EPCORE™ NHL-1 trial remain – the EAG's clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued, meaning that the resource use estimated by the company for epcoritamab for the progression-free, on treatment period should be observed for as long as treatment is given in the model. However, in contrast to this, epcoritamab patients in the model are assumed to incur less resource uses after [redacted].

The EAG also highlights the discrepancy between median PFS in the EPCORE™ NHL-1 trial and the company's base case model and of approximately [redacted] in population A and [redacted] in population B and that, and crucially, the EAG does not understand how median PFS from the trial should dictate resource use for patients on epcoritamab treatment in the model.

The EAG remains of the opinion that the company's base case approach is biased in favour of epcoritamab and artificially underestimates the disease management costs associated with the treatment, without a plausible clinical explanation. The EAG, therefore, conducted an exploratory analysis where the follow-up costs (PFS on-treatment costs) were incurred for epcoritamab while patients were on treatment and reports the results in Section 4.

Finally, the EAG remains unsure if the cost sources used to cost resource use in the model are double counting resources.

3 Company updated results at Technical Engagement

Table 26 presents the cost-effectiveness results of the company's updated probabilistic base case for epcoritamab vs R-based CIT, while Table 27 provides the equivalent deterministic results. Table 28 and Table 29 report the probabilistic and deterministic results for the comparison of epcoritamab and Pola + BR, respectively. The company applied a severity modifier of 1.2 to the incremental QALYs in their updated base case for the comparison of epcoritamab with R-based CIT and Pola + BR, which is appropriate based on the age; sex distribution (see The EAG considers that the uncertainty in QALYs and costs seen in the PSA comes from the uncertainty embedded in the survival curves used by the company, and the fact that these are key drivers of the economic results (as discussed in the EAG's exploratory analysis in Section 4.1). Furthermore, the EAG notes that the company's PSA is likely to be generating implausible results when survival curves are varied in the model as different combinations of curves might be leading to different crossing of survival curves between

epcoritamab and comparator treatments. Given the company's model is not set up to deal with the crossing of survival curves between treatment arms (as this does not happen in the company's base case), it is possible that different permutations of curves generate implausible probabilistic scenarios. However, the EAG recommends that the company confirms if this is the case before the first committee meeting.

Finally, the EAG noticed that the company included the cost of subsequent treatments in the PSA and disagrees with the company's approach given that the unit cost of drugs is not a parameter subject to uncertainty. Therefore, the EAG removed these from the PSA; however, this did not affect the PSA results and thus did not reduce the difference between deterministic and probabilistic ICERs for the comparisons of epcoritamab with Pola+BR and axi-cel.

Table 25); and total QALYs for R-based CIT and Pola + BR (according to the Schneider *et al*. calculator).

The EAG notes that it had to re-run the company's probabilistic ICER for Pola + BR as the company's response to TE did not include all of the estimates of costs, QALYs and life-years gained needed to complete the table of results.

Table 30 and Table 31 report the probabilistic and deterministic ICERs for the comparison of epcoritamab and axi-cel, respectively, where no severity modifier was used.

The company's probabilistic and deterministic results are broadly similar for R-based CIT. However, the deterministic and probabilistic ICERs for epcoritamab vs Pola + BR are moderately different, with the probabilistic ICER being approximately £3,500 higher than the deterministic ICER.

For the comparison of epcoritamab with axi-cel, even though both the probabilistic and deterministic ICERs are dominant, there is a considerable difference in the incremental QALYs and costs between the deterministic and probabilistic results.

As Figure 47 and Figure 48 show, the cost-effectiveness scatter plots for the two comparisons report that the highest source of uncertainty in the PSA results comes from the QALYs generated in the epcoritamab arm for both comparisons followed by the uncertainty in the costs for the same treatment (particularly for epcoritamab vs axi-cel).

The EAG considers that the uncertainty in QALYs and costs seen in the PSA comes from the uncertainty embedded in the survival curves used by the company, and the fact that these are key drivers of the economic results (as discussed in the EAG's exploratory analysis in Section 4.1). Furthermore, the EAG notes that the company's PSA is likely to be generating implausible results when survival curves are varied in the model as different combinations of curves might be leading to different crossing of survival curves between epcoritamab and comparator treatments. Given the company's model is not set up to deal with the crossing of survival curves between treatment arms (as this does not happen in the company's base case), it is possible that different permutations of curves generate implausible probabilistic scenarios. However, the EAG recommends that the company confirms if this is the case before the first committee meeting.

Finally, the EAG noticed that the company included the cost of subsequent treatments in the PSA and disagrees with the company's approach given that the unit cost of drugs is not a parameter subject to uncertainty. Therefore, the EAG removed these from the PSA; however, this did not affect the PSA results and thus did not reduce the difference between deterministic and probabilistic ICERs for the comparisons of epcoritamab with Pola+BR and axi-cel.

Table 25. Summary of preferred assumptions for general population QALY shortfall estimates

Factor	Population A (R-based CIT)	Population A (Pola + BR)	Population B
Sex distribution - % female	[redacted]	[redacted]	[redacted]
Baseline mean age - years	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life-year; Pola + BR, polatuzamab vedotin with bendamustine and rituximab; R-based CIT, rituximab-based chemoimmunotherapy.

Table 26. Company's base case probabilistic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-		-	-	-	-
R-based CIT	£79,726	[redacted]	0.867	[redacted]	[redacted]	[redacted]	[redacted]	£32,298	£26,915

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 27. Company's base case deterministic results – epcoritamab vs R-based CIT

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
R-based CIT	£79,708	[redacted]	0.863	[redacted]	[redacted]	[redacted]	[redacted]	£30,586	£25,488

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 28. Company's probabilistic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,310	£12,758

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 29. Company's deterministic scenario analysis – epcoritamab vs Pola + BR

Treatments	Total			Incremental				ICER incremental (£/QALY)	ICER incremental (£/QALY) with severity modifier
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pola + BR	£145,947	[redacted]	1.356	[redacted]	[redacted]	[redacted]	[redacted]	£11,719	£9,766

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 30. Company's base case probabilistic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£440,749	[redacted]	5.488	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 31. Company's base case deterministic results – epcoritamab vs axi-cel

Treatments	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	Undiscounted LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	£442,130	[redacted]	5.566	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 47: Cost-effectiveness scatter plot for epcoritamab Pola + BR (generated by the EAG)

[redacted]

Figure 48: Cost-effectiveness scatter plot for epcoritamab versus axi-cel (Figure 5 company's response to TE)

[redacted]

4 EAG preferred assumptions at Technical Engagement

4.1 Model corrections

The EAG disagrees with the implementation of the company's correction to the on- and off-treatment PFS costs in the Pola + BR arm of the model – the estimate inputted in the model for this correction is based on Pola + BR patients being on treatment for 6 cycles in the model, when patients receive a fixed duration of 4 cycles of treatment in the model. Therefore, the EAG corrected the company's approach to reflect a treatment duration of 4 cycles with Pola + BR and notes that this correction only impacts the company's base case for the comparison with Pola + BR.

4.1 Exploratory and sensitivity analyses undertaken by the EAG

The exploratory analysis conducted by the EAG were explained throughout the report. To note is that the changes made to the distributions used to model survival outcomes were done simultaneously for OS, PFS and TTD in each scenario analysis, for each comparator, as to do these individually would have created inconsistent intermediate results. The EAG's changes consist of the following:

1. For population A, for the comparison of epcoritamab with R-based CIT, the EAG used the company's 9/10 adjusted MAIC (scenario A.4) and used the exponential and generalised gamma models to estimate the OS curves for epcoritamab and R-based CIT; respectively. For PFS, the EAG used the generalised gamma curve for the epcoritamab arm (and the company's HR to generate the company's PFS curve). For TTD, the EAG used the lognormal curve.
2. For population A, for the comparison of epcoritamab with Pola + BR, the EAG used lognormal models to estimate the OS curves for epcoritamab and Pola + BR. For PFS, the EAG used the lognormal curve for the epcoritamab arm and a generalised gamma for the Pola + BR curve. For TTD, the EAG used the lognormal curve.
3. For population B, the EAG used the company's MAIC from scenario B.2. and used a lognormal model to estimate the OS curves for epcoritamab and did not make changes to the company's approach of estimating the axi-cel curve with a Gompertz model. For PFS, the EAG used a lognormal and generalised gamma to estimate PFS for epcoritamab and axi-cel, respectively. For TTD, the EAG used the lognormal curve.
4. Removing the monitoring costs from the axi-cel administration cost.

5. Using the EAG-preferred bridging costs for axi-cel.
6. Using the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model (as per Table 23 in the report). For the R-based CIT patients receiving subsequent palliative chemotherapy, the EAG undertook the simplifying assumption of removing the costs of rituximab from the subsequent R-based CIT combination used in the model. For subsequent CAR-T, the EAG removed the company's QALY adjustment to the scenario analysis.
7. Assuming that the follow-up costs (PFS on-treatment costs) are incurred for epcoritamab, while patients are on treatment and progression-free.
8. Reintroducing the LTR assumption for all comparator treatments, 2 years after the end of treatment which assumes no follow-up costs thereafter.
9. Allowing the estimated epcoritamab PFS curve to cross the PFS axi-cel curve.
10. Using a HR of 1.2 between the PFS and TTD epcoritamab curve to estimate TTD (difference in mean PFS and TTD of approximately 2 years).

Results of the EAG's exploratory analysis are provided in Table 33, Table 34 and Table 35 for the comparison of epcoritamab with R-based CIT Pola + BR; and axi-cel; respectively. In Table 32 the EAG reports the baseline age and sex distribution for each population in the EAG-preferred MAIC analysis (Scenario A4; A1; and B1, respectively for R-based CIT; Pola + BR; and axi-cel). Based on the latter, and the total QALYs estimated for each comparator, the EAG reports the results of its analysis with the appropriate severity modifier in Table 33, Table 34 and Table 35.

The EAG notes that comparator treatments are available in the NHS at a discount, according to patient access schemes (PASs). The EAG reports the results of its analysis with the respective PASs in a confidential appendix.

For all the analyses, the key drivers of the EAG's exploratory analysis are the following assumptions:

- using the EAG-preferred MAIC and survival distributions;
- the removal of the assumption that epcoritamab patients stop incurring follow-up costs in the NHS at [redacted] in the model, when paired with the EAG's preferred survival curves; and
- the reintroduction of the LTR assumption (for the comparisons with Pola + BR and axi-cel).

For population A, for the comparison to R-based CIT, the EAG's cumulative exploratory ICER amounts to £72,096 per QALY gained when the LTR is assumed and £71,949 when the LTR is not used in the model.

For population A, for the comparison to Pola + BR, the EAG's cumulative exploratory ICER amounts to £86,769 per QALY gained, with a 1.2 severity modifier applied, when the LTR assumption is not used in the model. When the EAG reintroduces the LTR assumption in the model, the ICER amounts to £6,035,898 per QALY gained, without a severity modifier applied given that the total QALYs associated with Pola + BR (3.07) exceed the severity modifier threshold.

For population B, the EAG's exploratory ICER remains dominant, and the severity modifier is not applicable in any scenario. There are two exceptions to this:

1. Where the LTR assumption is reintroduced for axi-cel, where the ICER becomes £438,014 (south-west quadrant). Nonetheless, the EAG caveats the results of this analysis by the fact that the latter lack face validity – the option in the model to reintroduce the LTR for axi-cel at 2 years generates higher QALYs associated with the PFS state for axi-cel than epcoritamab, even though the proportion of patients in the PFS epcoritamab curve remains higher (or the same) as that of axi-cel throughout the model. In the limited time available, the EAG could not fully explore the cause of this error or correct it in the model. Therefore, the EAG recommends that the company provides a corrected version of the model before the first committee meeting.
2. When the EAG used a HR of 1.2 to estimate the TTD epcoritamab curve by applying the HR to the epcoritamab PFS curve, leading to an ICER of £220,722 per QALY gained. This scenario was conducted in order to demonstrate the impact that the underestimation of the epcoritamab TTD curve in the comparison with axi-cel has on the final results. As discussed throughout the report, both the EAG and the company's survival curves used to estimate TTD for epcoritamab, lead to a difference between mean PFS and mean TTD in the model of [redacted]. Considering the company's original expectation (and the EPCORE™ NHL-1 TTD and PFS data) that epcoritamab is well tolerated and few patients discontinue due to AEs or toxicity, the EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation is an alarming discrepancy. This also implies that, on average, patients who stop treatment benefit from keeping in a progression-free state for [redacted] after concluding treatment before progressing, which is an unsubstantiated and likely a

clinically implausible benefit of treatment with epcoritamab. The EAG reinforces its point that the marketing authorisation for epcoritamab anticipates patients to be treated until progression or intolerable toxicity, and thus patients who are progression-free will continue to take the drug as long as it is tolerated. The EAG has not seen any data to: 1) suggest that the drug is poorly tolerated; or 2) indicate a large PFS benefit for a period after patients stop treatment. Figure 37, Figure 39, and Figure 41 show that the in latest data-cut, PFS and TTD curves are similar for the initial 6 months of treatment, with some curve separation thereafter and the more mature discontinuation data from EPCORE™ NHL-1 showing a discontinuation of [redacted] after 30 months of follow-up. In contrast, in the company's base case model, at 30 months, there were [redacted] of patients who had discontinued treatment. The EAG chose a HR of 1.2 as this provided a difference in mean PFS and TTD of approximately 2 years, which was broadly the difference observed for epcoritamab in population A when the EAG preferred curves are used. In Figure 49, the EAG reports the TTD curve when a HR of 1.2 is used, which shows a smaller gap between the PFS and TTD curves for epcoritamab when compared to the company's or the EAG's survival curves (Figure 50 and Figure 51, respectively) . The figure also shows that the estimated TTD curve with a HR of 1.2 provides a bad visual fit to the underlying KM TTD data. Nonetheless, the EAG notes that the [redacted] in the KM curve observed at approximately [redacted]) and should, therefore, be interpreted with caution.

Table 32. Summary of EAG-preferred assumptions for general population QALY shortfall estimates

Factor	Population A (R-based CIT scenario A4)	Population A (Pola + BR)	Population B (scenario B1)
Sex distribution - % female	[redacted]	[redacted]	[redacted]
Baseline mean age - years	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life-year; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; R-based CIT, rituximab-based chemoimmunotherapy.

Table 33. Results of the EAG's exploratory analyses – R-based CIT

	Results per patient	Epcoritamab	R-based CIT	Incremental value	Incremental value with severity modifier (1.2)
0	Company's base case				

	Total costs (£)	[redacted]	£79,708	[redacted]	[redacted]
	QALYs	[redacted]	0.86	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£30,586	£25,488
1	Using the company's 9/10 adjusted MAIC (scenario A.4); using an exponential and generalised gamma model to estimate the OS curves for epcoritamab and R-based CIT; respectively; using the generalised gamma curve for the epcoritamab PFS curve. For TTD, the EAG used the lognormal curve.				
	Total costs (£)	[redacted]	£94,755	[redacted]	[redacted]
	QALYs	[redacted]	1.25	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£58,654	£48,878
6	Using the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.				
	Total costs (£)	[redacted]	£71,108	[redacted]	[redacted]
	QALYs	[redacted]	0.86	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£37,994	£31,661
	Total costs (£) (cumulative)	[redacted]	£86,092	[redacted]	[redacted]
	QALYs (cumulative)	[redacted]	1.25	[redacted]	[redacted]
	Cumulative ICER	-	-	£76,714	£63,928
7	Assuming that the follow-up costs (PFS on-treatment costs) are incurred for epcoritamab while patients are on treatment and progression-free.				
	Total costs (£)	[redacted]	£79,708	[redacted]	[redacted]
	QALYs	[redacted]	0.86	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£30,215	£25,179
	Total costs (£) (cumulative)	[redacted]	£86,092	[redacted]	[redacted]
	QALYs (cumulative)	[redacted]	1.25	[redacted]	[redacted]
	Cumulative ICER	-	-	£86,339	£71,949
8	Reintroducing the LTR assumption for all comparator treatments, 2 years after the end of treatment and assuming no follow-up costs thereafter.				
	Total costs (£)	[redacted]	£78,990	[redacted]	[redacted]
	QALYs	[redacted]	0.87	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£30,887	£25,739
	Total costs (£) (cumulative)	[redacted]	£85,990	[redacted]	[redacted]
	QALYs (cumulative)	[redacted]	1.25	[redacted]	[redacted]
	Cumulative ICER	-	-	£86,515	£72,096

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

Table 34. Results of the EAG's exploratory analyses – Pola + BR

	Results per patient	Epcoritamab	Pola + BR	Incremental value	Incremental value with severity modifier (1.2)
0	Company's corrected base case				
	Total costs (£)	[redacted]	£144,085	[redacted]	[redacted]
	QALYs	[redacted]	1.36	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£13,358	£11,131
2	Using lognormal models to estimate the OS curves for epcoritamab and Pola + BR; respectively; using the lognormal model to estimate PFS for epcoritamab and the generalised gamma curve for the Pola + BR PFS curve. For TTD, the EAG used the lognormal curve.				
	Total costs (£)	[redacted]	£131,195	[redacted]	[redacted]
	QALYs	[redacted]	1.37	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£65,130	£54,275
6	Using the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.				
	Total costs (£)	[redacted]	£147,320	[redacted]	[redacted]
	QALYs	[redacted]	1.36	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£27,732	£23,110
	Total costs (£) (cumulative)	[redacted]	£134,372	[redacted]	[redacted]
	QALYs (cumulative)	[redacted]	1.37	[redacted]	[redacted]
	Cumulative ICER	-	-	£82,066	£68,388
7	Assuming that the follow-up costs (PFS on-treatment costs) are incurred for epcoritamab while patients are on treatment and progression-free.				
	Total costs (£)	[redacted]	£144,085	[redacted]	[redacted]
	QALYs	[redacted]	1.36	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£17,929	£14,940
	Total costs (£) (cumulative)	[redacted]	£134,372	[redacted]	[redacted]
	QALYs (cumulative)	[redacted]	1.37	[redacted]	[redacted]
	Cumulative ICER	-	-	£104,122	£86,769
8	Reintroducing the LTR assumption for all comparator treatments, 2 years after the end of treatment and assuming no follow-up costs thereafter.*				
	Total costs (£)*	[redacted]	£124,633	[redacted]	-
	QALYs*	[redacted]	3.07	[redacted]	N/A
	ICER (£/QALY)*			£4,024,948	N/A
	Total costs (£) (cumulative)	[redacted]	£127,558	[redacted]	-
	QALYs (cumulative)	[redacted]	3.07	[redacted]	N/A
	Cumulative ICER	-	-	£6,035,898	N/A

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

*this scenario has been conducted in combination with the EAG-preferred MAIC data and survival curves.

Table 35. Results of the EAG's exploratory analyses – axi-cel

	Results per patient	Epcoritamab	Axi-cel	Incremental value	Incremental value with severity modifier (1.2)
0	Company's base case				
	Total costs (£)	[redacted]	£442,130	[redacted]	-
	QALYs	[redacted]	5.57	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
3	Using the company's scenario B1; using the lognormal model to estimate the OS curves for epcoritamab; using a lognormal and generalised gamma to estimate PFS for epcoritamab and axi-cel, respectively. For TTD, the EAG used the lognormal curve.				
	Total costs (£)	[redacted]	£450,391	[redacted]	-
	QALYs	[redacted]	5.43	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
4	Removing the monitoring costs from the axi-cel administration cost				
	Total costs (£)	[redacted]	£440,588	[redacted]	N/A
	QALYs	[redacted]	5.57	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
	Total costs (£) (cumulative)	[redacted]	£448,850	[redacted]	-
	QALYs (cumulative)	[redacted]	5.43	[redacted]	N/A
	Cumulative ICER	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
5	Using the EAG-preferred bridging costs				
	Total costs (£)	[redacted]	£441,612	[redacted]	N/A
	QALYs	[redacted]	5.57	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
	Total costs (£) (cumulative)	[redacted]	£448,336	[redacted]	N/A
	QALYs (cumulative)	[redacted]	5.43	[redacted]	N/A
	Cumulative ICER	-	-	Dominant	N/A

	NHB at £20,000	-	-	[redacted]	N/A
6	Using the EAG's clinical expert opinion to inform the distribution of subsequent treatments given in the model.				
	Total costs (£)	[redacted]	£438,968	[redacted]	N/A
	QALYs	[redacted]	5.57	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
	Total costs (£) (cumulative)	[redacted]	£445,629	[redacted]	N/A
	QALYs (cumulative)	[redacted]	5.43	[redacted]	N/A
	Cumulative ICER	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
7	Assuming that the follow-up costs (PFS on-treatment costs) are incurred for epcoritamab while patients are on treatment and progression-free.				
	Total costs (£)	[redacted]	[redacted]	[redacted]	N/A
	QALYs	[redacted]	5.57	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	
	Total costs (£) (cumulative)	[redacted]	[redacted]	[redacted]	N/A
	QALYs (cumulative)	[redacted]	5.43	[redacted]	N/A
	Cumulative ICER	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
8	Reintroducing the LTR assumption for all comparator treatments, 2 years after the end of treatment and assuming no follow-up costs thereafter.*				
	Total costs (£)	[redacted]	£397,547	[redacted]	N/A
	QALYs	[redacted]	6.05	[redacted]	N/A
	ICER (£/QALY)	-	-	£729,896†	N/A
	NHB at £20,000	-	-	[redacted]	N/A
	Total costs (£) (cumulative)	[redacted]	£393,064	[redacted]	N/A
	QALYs (cumulative)	[redacted]	6.00	[redacted]	N/A
	Cumulative ICER	-	-	£438,014†	N/A
	NHB at £20,000	-	-	[redacted]	N/A
9	Allowing the estimated epcoritamab PFS curve to cross the PFS axi-cel curve.*,‡				
	Total costs (£)	[redacted]	£450,915	[redacted]	N/A
	QALYs	[redacted]	5.53	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
	Total costs (£) (cumulative)	[redacted]	£445,629	[redacted]	N/A

	QALYs (cumulative)	[redacted]	5.43	[redacted]	N/A
	Cumulative ICER	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
11	Using a HR of 1.2 between the PFS and TTD epcoritamab curve to estimate TTD (difference in mean PFS and TTD of approximately 2 years)‡				
	Total costs (£)	[redacted]	£442,130	[redacted]	-
	QALYs	[redacted]	5.57	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
	NHB at £20,000	-	-	[redacted]	N/A
	Total costs (£) (cumulative)	[redacted]	£445,629	[redacted]	-
	QALYs (cumulative)	[redacted]	5.43	[redacted]	N/A
	Cumulative ICER	-	-	£220,722	N/A
	NHB at £20,000	-	-	[redacted]	N/A

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PFS, progression-free survival; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

*this scenario has been conducted in combination with the EAG-preferred MAIC data and survival curves.

†south-west quadrant

‡No LTR included in this scenario because of issue described in text above

Figure 49. EAG preferred curves when a HR of 1.2 is used to generate the TTD curve for epcoritamab.

[redacted]

Figure 50. Company's base case curve

Figure 51. EAG preferred survival curves (TTD curve fitted instead of generated with a HR)

5 Conclusions

Issues with the clinical evidence

- Most of the clinical issues (key issues 1 to 10 in the EAG report) remain unresolved by the company's response to TE, with the exception of key issues 4 and 8 (see Table 1, and Sections 2.4 and 2.8);
- The EAG considers many of the remaining MAIC-related limitations to be unresolvable uncertainties when using the current comparator studies (Sections 2.3, 2.5, 2.9 and 2.10), but acknowledges that the studies used for Pola + BR and axi-cel comparisons may be the best available sources of evidence. The company could, however, provide more insight into the impact of different PFS definitions highlighted in Section 2.10 for the MAIC vs axi-cel using EPCORE™ NHL-1 IPD;
- However, the EAG still has concerns about the paper used to inform SCHOLAR-1 in the MAIC vs R-based CIT and considers that Crump *et al.* may provide a more robust analysis than Neelapu *et al.,* which is currently used (Sections 2.2 and 2.7.2).[1, 2] Although the EAG acknowledges that some limitations would remain (Section 2.3), the EAG considers that these would be fewer compared to using the Neelapu *et al.* paper;
- The EAG maintains that fully adjusted MAIC results, including adjustment for all reported baseline characteristics in comparator studies, are the most robust results. The EAG acknowledges that the company cites input from clinical experts suggesting fully adjusted MAIC results are not clinically plausible for each comparison and the company's concerns about reducing effective sample size and precision. However, the EAG considers this indicates a lack of comparability between the two studies in each MAIC and may be a result of unreported (and so unadjusted for) difference between studies. This is not a reason to favour a partially adjusted MAIC with imbalances remaining, which only masks their lack of comparability (Section 2.7). As a result, the EAG has concerns about whether any of the MAICs provide robust and reliable results and committee may wish to consider using the lower threshold for cost-effectiveness (£20,000 per QALY) to mitigate this unresolvable uncertainty and reduce decision risk;
- While fully adjusted MAICs have been provided in response to key issue 7 described above and in Section 2.7, the fact that fully adjusted MAICs could not be implemented in the

economic model for comparisons vs Pola + BR and axi-cel remains a limitation (Section 2.12.1) and the company retains a preference for partially adjusted MAIC results;

- Another issue related to the MAIC that remains unresolved is that MAICs vs R-based CIT and Pola + BR did not include an EPCORE™ NHL-1 population that was specific to that defined as population A in the company submission (CS; ineligible for intensive treatments) – the EAG acknowledges that there may be uncertainty with regards to whether comparator studies make the same restriction but considers it a possibility and that it would be useful to see the impact of bringing the EPCORE™ NHL-1 population in line with the definition in the CS;
- The other unresolvable issue concerns the population included in the EPCORE™ NHL-1 trial compared to the population that may be eligible for epcoritamab (Section 2.1) – the EAG considers the population not covered may be small but that it is worth considering in the decision-making process.

Issues with the economic analysis

- For all the analyses, the key drivers of the EAG's exploratory analysis are the following assumptions:
    - Using the EAG-preferred MAIC and survival distributions. The EAG caveats its preferred curves by the fact that these are still unlikely to be flexible enough to provide an accurate representation of the underlying KM data for several survival outcomes, across both treatment arms. Nonetheless, the EAG's approach offers advantages compared to the company's base case approach as it relies on the best-fitting and clinically plausible estimates, while providing a more conservative difference between the fitted curves, which is more representative of the underlying KM data than the company's base case approach.
    - The removal of the assumption that epcoritamab patients stop incurring follow-up costs in the NHS at [redacted] in the model.
    - The reintroduction of the LTR assumption (for the comparisons with Pola + BR and axi-cel).
- The EAG's concerns for the comparison of epcoritamab vs R-based CIT have been somewhat mitigated by the fact that the company has provided the results for the 9/10 adjusted MAIC for epcoritamab vs R-based CIT (scenario A4 in the company's model), and the company's approach to independently fitting survival curves. Nonetheless, the EAG remains concerned that:

- The source used to estimate OS for R-based CIT is not the EAG-preferred Crump *et al.* publication.
- The alternative parametric survival models used by the EAG in the model are unlikely to be flexible enough to accommodate the underlying change in the hazard of the KM OS curves for both treatments. Even though the EAG-preferred distributions provide more clinically plausible long-term survival for epcoritamab, (with [redacted] patients being alive when they would be 90 years old); the fitted curves are likely to underpredict survival when compared to the underlying KM data in both arms.
- The OS curve for R-based CIT is likely to considerably underpredict OS in the long-term for this treatment in the model. This directly impacts the estimated PFS curve for R-based CIT, given the company's approach of applying a HR to the OS R-based CIT curve to estimate the PFS R-based CIT curve.
- The company's assumption to estimate a PFS curve for R-based CIT is based on the OS gain for epcoritamab being proportionately the same as the PFS gain associated with the treatment.
- The company's approach to modelling TTD for R-based CIT overestimates the treatment costs associated with R-based CIT.

- The EAG's concerns for the comparison of epcoritamab vs Pola + BR have been somewhat mitigated by the fact that the company has independently fitted survival curves. Nonetheless, the EAG notes that this analysis is not based on the fully adjusted MAIC epcoritamab curves, therefore, the EAG remains concerned that this analysis is still based on fundamentally flawed data and crucially, that the using the partially adjusted curves in the analysis leads to an overestimation of the survival benefit (both for OS and PFS) associated with epcoritamab when comparted to the fully adjusted MAIC curves. Furthermore, the EAG remains concerned with the following:
  - The EAG-preferred curves used in the exploratory analysis are still likely to underpredict the survival trend observed in the Pola + BR curve as none of the alternative curves provided by the company for Pola + BR were particularly good at replicating the underlying change in hazard observed in the Pola + BR KM data. Therefore, the survival benefit for epcoritamab in comparison with Pola + BR for the partially adjusted MAIC is also overestimated.

- The company's approach to modelling TTD for R-based CIT overestimates the treatment costs associated with Pola + BR.

- The EAG fully adjusted KM OS and PFS curves in population B do not show much of a difference in trajectory to the KM curves used by the company, therefore, the EAG's concerns around the company not using fully adjusted MAIC PFS curves is somewhat mitigated in this comparison. Nonetheless, the EAG remains concerned with the following:
  - The best-fitting curves available for epcoritamab still do not provide the needed flexibility to accurately predict the shape of the underlying KM OS data, therefore the EAG-preferred curves are still likely to overestimate the survival benefit associated with epcoritamab.
  - The EAG remains concerned with the long-term predictions of survival in the epcoritamab curve even when the EAG-preferred curves are used – at 35 years in the model, when patients would be 90 years old, there are still [redacted] of patients alive. Considering the severity of r/r 3L+ LBCL, the EAG is concerned with the plausibility of the long-term survival estimates for epcoritamab in population B.
  - When using the best-fitting curve to estimate TTD for epcoritamab, the mean TTD and mean PFS in the model is [redacted], respectively. Considering the company's original expectation (and the EPCORE™ NHL-1 TTD and PFS data) that epcoritamab is well tolerated and very few patients discontinue due to AEs or toxicity, the EAG considers that a difference of [redacted] in mean time to progression and mean time to discontinuation is an alarming discrepancy, therefore, the treatment costs for epcoritamab remain underestimated in the EAG's exploratory analysis.

- The EAG's original concerns around the company's assumption that clinicians treating patients with epcoritamab in the NHS would decrease their follow-up at [redacted] of treatment remain. The company based this on median PFS in the EPCORE™ NHL-1 trial, which the EAG finds an inappropriate justification. The EAG's clinical experts indicated that they would want to follow epcoritamab patients in the same manner as long as treatment continued, meaning that the resource use estimated by the company for epcoritamab for the progression-free, on treatment period should be observed for as long as treatment is given in the model. For example, in population B, patient are on treatment for [redacted],

however, their follow-up costs decrease to those reflective of a PFS-off treatment state after [redacted] (even though treatment costs are still incurred). The EAG remains of the opinion that the company's base case approach is biased in favour of epcoritamab and artificially underestimates the disease management costs associated with the treatment, without a plausible clinical explanation.

- The EAG reintroduced the LTR assumption for comparator treatments in the model given the EAG's clinical experts' view that patients who have finished treatment with R-based CIT, Pola + BR and axi-cel and are progression-free 2 years after the end of treatment would be considered to be in LTR. The EAG caveats its approach by the following:
    - Given the EAG had to assume the epcoritamab and axi-cel PFS curves become the same in the model after crossing, when the EAG reintroduced the LTR assumption for axi-cel in the model this indirectly applied the LTR assumption to the PFS epcoritamab curves.
    - When the LTR was reintroduced for the Pola + BR curves (which creates a plateau in the PFS Pola + BR curve), the EAG also had to assume that Pola + BR and epcoritamab curves became the same after the crossing of the curves.
    - As originally noted by the EAG's clinical experts, they explicitly stated that a LTR should not be assumed while patients are on treatment (which is the case for epcoritamab patients), therefore the epcoritamab PFS (and OS) curves are likely to be considerably overestimated in the EAG's exploratory analysis.

Finally, the EAG recommends that the company undertakes the following analysis before the first committee meeting:

1. The EAG presents the impact of switching on the LTR assumption in the model for each comparator, 2 years after the end of treatment. The EAG could not conduct the same analysis for epcoritamab as the company's model did not directly track which patients stopped treatment with epcoritamab (as opposed to the comparator treatments which have a fixed duration).
2. Assesses the potential impact of using the population from EPCORE™ NHL-1 that matches the definition of population A in the CS (i.e., patients ineligible to receive CAR-T), both to conduct the MAICs and the utility analysis for population A.

3. Assesses the potential impact of conducting the utility analysis for population B in the DLBCL population.
4. Investigates what is driving the uncertainty in QALYs and costs seen in the PSA results – potentially confirming the EAG view that it comes from the uncertainty embedded in the survival curves used by the company, and the fact that these are key drivers of the economic results (as discussed in the EAG's exploratory analysis in Section 4.1).
5. The option in the model to reintroduce the LTR for axi-cel at 2 years (when the EAG-preferred curves are used) generates higher QALYs associated with the PFS state for axi-cel than epcoritamab, even though the proportion of patients in the PFS epcoritamab curve remains higher (or the same) as that of axi-cel throughout the model. In the limited time available, the EAG could not fully explore the cause of this error or correct it in the model. Therefore, the EAG recommends that the company provides a corrected version of the model for this scenario before the first committee meeting.

6 References

1. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Reagan PM, Miklos DB, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. *Blood advances* 2021; **5**: 4149-55.
2. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017; **130**: 1800-8.
3. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol* 2019; **20**: 31-42.
4. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2020; **38**: 155-65.
5. Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. *Blood advances* 2022; **6**: 533-43.
6. EUnetHTA. PTJA06 – Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, 2020. Available from: https://www.eunethta.eu/ptja06/ Date accessed: Dec 22.
7. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D, et al. Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. *Blood Adv* 2022; **6**: 2920-6.
8. National Institute for Health and Care Excellence (NICE). Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments: Final scope, 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10931/documents/final-scope. Date accessed: May 2023.
9. AbbVie Advisory Board. Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL). 2022.
10. Parker C, Liu FF, Deger KA, Franco-Villalobos C, Proskorovsky I, Keating SJ, et al. Cost-Effectiveness of Lisocabtagene Maraleucel Versus Axicabtagene Ciloleucel and Tisagenlecleucel in the Third-Line or Later Treatment Setting for Relapsed or Refractory Large B-cell Lymphoma in the United States. *Advances in Therapy* 2023; **40**: 2355-74.
11. National Institute for Health and Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies: Technology appraisal guidance [TA872], 2023. Available from: https://www.nice.org.uk/guidance/ta872. Date accessed: Jun 23.
12. National Institute of Health and Care Excellence (NICE). Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma. www.nice.org.uk/guidance/ta649: National Institute of Health and Care Excellence,, 2020 23 September 2020. Report No.
13. Alarcon Tomas A, Fein JA, Fried S, Flynn JR, Devlin SM, Fingrut WB, et al. Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma. *Leukemia* 2023; **37**: 154-63.
14. Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. 5-Year Follow-Up Supports Curative Potential of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1). *Blood* 2023: blood.2022018893.
15. Kuhnl A, Roddie C, Kirkwood AA, Tholouli E, Menne T, Patel A, et al. A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience. *Br J Haematol* 2022; **198**: 492-502.

16. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32**: 3059-68.
17. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25**: 579-86.
18. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data, 2011. Available from: https://www.sheffield.ac.uk/nice-dsu. Date accessed.
19. Mounier N, El Gnaoui T, Tilly H, Canioni D, Sebban C, Casasnovas R-O, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica* 2013; **98**: 1726.
20. Cazelles C, Belhadj K, Vellemans H, Camus V, Poullot E, Gaulard P, et al. Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation. *Leuk Lymphoma* 2021; **62**: 2161-8.

7 Appendix

Figure 52. PFS curves for epcoritamab (lognormal) and for axi-cel (generalised gamma) uncapped

EAG appendix: PFS extrapolations for epcoritamab (adjusted) vs R-based CIT

Company's preferred curves (using scenario A4 for 9/10 adjusted MAIC)

EAG base-case extrapolations (using scenario A4 for 9/10 adjusted MAIC)