NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Incyte

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Lymphoma Action
   b. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Professor Andrew Davies – clinical expert, nominated by Incyte
   b. Dr Kate Cwynarski – clinical expert, nominated by Incyte and National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

8. **Technical engagement responses from consultees and commentators:**
   a. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

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

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Single technology appraisal

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Document B

Company evidence submission

May 2022

File name	Version	Contains confidential information	Date
ID3795 Tafasitamab for DLBCL_NICE Document B_19 May 2022 redacted.docx	**1.0**	**no**	**19 May 2022**

Contents

Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
3L	Third line
4L	Fourth line
ABC	Activated B-cell
ACVBP	Doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisone
ADCC	Antibody-directed cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
AICC	Corrected Akaike Information Criterion
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
ASCT	Autologous stem cell transplant
ASHAP	Doxorubicin, solumedrol, cytarabine, and platinum
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
axi-cel	Axicabtagene ciloleucel
B-ALL	B-cell acute lymphoblastic leukaemia
BCL	B-cell lymphoma
BCR	B-cell receptor
BEAM	Carmustine, etoposide, cytarabine, and melphalan
Benda	Bendamustine
BIA	Budget impact analysis
BIC	Bayesian Information Criterion
BIM	Budget impact model
BL	Baseline
BL	Burkitt's lymphoma
BNF	British National Formulary
BOR	Best overall response
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
BSH	British Society for Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor T-cell

Abbreviation	Definition
CASP	Critical Appraisal Skills Programme
CBC	Complete blood count
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CEA	Cost-effectiveness analysis
CENTRAL	Central Register of Controlled Trials
CEOP	Cyclophosphamide, etoposide, vincristine, prednisone
CEPP	Cyclophosphamide, etoposide, prednisone, procarbazine
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CLP	Chilean peso
CNS	Central nervous system
COO	Cell of origin
Cov	Covariate
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRR	Complete response rate
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CUA	Cost-utility analysis
DA	Dose adjusted
DCR	Disease control rate
DFS	Disease-free survival
DHAOx	Dexamethasone, cisplatin, oxaliplatin
DHAP	Dexamethasone, cisplatin, cytarabine
DLBCL	Diffuse large B-cell lymphoma
DME	Durable medical equipment
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
E/E	Number of events in TAFA+LEN/the observational cohort
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic market information tool

Abbreviation	Definition
ENR	Enrolled
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of treatment
EPAR	European public assessment report
EPIC	Etoposide, ifosfamide, cisplatin
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
ePS	Estimated propensity score
ER	Emergency room
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
EUR	Euro
FACT-CNS	Functional Assessment of Cancer Therapy-Central Nervous System
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Lym	Functional Assessment of Cancer Treatment-Lymphoma
FAS	Full analysis set
Fc	Fragment crystallisable
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FL	Follicular lymphoma
FU	Follow-up
GBP	British pound
GCB	Germinal centre B-cell
GDP	Gemcitabine, dexamethasone, cisplatin or carboplatin
GDP	Gross domestic product
GEMOX	Gemcitabine, oxaliplatin
GEP	Gastroenteropancreatic
GHS	Global Health Status
HAS	Haute Autorité de Santé
HBV	Hepatitis B virus
HCRU	Healthcare resource utilisation
HDC	High-dose chemotherapy
HE	Health economic
HHA	Home health agency
HIV	Human immunodeficiency virus
HR	Hazard ratio

Abbreviation	Definition
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HTA	Health technology assessment
HUI	Health Utility Index
IAS	Immunogenicity analysis set
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IEV	Ifosfamide, etoposide, epirubicin
IGEV	Ifosfamide, gemcitabine, vinorelbine, prednisone
IHC	Immunohistochemistry
IMiD	Immunomodulatory drug
INV	Investigator
IPI	International Prognostic Index
IQR	Interquartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRC	Independent radiology/clinical review committee
ITT	Intent to treat
IV	Intravenous
IVIg	Intravenous immunoglobin
IWGRC	International Working Group Response Criteria
JPY	Japanese yen
KM	Kaplan-Meier
KOL	Key opinion leader
LBCL	Large B-cell lymphoma
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LFT	Liver function test
liso-cel	Lisocabtagene maraleucel
LOS	Length of stay
LY	Life year
LYG	Life years gained
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MAS	Matched analysis set
MAS_Cal	Matched analysis set with calliper
MCID	Minimal clinically important difference
MCM	Mixture-cure model

Abbreviation	Definition
MDASI	MD Anderson Symptom Index
mFAS	Modified full analysis set
MID	Minimally important difference
MINE	Mesna, ifosfamide, mitoxantrone, etoposide
mMAS	Modified matched analysis set
MOA	Mechanism of action
mOb	Modified observational
MRI	Magnetic resonance imaging
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NEAE	Neurologic adverse event
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NMB	Net monetary benefit
NN	Nearest-neighbour
NR	Not reported
NYHA	New York Heart Association
Ob	Observational
ONS	Office of National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
p.o.	Taken orally
pALL	Paediatric acute lymphoblastic leukaemia
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PET	Positron emission tomography
PFLY	Progression-free life year
PFS	Progression-free survival
PICOS	Population, intervention, comparators, outcomes, and study design
PIM	Promising innovative medicine
PIX	Pixantrone
PKAS	Pharmacokinetic analysis set
PLL	Prolymphocytic leukaemia
PMBCL	Primary mediastinal B-cell lymphoma
PMPM	Per member per month

Abbreviation	Definition
Pola	Polatuzumab vedotin
Pola-BR	Polatuzumab vedotin with bendamustine and rituximab
PPS	Per protocol set
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
P-VEBEC	Prednisone, vinblastine, epirubicin, bleomycin, etoposide, cyclophosphamide
PYE	Patient-years of exposure
Q	Quartile
QALY	Quality-adjusted life year
QoL	Quality of life
R	Rituximab
R/R	Relapsed/refractory
RBC	Red blood cell
BR	Rituximab-bendamustine
R-CHOP	Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy
RCT	Randomised controlled trial
R-CyclOBEAP	Rituximab, cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, and prednisolone
R-DECC	Rituximab, dexamethasone, etoposide, chlorambucil, lomustine
REAL	Revised European American Lymphoma
R-Gem	Rituximab with gemcitabine
R-GemOx	Rituximab in combination with gemcitabine, oxaliplatin
RIPD	reconstructed individual-patient data
RL	Relapse
R-P-MitCEBO	Rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine
RR	Response rate
R-THP-COP	Rituximab, cyclophosphamide, vincristine, prednisolone, and pirarubicin
Saa	Secondary age-adjusted
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCR	Salvage chemotherapy regimen
SCT	Stem cell transplantation

Abbreviation	Definition
SD	Stable disease
SD	Standard deviation
SE	Standard error
SF-12	12-Item Short Form Health Survey
SF-36	36-item Short Form health survey
SF-36	36-Item Short Form Health Survey
SF-6D	Short-Form Six-Dimension
SGD	Singapore dollar
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SmPC	Summary of product characteristics
SNF	Skilled nursing facility
SoC	Standard of care
SSA	Sub-Saharan Africa
STA	Single technology assessment
TA	Technology appraisal
TAFA+LEN	Tafasitamab + lenalidomide
TEAE	Treatment-emergent adverse event
TFI	Treatment-free interval
tisa-cel	Tisagenlecleucel
TTD	Time to discontinuation
TTNT	Time-to-next treatment
TTP	Time to progression
Tx	Treatment
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	United States dollar
VAS	Visual analogue scale
WTP	Willingness to pay

Tables and figures

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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 DLBCL and who are not eligible for ASCT	Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for ASCT.	N/A
Intervention	Tafasitamab with lenalidomide followed by tafasitamab monotherapy	Tafasitamab (Minjuvi®) in combination with lenalidomide, followed by tafasitamab monotherapy	N/A
Comparator(s)	Established clinical management without tafasitamab which may include: • chemotherapy with or without rituximab: R-GemOx (rituximab, gemcitabine oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine), (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (bendamustine, rituximab) • pixantrone • polatuzumab vedotin in combination with bendamustine and rituximab (Pola-BR) best supportive care	The following comparators are considered for the submission: • Pola-BR • rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) • rituximab in combination with bendamustine (BR)	Although the scope identifies other rituximab and chemotherapy regimens, clinical experts interviewed as part of a UK advisory board confirmed that Pola-BR, R-GemOx and BR were the most relevant comparators.
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • response rates • adverse effects of treatment	Efficacy endpoints considered in the submission include: • OS • PFS) • response rates (e.g. complete response [CR], partial response [PR]) • adverse effects of treatment	N/A. The outcomes specified in the scope are included in the submission, with the addition of TTD endpoint used to evaluate time on treatment for the economic model; additional data e.g., duration of response (DoR) are

<table>
<tr><th></th><th>Final scope issued by NICE</th><th>Decision problem addressed in the company submission</th><th>Rationale if different from the final NICE scope</th></tr>
<tr><td></td><td>health-related quality of life</td><td>• health-related quality of life
• time to treatment discontinuation or death (TTD)
Safety Endpoints:
• Adverse Events (AEs)
• Serious Adverse Events (SAEs)
• AEs leading to a permanent discontinuation of study drug, a dose reduction or dose interruption</td><td>also discussed as supportive clinical evidence.</td></tr>
<tr><td>Economic analysis</td><td>Economic analysis</td><td></td><td></td></tr>
<tr><td>Subgroups to be considered</td><td>N/A</td><td></td><td></td></tr>
<tr><td>Perspective for outcomes</td><td></td><td>NHS healthcare</td><td></td></tr>
<tr><td>Perspective for costs</td><td></td><td>NHS healthcare</td><td></td></tr>
<tr><td>Time horizon</td><td></td><td>45</td><td></td></tr>
<tr><td>Synthesis of evidence on health effects</td><td></td><td>N/A</td><td></td></tr>
<tr><td>Measuring and valuing health effects</td><td></td><td><table><tr><td>OS</td><td>Lognormal distribution for TAFA+LEN based on L-MIND
Lognormal distribution for R-GemOx and constant HR for BR based on RE-MIND2
Time-varying HRs with 4-month split for Pola-BR-based on MAIC</td></tr><tr><td>PFS</td><td>Generalised gamma distribution for TAFA+LEN based on L-MIND
Lognormal distribution for R-GemOx and BR-based on RE-MIND2
Time-varying HRs with 4-month split for Pola-BR-based on MAIC</td></tr></table></td><td></td></tr>
</table>

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		TTD: Lognormal distribution for tafasitamab; KM curves for other (fixed duration) treatments AE frequency: Various AE duration: Various	
Source of data for measurement of health-related quality of life		N/A	
Source of preference data for valuation of changes in health-related quality of life		NICE TA559(1)	
Equity considerations		N/A	
Evidence on resource use and costs		NHS reference costs 2019/20.(2) PSSRU Unit Costs of Health and Social Care 2020(3) L-MIND CSR(4) NICE TA649(5) NICE TA567(6)	
Discounting		3.5%	

Abbreviations: AE = adverse event; ASCT = autologous stem cell transplant; BR = rituximab in combination with bendamustine; CR = complete response; DLBCL = diffuse large B-cell 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 bendamustine and rituximab; PR = partial response; R-DECC = rituximab, dexamethasone, etoposide, chlorambucil, lomustine; PSS = Personal Social Services; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; R-Gem = rituximab in combination with gemcitabine; R-P-MitCEBO = rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine; SAE = serious adverse event; TTD = time to treatment discontinuation or death; UK = United Kingdom

B.1.2. Description of the technology being appraised

A summary of tafasitamab is shown in Table 2, and the draft summary of product characteristics is included in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	**Tafasitamab (MINJUVI®)**
Mechanism of action	Tafasitamab is an Fc-enhanced monoclonal antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes.(7) Upon binding to CD19, tafasitamab mediates B-cell lysis through:(7) • Engagement of immune effector cells like natural killer cells, γδ T cells and phagocytes • Direct induction of cell death (apoptosis) The Fc modification results in enhanced antibody dependent cellular cytotoxicity and antibody dependent cellular phagocytosis. Tafasitamab in combination with lenalidomide resulted in increased cytotoxicity in vitro, greater than the effects of either agent alone.(7) Tafasitamab has potential synergy with lenalidomide, an immunomodulatory agent that enhances the activity and recruitment of NK cells, and that has been shown to enhance NK-cell mediated antibody directed cellular cytotoxicity in pre-clinical studies.(8)
Marketing authorisation/CE mark status	Approved by EMA August 2021 (9) UK product licence granted 8 Oct 2021. EMA Orphan Designation also accepted by MHRA(10)
Indications and any restriction(s) as described in the summary of product characteristics	Tafasitamab is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT.(9)
Method of administration and dosage	The recommended dose of tafasitamab is 12 mg per kg body weight administered as an intravenous infusion according to the following schedule: Cycle 1: infusion on day 1, 4, 8, 15 and 22 of the cycle. Cycles 2 and 3: infusion on day 1, 8, 15 and 22 of each cycle. Cycle 4 until disease progression: infusion on day 1 and 15 of each cycle. Each cycle has 28 days. In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 25 mg daily on days 1 to 21 of each cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide SmPC. Tafasitamab plus lenalidomide in combination is given for up to 12 cycles. Treatment with lenalidomide should be stopped after a maximum of 12 cycles of combination therapy. Patients should continue to receive tafasitamab infusions as single agent on day 1 and 15 of each 28 day cycle, until disease progression or unacceptable toxicity. Dose modifications For dose modifications regarding lenalidomide, please refer to the lenalidomide SmPC.

UK approved name and brand name	**Tafasitamab (MINJUVI®)**
Additional tests or investigations	No additional tests or investigations
List price and average cost of a course of treatment	£705 per vial of tafasitamab containing 200 mg powder for concentrate for solution for infusion. Assuming a mean patient weight of [redacted] for tafasitamab, and [redacted] for lenalidomide, expected treatment costs for TAFA+LEN are [redacted]
Patient access scheme (if applicable)	Incyte has submitted application for a simple PAS (pending approval by PASLU). Refer to PAS submission for this appraisal.

Abbreviations: ADCC = antibody-directed cellular cytotoxicity; ASCT = autologous stem cell transplant; CE = cost-effectiveness; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; Fc = fragment crystallisable; NK = natural killer; 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

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of haematological malignancies that originate in the lymphocyte cells of the immune system.(11) Approximately 90% of NHL originates from B cells (B-cell lymphoma) and the remaining cases of NHL originate from T cells or natural killer (NK) cells. There are at least 30 subtypes of mature B-cell NHL malignancies, which are classified into high- and low-grade NHL subtypes.(11) The high-grade subtypes have a worse prognosis than the low-grade forms. Diffuse large B-cell lymphoma (DLBCL) is a high-grade subtype of B-cell NHL.(11)

DLBCL is classified as a rare disease, and represents approximately 40% of all newly diagnosed NHL cases.(11-13) DLBCL is composed of large neoplastic B lymphoid cells expressing pan B-cell antigens, including CD19 and CD20.(14) While there is no single cytogenetic change that is typical or diagnostic of DLBCL, genetic abnormalities are common.(14) As a result, treatment is focused on B-cell antigen expression (Section B.1.3.5.).

B.1.3.2. Epidemiology

DLBCL affects approximately 2.5 in 10,000 people in the European Union (EU).(15) In the United Kingdom (UK), the Office of National Statistics (ONS) suggests that there will be approximately 4,826 new cases of DLBCL each year. Patients with newly diagnosed DLBCL are generally older (median age of 66 years) and there is a slightly higher incidence of DLBCL in men.(11, 16, 17)

B.1.3.3. Prognosis

Although DLBCL is aggressive if left untreated, patients display high response rates to chemotherapy in the first line (1L), ranging from 88% to 91% depending on the classification system used. In the UK, the five-year survival rate for patients with 1L DLBCL therapy is approximately 61%.(18)

Despite good initial response rates, between 10% and 20% of patients with DLBCL are refractory to standard 1L chemotherapy,(19-22) and another 30% of patients will ultimately relapse.(23, 24) There has been limited improvement in the survival of adults with DLBCL at subsequent lines of therapy.

In patients with relapsing DLBCL, less than half of patients will survive the 12 months following diagnosis (41%; median survival, 10 months).(25) Age is an important prognostic indicator in patients with DLBCL who relapse—patients aged ≥65 years have a worse prognosis than those younger than 65.(25)

Prognosis is worse for patients who are refractory to 1L therapy. Median overall survival was 6.3 months, with only 22% of patients alive at two years, in a large pooled retrospective analysis of patients with refractory DLBCL (SCHOLAR-1 study).(26)

Patients with relapsed/refractory (R/R) DLBCL have a worse prognosis and a greater symptomatic burden than patients with newly diagnosed DLBCL due to the progressive nature of the disease and the cumulative adverse effects of intensive treatment.

B.1.3.4. Disease burden

Patient burden

Patients with DLBCL typically present with a rapidly enlarging lymphadenopathy, most commonly a nodal enlargement in the neck or abdomen, and systemic symptoms that require immediate treatment.(27) Systemic "B" symptoms (i.e., fever, weight loss, drenching night sweats, fatigue and pruritus) are observed in approximately 30% of patients.(12, 20)

Approximately 60% of patients will present with advanced-stage DLBCL (Ann Arbor stage III or IV disease). In approximately 40% of cases, the disease arises in extranodal medullary tissues.(28)

While data on the impact of DLBCL on patients' quality of life (QoL) are limited, it is well established that patients with high-grade NHL demonstrate a lower QoL compared with patients with low-grade NHL, including physical, social/family, emotional factors and functional well-being.(29) Patients with high-grade NHL also demonstrate higher levels of anxiety than patients with low-grade NHL.(29) The negative impact of high-grade NHL on patient QoL has been attributed to(30):

- Uncertainties around disease prognosis
- Side effects of treatment
- Fear of relapse

Patients who achieve a complete response (CR) after 1L treatment have demonstrated significant improvements in QoL compared with patients not achieving a CR.(31) Patients who are relapsed or refractory to first line treatment experience worse health-related QoL (HRQoL) due to the poorer prognosis of their condition and the need for additional, often more intensive subsequent treatment.(31). Achieving a CR even in later lines of treatment is therefore a key treatment goal in patients with R/R DLBCL.

Healthcare burden

DLBCL is the most costly lymphoma to treat in Europe, when compared with Hodgkin's lymphoma and follicular lymphoma. This is mainly driven by inpatient hospital stays, medication, and productivity loss.(32) DLBCL treatment across all lines of therapy is complex, involving multiple sites of care and treatment types.(33)

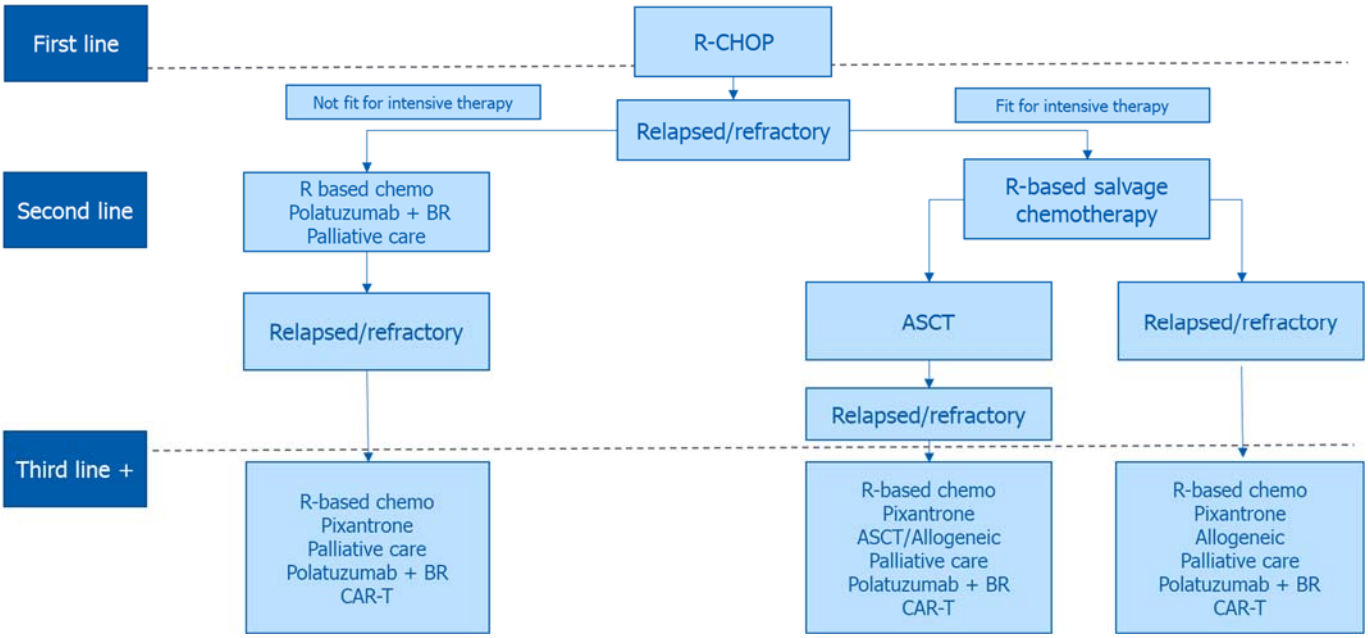
In a prevalence-based estimate of costs in the UK, the total cost associated with treating new patients with DLBCL over a one-year period was approximately £88 to £92 million.(34) However, limited cost studies have been completed for treatments used in later lines.

B.1.3.5. Clinical pathway of care

The treatment pathway for patients with DLBCL, including R/R DLBCL, is provided by National Institute for Health and Care Excellence (NICE) 2016 guidance NG52, the British Society for Haematology (BSH), the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN).(1, 5, 6, 24, 35, 36) Subsequent to the publication of these guidelines, new treatments have become available which have been included in the treatment pathway.(1, 5, 6)

An overview of the treatment pathway is shown in Figure 1.

Figure 1. NICE-recommended treatment pathway for R/R DLBCL – updated to reflect current UK clinical practice



Sources: NICE guidance NG52;(36) NICE technology appraisal (TA)649;(5) NICE TA567;(6) NICE TA559;(1) NICE TA306;(35) Tilly 2015(24)

Abbreviations: ASCT = autologous stem cell transplant; BR = bendamustine with rituximab; CAR-T = chimeric antigen receptor T-cell; R = rituximab; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R = relapsed/refractory

1L treatment

SoC 1L therapy for DLBCL is chemoimmunotherapy, usually comprising rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (R-CHOP).(24, 36)

2L treatment

Patients who relapse or are refractory to 1L treatment have a poor prognosis and few available and effective treatment options.(37, 38) The first step of R/R DLBCL treatment is to assess whether the patient is fit for intensive salvage therapy and potentially for autologous stem cell transplant (ASCT).(38)

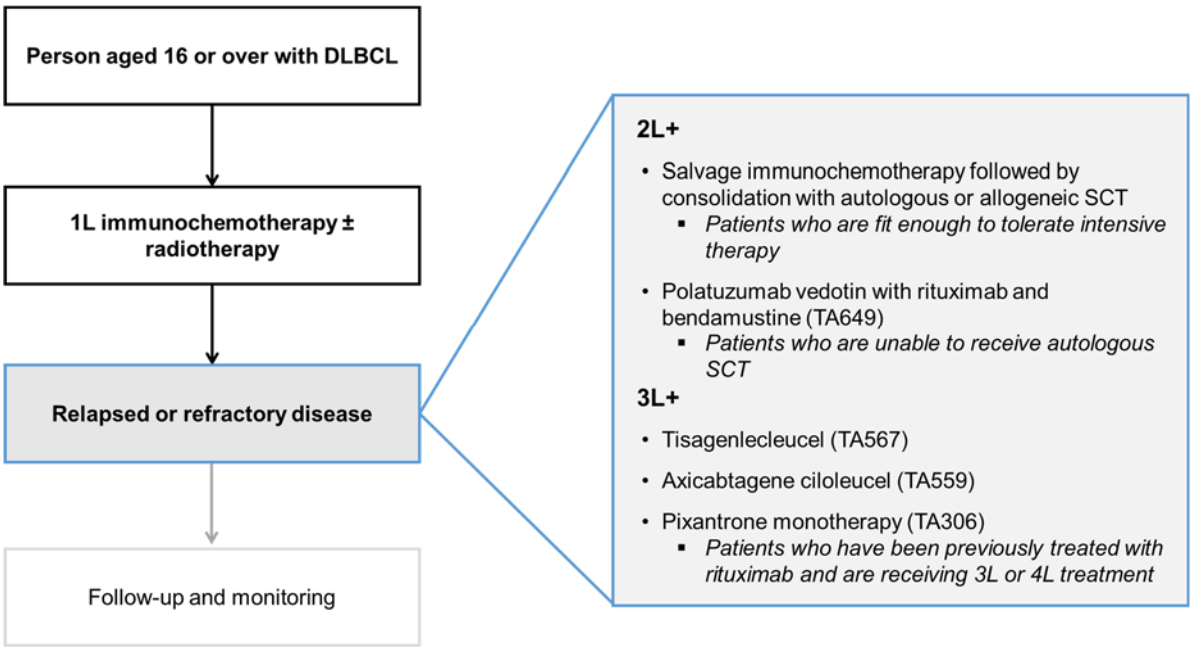
Approximately 50% of patients are not transplant eligible, either because they are: 1) chemo-refractory to salvage chemotherapy administered prior to ASCT; 2) they have advanced disease or comorbidities, severe concomitant medical or psychiatric illness, active central nervous system involvement or human immunodeficiency virus (HIV) seropositivity; or 3) they have treatment failure following a prior ASCT.(39, 40)

Not all eligible patients go on to receive a transplant. Retrospective studies have shown that only 25% to 38% of patients who relapsed following rituximab chemotherapy underwent ASCT.(24, 39)

Transplant-ineligible patients

There is no clear SoC for patients with R/R DLBCL who are unable to tolerate intensive therapy or are ineligible for ASCT. As the guidelines were developed prior to the availability of newer targeted therapies, such as polatuzumab vedotin with bendamustine and rituximab (pola-BR) and chimeric antigen receptor T-cell (CAR-T)-cell therapies, the suggested treatment options for patients who relapse and are not eligible for transplant are clinical studies with novel drugs or palliative care. Current NICE recommendations for patients with R/R DLBCL who are ineligible for transplant in the UK are shown in Figure 2. The treatment goal remains the same across the guidelines and guidance's being improving and prolonging survival.(41)

Figure 2. Current NICE recommendations for patients with R/R DLBCL who are not eligible for transplant



Source: Adapted from NICE pathways: Treating diffuse large B-cell lymphoma(41)
Abbreviations: 1L = first line; 2L+ = second line or later; 3L = third line; 3L+ = third line or later; 4L = fourth line; DLBCL - diffuse large B-cell lymphoma; SCT = stem cell transplant; TA = technology appraisal

SCHOLAR-1 is the largest international, retrospective, patient-level, pooled-analysis to evaluate response and survival rates in patients with R/R-DLBCL. These data

are particularly important because they represent a large number of patients treated in the modern rituximab era. Patient-level data were collected from medical records for patients with refractory DLBCL.(26)

The study (pooled N=636) revealed a median overall survival (OS) of 6.3 months (95% confidence interval [CI]: 5.9, 7.0 months), with a one-year survival rate of 28% and a two-year OS of 20%. Patients achieved a response rate (RR), CR and partial response (PR) of 26% (95% CI: 21%, 31%), 7% (95% CI: 3%, 15%), and 18% (95% CI: 13%, 23%), respectively.(26) The data show that even with the availability of multiple rituximab-based regimens, outcomes among patients with R/R DLBCL remain dismal—a finding which underlines the high unmet need of this patient population.

A recent systematic review by Vander Velde et al., (2019),(42) identified 19 studies of patients with R/R DLBCL, of which six studies were randomised controlled trials (RCT) and 13 were prospective, observational, single-arm trials.(42) The review reported a median progression-free survival (PFS) range of 2.6 to 17.1 months (n=11 studies) and an OS of 5.0 to 22.2 months (n=11 studies) in patients with R/R DLBCL. It further concluded that there was a paucity of published RCTs demonstrating comparative efficacy of R/R DLBCL treatments which in turn reflected the lack of proven treatment options in this stage of the pathway.(42)

A UK, single-centre, retrospective analysis of patients with DLBCL who had an R/R event demonstrated an objective response rate (ORR) of 46.1% in the 2L, 27.0% in the 3L, and 9.8% in the fourth line (4L) and later. Overall, patients with R/R DLBCL had a two-year OS of 30.6%.(43) Detailed response rates are shown in Table 3.

Table 3. Treatment response in patients with R/R DLBCL by line of treatment (Christie National Health Service Foundation Trust Database, 2011 to 2017)

Line of therapy	R/R DLBCL (n)	CR% (95% CI)	PR% (95% CI)	Median OS (days) (95% CI)
2L	89	27.0 (18.4, 37.6)	19.1 (11.8, 29.1)	320 (276, 490)
3L	63	17.5 (9.5, 29.5)	9.5 (3.9, 20.2)	195 (123, 287)
4L+	41	2.4 (0.1, 14.4)	7.3 (1.9, 21.0)	88 (70, 125)

Source: Radford et al, 2019(43)

Abbreviations: 2L = second line; 3L = third line; 4L+ = fourth line and later; CI = confidence interval; CR = complete response; OS = overall survival; PR = partial response

Pola-BR

ESMO and BSH recommendations were developed prior to the availability of pola-BR.(24, 44) In the 2L setting, patients who are transplant ineligible may now receive pola-BR.

Polatuzumab vedotin (pola) is a CD79b-targeted antibody drug conjugate delivering a microtubule inhibitor. CD79b is a signalling component of the B-cell receptor located on most mature B-cell malignancies, including >95% of DLBCL.

Pola-BR was compared with BR in a randomly assigned multicohort of patients (N=80) with transplant-ineligible R/R DLBCL. Patients aged ≥18 years were eligible if they had biopsy-confirmed R/R DLBCL (excluding transformed lymphoma) after ≥1 prior line of therapy, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, grade ≤1 peripheral neuropathy, and were considered transplantation ineligible by the treating physician or experienced treatment failure with prior ASCT.(21)

In 40 patients with R/R DLBCL, pola-BR demonstrated an ORR of 45%, a CR rate of 40%, a median PFS of 9.5 months (95% CI: 6.2, 13.9 months), and OS of 12.4 months (9.0 months, not reached). In the pola-BR treatment arm, 33.3% of patients discontinued all treatment due to adverse events (AE), most commonly thrombocytopaenia and neutropaenia. Peripheral neuropathy (including peripheral motor neuropathy, peripheral sensory neuropathy, decreased vibratory sense, hypaesthesia and paraesthesias) occurred in 43.6% of patients in the pola-BR combination treatment arm (all grades 1 to 2) and resulted in treatment delays in one patient.(21)

Pola-BR has some limitations. The treatment targets the CD20 antigen, which has been shown to undergo a negative transformation (or loss of expression) in up to 60% of patients after treatment with rituximab-containing chemotherapy.(45-48) Therefore, pola-BR may not be appropriate for treatment in this potentially large proportion of patients who experience a loss of CD20 antigen expression after rituximab therapy.

Subsequent lines of treatment

CAR T-cell therapies and pixantrone monotherapy are currently funded by NICE in the 3L setting.

CAR-T therapy may be offered via the Cancer Drugs Fund if the patient is healthy enough to undergo the treatment and has had ≥2 lines of prior systemic therapy.(24, 49)

While pixantrone monotherapy is currently recommended by NICE in the 3L and 4L settings, limited efficacy data in the real world (median OS 3.4) have restricted its use in clinical practice.(50) In addition, interviews with clinical experts in the UK did not consider pixantrone a suitable treatment option in this patient population.{Incyte Corporation, 2020 #316}

B.1.3.6. Tafasitamab and its place in therapy

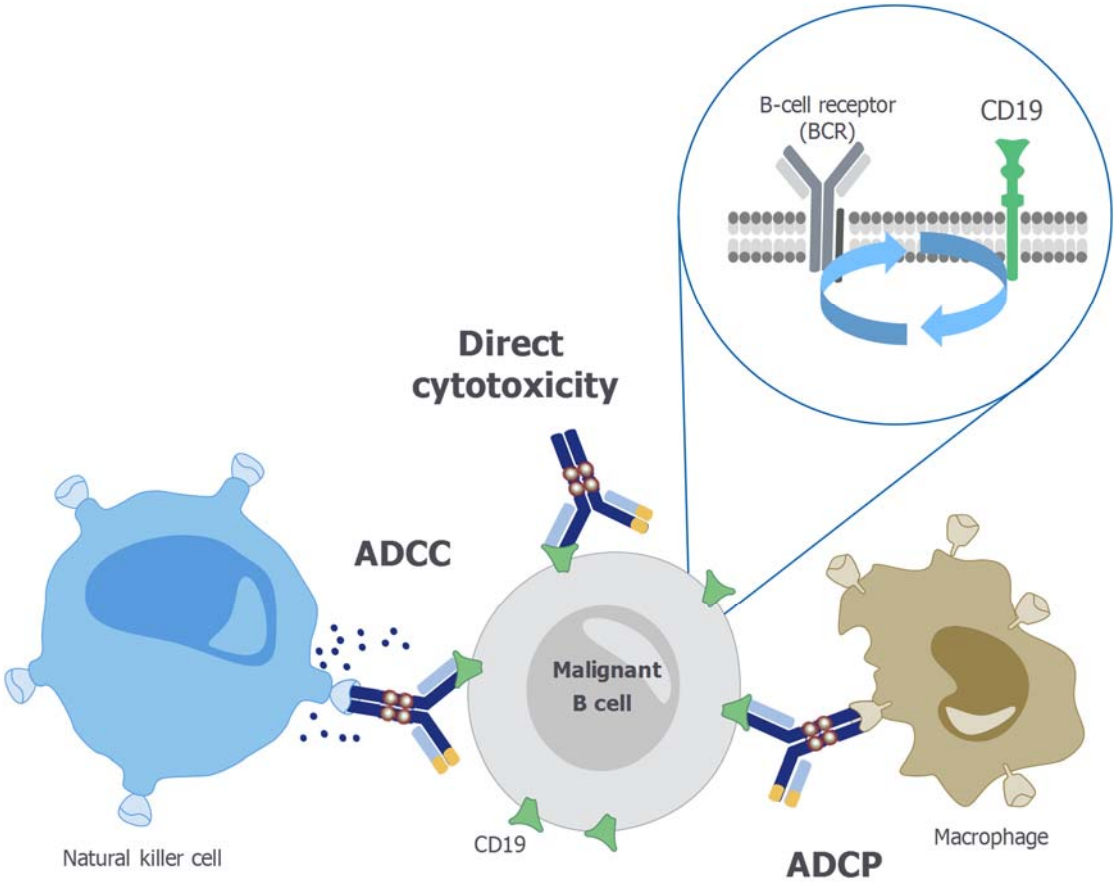
Patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant have no established SoC. While the treatment aim remains to improve and prolong survival, recent data suggests poor overall survival with currently available treatment options.(43)

Tafasitamab is a novel treatment that has shown efficacy as a single agent in patients with DLBCL (Section B.1.2.). Tafasitamab was granted orphan designation by the European Medicines Agency (EMA) in 2014; in 2021, orphan designation was maintained by the EMA and granted by the MHRA for tafasitamab for the treatment of DLBCL.(10)

Tafasitamab is a fragment crystallisable (Fc)-enhanced mAb that targets the CD19 antigen expressed on the surface of pre-B and mature B-lymphocytes across different B-cell malignancies, including DLBCL. Upon binding to CD19, tafasitamab mediates B-cell lysis through the engagement of immune effector cells like NK cells, γδ T cells and phagocytes, and direct induction of cell death (apoptosis). The Fc modification results in enhanced antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP; Figure 3).(7)

Preclinical data suggested that tafasitamab acts synergistically with lenalidomide, an immunomodulatory agent that enhances the activity and recruitment of NK cells, and that has been shown to enhance NK cell-mediated antibody-directed cellular cytotoxicity).(51-53) The novel mechanism of action of tafasitamab with lenalidomide is an innovative treatment approach that has been demonstrated to be an effective, well-tolerated, immunomodulatory, chemotherapy-free treatment option for patients with R/R DLBCL who are ineligible for ASCT or who have relapsed after ASCT (Section B.2.6.).(54)

Figure 3. Tafasitamab mechanism of action



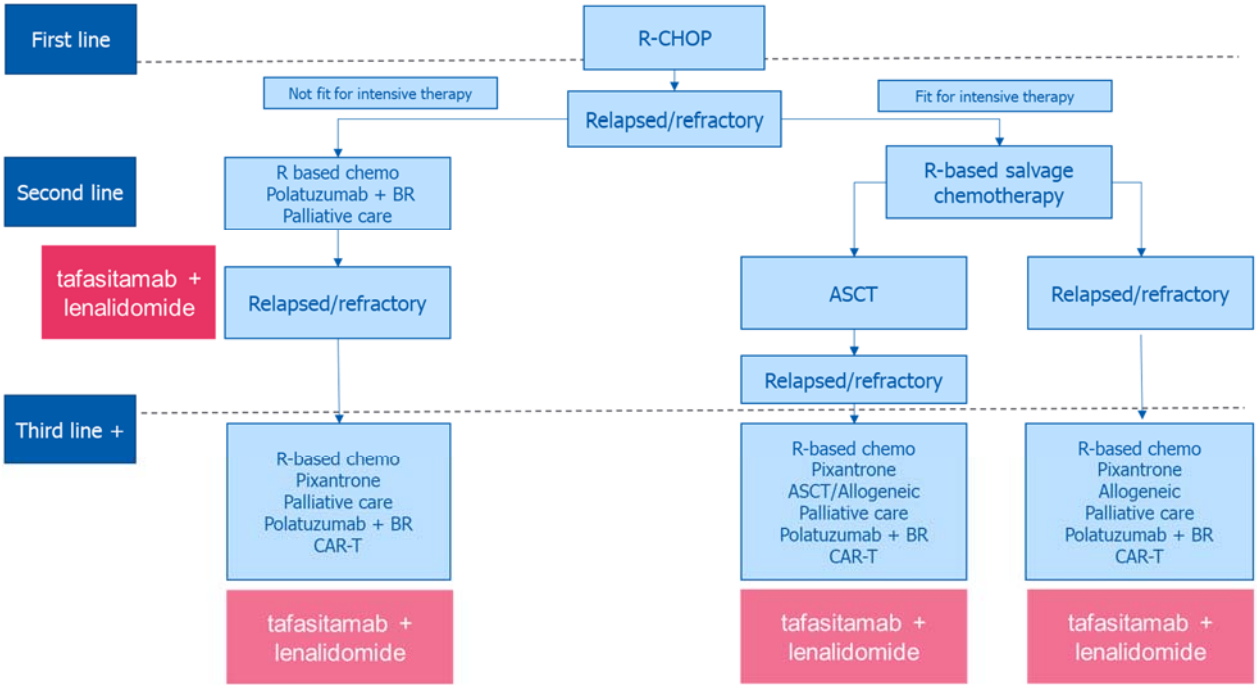
Source: Poe et al., 2012(55)

Tafasitamab is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adults with R/R DLBCL who are not eligible for ASCT.(9) Figure 4 shows the proposed placement of tafasitamab + lenalidomide (TAFA+LEN) in the treatment of patients with R/R DLBCL who are not eligible for ASCT.

The following patients could be considered eligible for TAFA+LEN

- R/R 2L patients who are ineligible for ASCT
- R/R 3L patients (or beyond) who are ineligible for ASCT (including those who relapse following ASCT or receive salvage chemotherapy but fail to respond, and are therefore considered transplant ineligible)

Figure 4. Proposed place for tafasitamab in the pathway of care for patients with R/R DLBCL who are transplant ineligible – updated to reflect current UK clinical practice



Sources: NICE guidance NG52;(36) NICE technology appraisal (TA)649;(5) NICE TA567;(6) NICE TA559;(1) NICE TA306;(35) Tilly 2015(24)

Abbreviations: ASCT = autologous stem cell transplant; BR = bendamustine with rituximab; CAR-T = chimeric antigen receptor T-cell; R = rituximab; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R = relapsed/refractory

The combination therapy of TAFA+LEN followed by tafasitamab monotherapy is being studied in the pivotal L-MIND study described in Section B.2.9. Data supporting long-term maintenance of response with tafasitamab monotherapy following TAFA+LEN are also presented. Evidence of the clinical effectiveness of the combined therapy is also supported by an indirect comparison with the RE-MIND study, a retrospective chart review of patients with R/R disease treated with lenalidomide monotherapy and the RE-MIND2 retrospective chart review study of

patients with R/R disease receiving other treatments that are routinely administered in clinical practice. The comparative efficacy results are presented in Section B.2.9.

B.1.4. Equality considerations

There are no known equality issues relating to the use of tafasitamab in patients with R/R DLBCL who are not eligible for ASCT.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence in R/R DLBCL. Searches were conducted on 9 February 2021 and updated on 29 June 2021. A total of nine reports were identified from 32 unique studies. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are included in Appendix D.

B.2.2. List of relevant clinical-effectiveness evidence

B.2.2.1. L-MIND phase II study (TAFA+LEN)

The submission is supported by data on the safety and efficacy of TAFA+LEN from the pivotal, phase II, open-label, single-arm, multicentre L-MIND study (MOR208C203; NCT02399085). Data sources for L-MIND included Salles et al., 2020,(53) the L-MIND clinical study reports (CSR),(56, 57) Salles et al., 2020 European Hematology Association,(58), Duell et al., 2021(54) and Incyte data on file. Table 4 summarises the L-MIND study.

Table 4. Clinical-effectiveness evidence—L-MIND (MOR208C203)

Study	**L-MIND**
Study design	Open-label, single-arm, multicentre, phase II study
Population	Adults with R/R DLBCL ineligible for ASCT
Intervention(s)	Cycle 1 – Weekly, with additional loading dose on D4 Cycle 2-3 – weekly Cycle 4-12 – every 2 weeks Len given orally for 21/28 day cycle.

Study	L-MIND				
Comparator(s)	NA				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	The L-MIND study provides the pivotal clinical-effectiveness and safety data for TAFA+LEN in the treatment of adults with R/R DLBCL who are not eligible for ASCT; it forms the basis for the cost-effectiveness model.				
Reported outcomes specified in the decision problem*	Best ORR (assessed by IRC) Best ORR (by INV) DCR DoR **PFS** TTP assessed by INV TTP assessed by IRC **OS** TTNT Safety of TAFA+LEN				
All other reported outcomes*	N/A				

*Outcomes marked in bold are incorporated into the economic model.
Source: Salles et al., 2020(53)

Abbreviations: ASCT = autologous stem cell transplantation; DCR = disease control rate; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; INV = investigator; IRC = independent radiology/clinical review committee; IV = intravenous; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R/R = relapsed or refractory; TAFA+LEN = tafasitamab + lenalidomide; TTNT = time-to-next treatment; TTP = time to progression

B.2.2.2. MOR208C201 phase IIa study – DLBCL cohort (tafasitamab monotherapy)

Additional supportive data with tafasitamab monotherapy are provided by the DLBCL cohort of the phase IIa, open-label, multicentre MOR208C201 study in patients with R/R B-cell NHL (Table 5).

Table 5. Clinical-effectiveness evidence—MOR208C201

Study	MOR208C201, NCT01685008
Study design	Open-label, single-arm, multicentre, phase IIa study. The study employed a two-stage design where the decision to further enrol any NHL subtype in stage 2 depended on the best responses after 2 or 3 cycles in stage 1.
Population	Adults with R/R B-cell NHL who have received ≥1 prior therapy containing rituximab. The study enrolled patients from four different NHL subtypes: follicular lymphoma, DLBCL, mantle-cell lymphoma, and other indolent NHL (e.g., marginal zone lymphoma and mucosa-associated lymphoid tissue lymphoma).
Intervention(s)	IV tafasitamab (12 mg/kg) for up to two cycles (28 days each) for a total of eight infusions. Those with a PR or CR after 12 weeks could receive extended tafasitamab treatment (12 mg/kg, either monthly or every second week) until progression.

Study	**MOR208C201, NCT01685008**				
Comparator(s)	NA				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	
	No			No	✓
Rationale for use/non-use in the model	The model is based on the pivotal, phase II, L-MIND study of the TAFA+LEN combination in adult patients with R/R DLBCL who are not eligible for transplant.(53)				
Reported outcomes specified in the decision problem	NA				
All other reported outcomes	ORR (ORR=CR + PR) as assessed by IRC DoR TTP PFS				

*Outcomes marked in bold are incorporated into the economic model.
Source: Incyte, data on file (MOR208C201 CSR)(59)

Abbreviations: CR = complete response; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; IRC = independent radiology/clinical review committee; IV = intravenous; NA = not applicable; NHL = non-Hodgkin's lymphoma; ORR = objective response rate; PFS = progression-free survival; PR = partial response; R/R = relapsed or refractory; TAFA+LEN = tafasitamab + lenalidomide; TTP = time to progression

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

A summary of the L-MIND methodology is provided in Table 6.

Table 6. L-MIND methodology

Trial number(s)	**MOR208C203; NCT02399085**
Location of study centres	L-MIND (MOR208C203) enrolled participants at 35 academic and community centres in Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, UK, and the US.
Study design	A phase II, open-label, single-arm, multicentre study to evaluate the efficacy and safety of TAFA+LEN in adults with R/R DLBCL who were ineligible for HDC and ASCT.
Study objectives	Primary: To determine the activity of a combination of TAFA+LEN in terms of ORR (ORR=CR + PR) in adults with R-R DLBCL
Key inclusion/exclusion criteria	Key inclusion criteria: • Age ≥18 years • Histologically confirmed diagnosis of: o DLBCL not otherwise specified o T-cell/histiocyte rich large B-cell lymphoma o EBV-positive DLBCL of the elderly (EBV-positive DLBCL) o Grade 3b follicular lymphoma o Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/WHO classification

Trial number(s)	MOR208C203; NCT02399085
	○ Histological transformation to DLBCL from an earlier diagnosis of low-grade lymphoma (e.g., an indolent pathology such as follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukaemia) into DLBCL with a subsequent DLBCL relapse • Available sample of fresh tumour tissue for central pathology review and correlative studies. If it was not possible to obtain a fresh tumour tissue sample from the patient, archival paraffin-embedded tumour tissue acquired ≤3 years prior to screening for the study had to be available for this purpose. • Patients had to demonstrate: ○ R/R disease ○ ≥1 bi-dimensionally measurable disease site with a greatest transverse diameter of ≥1.5 cm and a greatest perpendicular diameter of ≥1.0 cm at baseline. The lesion had to be positive on PET scan ○ ≥1 but ≤3 previous systemic regimens for the treatment of DLBCL and one therapy line had to include a CD20-targeted therapy (e.g., rituximab) ○ ECOG performance status of 0–2 • Patients not considered eligible in the opinion of the investigator, or patients unwilling to undergo intensive salvage therapy including ASCT because of, but not limited to, advanced age, comorbidities, impossibility or, refusal to perform ASCT. Documentation of the reason for a patient's ineligibility had to be provided in the patient's source data. • Patients had to meet the following laboratory criteria at screening: ○ Absolute neutrophil count ≥1.5×10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy) ○ Platelet count ≥90×10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy) ○ Total serum bilirubin ≤2.5×ULN unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or with documented liver involvement by lymphoma may have been included if their total bilirubin was ≤5 × ULN (see exclusion criterion *'patients exhibiting history or evidence of severe hepatic impairment')* ○ ALT, AST and AP ≤3×ULN or <5×ULN in cases of documented liver involvement) serum creatinine clearance had to be ≥60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula • Females not pregnant or breastfeeding; ongoing pregnancy testing. Females (of any age) must refrain from donating blood or oocytes during the study and for three months after. Females must have committed to abstinence or effective uninterrupted contraception during the study and for 3 months after. Males had to use an effective barrier method of contraception without interruption and refrain from donating blood or sperm during the study and for three months after last dose. • In the opinion of the investigator, patients must: ○ Be able and willing to receive adequate prophylaxis for thromboembolic events ○ Be able to understand, give written informed consent, and comply with all study-related procedures, medication use and evaluations ○ Not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative ○ Be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement
	Key exclusion criteria: Patients who had:

Trial number(s)	MOR208C203; NCT02399085
	• Any other histological type of lymphoma including primary mediastinal (thymic) large B-cell or Burkitt lymphoma • Primary refractory DLBCL* • A history of "double-/triple-hit" genetics DLBCL characterised by simultaneous detection of MYC with BCL-2 and/or BCL-6 translocation(s) defined by fluorescence in-situ hybridisation. MYC, BCL-2, BCL-6 testing prior to study enrolment was not required. Patients who had, within the 14 days prior to day 1 dosing: • Not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anti-cancer therapy or other lymphoma-specific therapy • Undergone major surgery or suffered from significant traumatic injury • Received live vaccines • Required parenteral antimicrobial therapy for active, intercurrent infections Patients who: • Had, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies • Were previously treated with CD19-targeted therapy or IMiDs (e.g., thalidomide, lenalidomide) • Had a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs and/or the excipients contained in the study drug formulations • Had undergone ASCT within the period ≤3 months prior to the signing of the informed consent form. Patients who had a more distant history of ASCT had to exhibit full haematological recovery before enrolment into the study • Had undergone previous allogeneic stem cell transplant • Had a history of deep venous thrombosis/embolism • Threatening thromboembolism or known thrombophilia or were at a high risk for a thromboembolic event in the opinion of the investigator and who were not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period Concurrently used other anti-cancer or experimental treatments Prior history of malignancies other than DLBCL, unless the patient had been free of the disease for ≥5 years prior to screening. Exceptions to the ≥5-year time limit included history of the following: • Basal cell carcinoma of the skin • Squamous cell carcinoma of the skin • Carcinoma in-situ of the cervix • Carcinoma in-situ of the breast • Carcinoma in-situ of the bladder • Incidental histological finding of prostate cancer (Tumour/Node/Metastasis stage of T1a or T1b) Patients exhibiting: • Positive hepatitis B and/or C serology • Known seropositivity for or history of active viral infection with human immunodeficiency virus • CNS lymphoma involvement–present or past medical history • History or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that in the investigator's opinion precluded participation in the study or compromised the patient's ability to give informed consent • History or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption • Gastrointestinal abnormalities including the inability to take oral medication, requiring IV alimentation, or prior surgical procedure affecting absorption

Trial number(s)	MOR208C203; NCT02399085
	• History or evidence of severe hepatic impairment (total serum bilirubin >3 mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion: *'laboratory criteria at screening, total serum bilirubin ≤2.5×ULN')*
Trial drugs	TAFA+LEN
Premedication for tafasitamab infusions	To mitigate infusion-related reactions, premedication was administered between 30 minutes and two hours prior to the tafasitamab infusions: • Antipyretics (e.g., acetaminophen [paracetamol] 1000 mg per dose per mouth [p.o.] or IV or equivalent) • Histamine H1 receptor blockers (e.g., diphenhydramine 25 to 50 mg per dose IV or equivalent) • Histamine H2 receptor blockers (e.g., cimetidine 300 mg p.o., ranitidine 150 mg tablet p.o. or equivalent), glucocorticosteroids (methylprednisolone 80–120 mg per dose IV or equivalent) • Meperidine (25 mg per dose p.o. or IV) added as required for rigours or chills
Permitted and disallowed concomitant medication	Concomitant medications were permitted to treat comorbidities or AEs during the study, as well as therapy to mitigate side effects of the study medication, and BSC.
Primary endpoints	ORR (ORR=CR + PR) as assessed by IRC
Secondary endpoints	DCR (DCR=ORR + SD) DoR (duration of CRs or PRs until progression or relapse was evaluated) PFS TTP (first dose of study drug until time of progression or death from lymphoma only) OS TTNT
Safety assessments	Safety and tolerability assessed by evaluating the frequency, duration and severity of AEs
Additional endpoints	Determination and characterisation of anti-tafasitamab antibody formation Pharmacokinetic analysis of tafasitamab Absolute and percentage change from baseline in B-, T-, and NK cell populations Analysis of exploratory and diagnostic biomarkers from blood and tumour tissue (e.g., CD19, CD20, B-cell lymphoma-2, B-cell lymphoma-6 expression, CD16 expression on NK cells, and ADCC capacity), GEP for cell of origin subtyping and evaluation of AEs and ORR by FcγRIIIa and FcγRIIa polymorphism
Subgroup	Prespecified exploratory subgroup analysis of objective response by baseline characteristics

*Note: The definition of primary refractory DLBCL was revised (Protocol Amendment 2, Final Version 5.0 [27 Jun 2016]), (less than a PR to 1L therapy or progression within six months from completion of 1L therapy) and removed the need to have DLBCL relapse/progression after at least three months from completion of prior CD20 containing therapy; exclusion criterion 1b was updated to reflect this.

Source: Incyte, data on file (L-MIND CSR)(56)

Abbreviations: AE = adverse event; ADCC = antibody-dependent cellular cytotoxicity; ALT = alanine transaminase; AP = alkaline phosphatase; AST = aspartate aminotransferase; ASCT = autologous stem cell transplant; BCL = B-cell lymphoma; BSC = best supportive care; CNS = central nervous system; CR = complete response; DCR = disease control rate; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; EBV = Epstein Barr virus; ECOG = Eastern Cooperative Oncology Group; GCB = germinal centre B-cell; GEP = gastroenteropancreatic; HDC = high-dose chemotherapy; IMiD = immunomodulatory drug; IRC = independent radiology/clinical review committee; IV = intravenous; NK = natural killer; ORR = overall response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; p.o. = taken orally; PR = partial response; R/R = relapsed or refractory; SD = stable disease; TAFA+LEN = tafasitamab + lenalidomide; TTNT = time-to-next treatment; TTP = time-to-progression; UK, United Kingdom; ULN = upper limit of normal;

US, United States; WHO = World Health Organization

The methodology of MOR208C201 study is summarised in Table 7.

Table 7. MOR208C201 methodology

Trial number(s)	**MOR208C201, NCT01685008**
Location of study centres	MOR208C201 enrolled participants at 26 centres in Belgium, Germany, Spain, Hungary, Italy, Poland and the US.
Study design	A phase IIa, open-label, single-arm, multicentre study to evaluate the efficacy and safety of tafasitamab in adults with R/R B-cell NHL who have received at least one prior therapy containing rituximab
Study objectives	Primary: To assess the antitumour activity of tafasitamab in adults with R/R NHL who have received at least one prior therapy containing rituximab
Key inclusion/exclusion criteria	Key inclusion criteria: • Age ≥18 years • Histologically confirmed diagnosis, according to the REAL/WHO classification, of the following B-cell lymphomas o Follicular lymphoma o Indolent NHL o DLBCL o Mantle-cell lymphoma • For transformed lymphomas, the subtype at screening (not at initial diagnosis) was relevant for the assignment to the respective subtype. • NHL progressed after ≥1 prior rituximab-containing regimen • At least one site of measurable disease by MRI or CT, defined as at least one lesion that measured ≥1.5x1.5 cm • If previous ASCT, must be ≥4 weeks • Discontinued previous mAb therapy (except rituximab) or radioimmunotherapy administration for at least 60 days prior to study drug initiation • Discontinued rituximab for ≥14 days prior to screening visit and confirmed refractory or disease progression after rituximab treatment • Positive FDG-PET scan at baseline for DLBCL • Life expectancy of >3 months • ECOG performance status score of <3 Laboratory criteria: • ANC ≥1.0×10^9/L • Platelet count ≥75×10^9/L without previous transfusion within 10 days of first study drug administration • Haemoglobin ≥8.0 g/dL (may have been transfused) • Serum creatinine <2.0×ULN • Total bilirubin ≤2.0×ULN • ALT and AST ≤2.5×ULN • Females not pregnant or breastfeeding; ongoing pregnancy testing. Males refrain from donating blood or sperm for during study and for 3 months after last dose Key exclusion criteria: • Previous chemotherapy, immunotherapy, radiotherapy, or other lymphoma-specific therapy within 14 days before screening or if patient had not recovered from side effects of previous therapy

Trial number(s)	MOR208C201, NCT01685008
	• Treatment with a systemic investigational agent within 28 days before screening • Previous treatment with anti-CD19 therapy • Previous ASCT • Known or suspected hypersensitivity to the excipients contained in the study drug formulation • Clinically significant cardiovascular disease or cardiac insufficiency (NYHA class III–IV), cardiomyopathy, pre-existing clinically significant arrhythmia, acute myocardial infarction, or angina pectoris within 3 months of enrolment • Positive hepatitis serology • HIV • Active systemic infection requiring active parenteral antibiotic therapy within 4 weeks of study drug administration • Current treatment with immunosuppressive agents other than prescribed corticosteroids • Major surgery or radiation therapy within 4 weeks of first study drug administration • Systemic disease that would have prevented study treatment (investigator's opinion) • History or clinical evidence of CNS, meningeal, or epidural disease, including brain metastasis • Active treatment/chemotherapy for another primary malignancy within the past 5 years • Pregnancy or breastfeeding • History of noncompliance
Trial drugs	Tafasitamab
Premedication for tafasitamab infusions	To mitigate infusion-related reactions, premedication was administered between 30 minutes and two hours prior to the tafasitamab infusions: Antipyretics (e.g., acetaminophen [paracetamol] 1000 mg per dose per mouth [p.o.] or IV or equivalent) Histamine H1 receptor blockers (e.g., diphenhydramine 25 to 50 mg per dose IV or equivalent) Glucocorticosteroids (methylprednisolone 80–120 mg per dose IV or equivalent) Meperidine (25 mg per dose p.o. or IV) added as required for rigours or chills.
Permitted and disallowed concomitant medication	Concomitant medications were permitted to treat comorbidities or AEs during the study, as well as therapy to mitigate side effects of the study medication, and BSC.
Primary endpoints	ORR (ORR=CR + PR) as assessed by IRC
Key secondary endpoints	SD (rate) DoR TTP PFS
Safety assessments	Safety and tolerability assessed by evaluating the frequency, duration, and severity of AEs

Source: Incyte, data on file (MOR208C201 CSR)(59)

Abbreviation: AE = adverse event; ALT = alanine transaminase; ANC = absolutely neutrophil count; AST = aspartate aminotransferase; ASCT = autologous stem cell transplant; BSC = best supportive care; CNS = central nervous system; CR = complete response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; FDG-PET = [18F]-fluorodeoxyglucose-positron emission tomography; HIV = human immunodeficiency virus; IRC = independent radiology/clinical review committee; IV = intravenous; mAb = monoclonal antibody; MRI =

magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; NYHA = New York Heart Association; ORR = overall response rate; PFS = progression-free survival; PR = partial response; REAL = Revised European American Lymphoma; R/R = relapsed/refractory; SD = stable disease; TTP = time-to-progression; ULN = upper limit of normal; US = United States; WHO = World Health Organization.

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

B.2.4.1. Analysis population–L-MIND

In the L-MIND study, the following analysis populations were assessed(56):

- **All patients screened:** Consisted of all patients who signed informed consent and had a completed 'informed consent' electronic case report form (eCRF) page
- **Enrolled patients:** Consisted of all patients who received at least one dose of any study drug (tafasitamab or lenalidomide)
- **Full analysis set (FAS):** The FAS included all patients who received at least one dose of tafasitamab and at least one dose of lenalidomide. This meant that both study drugs had to be administered at least once. The FAS was the primary population for the analysis of efficacy and baseline characteristics. Of the 81 patients enrolled and treated in the study, one patient received tafasitamab only. Therefore, the FAS varied from 80 to 81 patients.
- **Per protocol set (PPS):** The PPS included all patients in the FAS who did not have any major protocol deviations that could confound the interpretation of the primary analyses conducted on the FAS. The PPS included all patients in the FAS who had received at least one dose of TAFA+LEN and underwent at least one post-baseline response assessment.
- **Safety analysis set (SAS):** The SAS included all patients who received at least one dose of tafasitamab or lenalidomide and had at least one post-baseline safety assessment. Valid safety assessments included documentation of death or a 'no AE' record. Analyses using the SAS were based on the study drug actually received.
- **Pharmacokinetic analysis set (PKAS):** The PKAS included all patients who received at least one dose of tafasitamab and had at least one quantifiable tafasitamab serum concentration.

- **Immunogenicity analysis set (IAS):** The IAS included patients who had at least one anti-tafasitamab antibody assessment.
- ***Post-hoc:*** **DLBCL FAS and DLBCL SAS:** These consisted of the efficacy and safety analysis sets for the population with a centrally confirmed DLBCL diagnosis, used for a post-hoc analysis.

B.2.4.2. Analysis population–MOR208C201 study

In the MOR208C201 study, the following analysis populations were assessed (59):

- **Intent-to-treat (ITT) population:** Consisted of all patients who received at least one dose of study drug. Patients without any post-baseline assessment of NHL response were included as non-responders.
- **Safety population:** Consisted of all patients who received at least one dose of study drug

B.2.4.3. Statistical analyses

The primary and secondary endpoints in L-MIND were analysed descriptively for each analysis population using appropriate statistics (counts/percentages for discrete variables, mean, median, standard deviation, minimum, maximum, number of valid observations for continuous variables). For specific variables, p-values and 95% CIs were presented. No formal statistical hypothesis testing was planned.(56)

Similar to the L-MIND study, in the MOR208C201 study, endpoints were analysed descriptively.(59)

B.2.5. Quality assessment of the relevant clinical-effectiveness evidence

The quality assessments of L-MIND (Salles et al., 2020) and MOR208C201(59) are summarised in Table 8. Quality assessments of the studies identified by the SLR are summarised in Appendix D.

Table 8. Quality assessment for L-MIND (MOR208C203) and MOR208C201

Study question	L-MIND(53)	MOR208C201(59)
Was randomisation carried out appropriately?	NA	NA
Was the concealment of treatment allocation adequate?	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors (e.g., disease severity)?	NA	NA
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. An open-label, single-arm study was conducted due to a lack of a SoC for R/R DLBCL and variation in treatment availability between regions and countries. The open-label design is associated with a potential risk of bias in assessing efficacy responses; however, responses were confirmed by an IRC to minimise this risk.	No. Open-label, single-arm designs risk bias in assessing efficacy outcomes.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	NA	NA
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the FAS included patients who had received ≥1 dose of both tafasitamab and lenalidomide. A per-protocol analysis was also performed in patients without any major protocol deviations that could confound the primary analysis.	Yes, patients without post-baseline assessments were included in the ITT analysis as non-responders.

Abbreviations: DLBCL = diffuse large B-cell lymphoma; FAS - full analysis set; IRC = independent radiology/clinical review committee; ITT = intention to treat; NA = not applicable; R/R = relapsed/refractory; SoC = standard of care

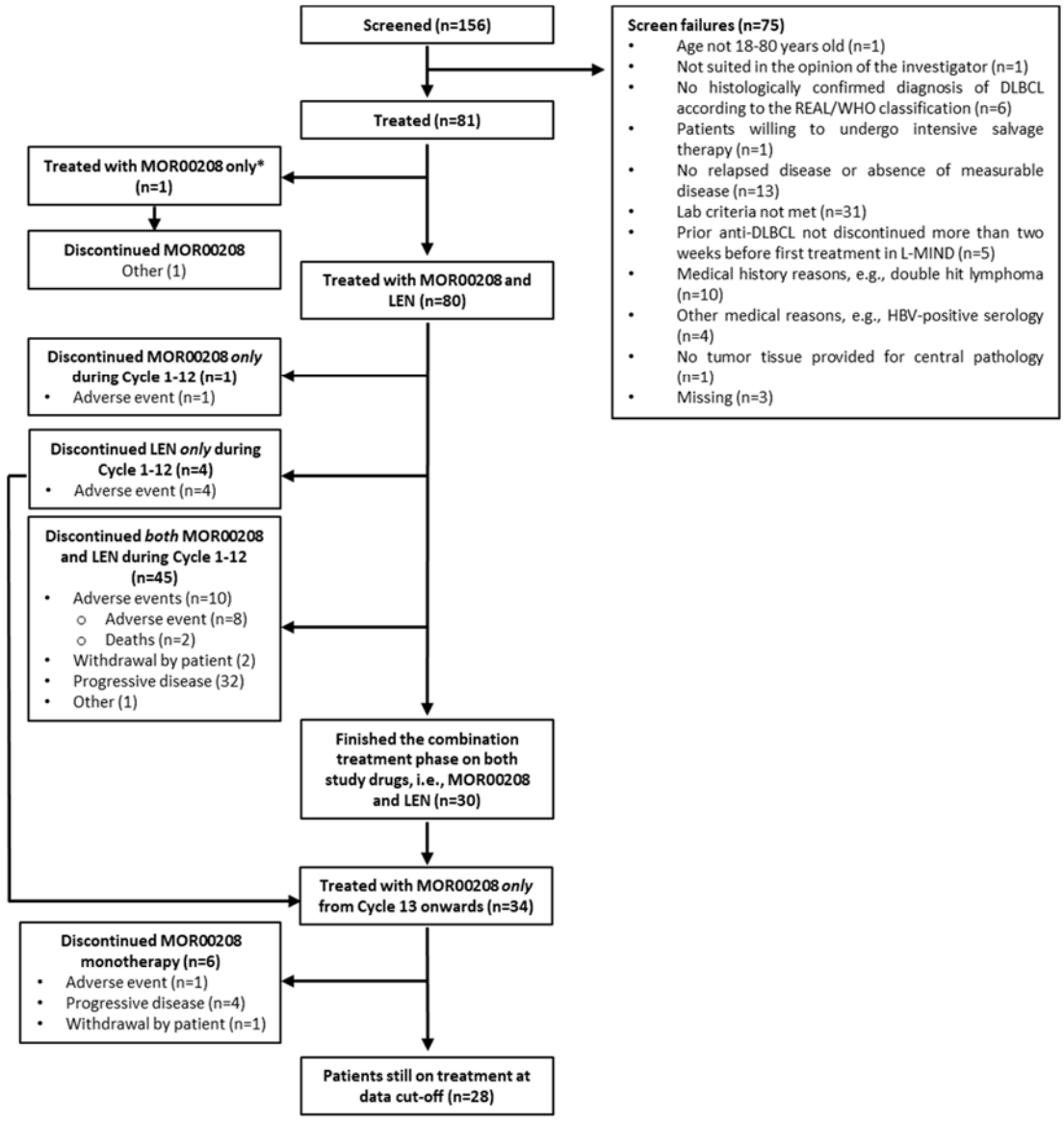
B.2.6. Clinical-effectiveness results of the relevant trials

B.2.6.1. L-MIND study (TAFA+LEN)

B.2.6.2. Patient disposition–L-MIND

In total, 156 patients were screened and 81 patients were enrolled in the L-MIND study. Overall, 30 (37.0%) completed the combination treatment phase on both study drugs (12 cycles). Patient disposition for L-MIND is summarised in Figure 5.

Figure 5. L-MIND study: patient disposition (all patients enrolled)



Source: Incyte, data on file (L-MIND CSR)(56)

Abbreviations: DLBCL = diffuse large B-cell lymphoma; HBV = hepatitis B virus; LEN = lenalidomide; MOR00208, tafasitamab; REAL = Revised European American Lymphoma; WHO = World Health Organization

As of the 30 October 2020 data cut-off, 19 patients remained on treatment and the median follow-up was 33.9 months (95% CI: 26.5, 35.4 months).(57)

Baseline characteristics–L-MIND

The L-MIND study enrolled a diverse group of patients, including difficult-to-treat subgroups, who represented patients treated in routine clinical practice. This suggested that the L-MIND study results would be reproducible in the real world.

Table 9 presents the baseline demographics and disease characteristics of the patients enrolled in L-MIND.

Table 9. L-MIND study: selected demographics and baseline characteristics

Characteristics	TAFA+LEN (N=81)
Age (years)	
Median (range)	72 (62–76)
Sex, n (%)	
Male	44 (54)
Female	37 (46)
Race, n (%)	
Asian	2 (2)
White	72 (89)
Other	1 (1)
Data missing	6 (7)
Median time since first DLBCL diagnosis, months	26·9 (17–51)
Previous lines of systemic therapy n (%)	
1	40 (50)
2	35 (43)
3	5 (6)
4	1 (1)
Median (range)	2 (1–4)
Previous anti-CD20 therapy, n (%)	
Yes	81 (100)
No	0 (0)
Previous anthracycline therapy, n (%)	
Yes	81 (100)
No	0 (0)
Primary refractory, n (%)*	
Yes	15 (19)
No	66 (81)
Rituximab refractory, n (%)	
Yes	34 (42)
No	46 (57)
Unknown	1 (1)
Refractory to most recent previous therapy, n (%)	
Yes	36 (44)
No	45 (56)
Prior ASCT n (%)	

Characteristics	TAFA+LEN (N=81)
Yes	9 (11)
No	72 (89)
Ann Arbor Disease Staging dichotomised, n (%)	
Stage I and II	20 (25)
Stage III and IV	61 (75)
ECOG performance status, n (%)	
0	29 (36)
1	45 (56)
2	7 (9)
IPI category, n (%)	
Low and low-intermediate risk (IPI score 0–2)	40 (49)
High and intermediate-high risk (IPI score 3–5)	41 (51)
Bulky disease,† n (%)	
Present	15 (19)
Absent	65 (80)
Data missing	1 (1)
LDH levels at baseline, n (%)	
Elevated	45 (56)
Within reference range	36 (44)
Cell of origin by immunohistochemistry, n (%)	
GCB	38 (47)
Non-GCB	21 (26)
Missing	22 (27)
Cell of origin by gene-expression profiling, n (%)	
GCB	7 (9)
Non-GCB	19 (24)
Unclassified	6 (7)
Unknown	49 (60)
Patients with DLBCL arising from a previous indolent lymphoma	7 (9)
Reasons for ASCT ineligibility, n (%)	
Aged >70 years	37 (46)
Chemorefractory‡	19 (23)
Refusal	13 (16)
Comorbidity§	11 (14)
Other**	1 (1)

*Patients who were defined as primary refractory were excluded from the study. After a protocol revision, primary refractory disease was defined as disease progressing in the course of the 1L treatment as per International Working Group response criteria, and/or showing a response of less than a PR to 1L treatment or disease recurrence/progression within <6 months from the completion of 1L therapy. Note that an initial definition of

primary refractory DLBCL led to exclusion of relapses within three months of a prior anti-CD20 therapy. After revision, 15 patients in the L-MIND study (18.5%) were classified as having primary refractory disease.

[†]Defined as having a longest lesion diameter of ≥7.5 cm (by central assessment)
[‡]Patients without a PR or CR with salvage therapy or who had ASCT before enrolment
[§]All patients who are not chemorefractory and who have comorbidities
[**]Other reasons include inability to successfully collect stem cells.
Source: Salles et al., 2020.(53)

Abbreviations: ASCT = autologous stem cell transplantation; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB, germinal centre B-cell; IHC, immunohistochemistry; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PR, partial response; TAFA+LEN = tafasitamab + lenalidomide

Duration of treatment–L-MIND

In the primary analysis (30 November 2018 data cut-off), the median duration of exposure to study treatment (either TAFA+LEN or monotherapy with tafasitamab) in L-MIND was [redacted] months (interquartile range [IQR]: [redacted] months). The median duration of exposure to lenalidomide was 6.2 months (IQR: [redacted] months) and to tafasitamab monotherapy (following discontinuation of lenalidomide) was [redacted] months (IQR: [redacted] months).(53)

After the 30 October 2020 data cut-off, the median duration of exposure to study treatment (either TAFA+LEN or monotherapy with tafasitamab), was 9.2 months (range: [redacted] months–[redacted] months).(54) The median duration of exposure to lenalidomide was [redacted] weeks (range: [redacted] weeks–[redacted] weeks).(57) The median duration of exposure to monotherapy with tafasitamab after lenalidomide discontinuation was [redacted] months (range: [redacted] months).(57)

B.2.6.3. MOR208C201 study (tafasitamab monotherapy)

Patient disposition–MOR208C201 DLBCL cohort

Fourteen patients with DLBCL were enrolled in stage 1 of the MOR208C201 study; this DLBCL cohort was expanded to 35 patients in stage 2. Ten patients in the DLBCL cohort discontinued the study (five from progressive disease, three died, one was withdrawn by the investigator, and one discontinued due to a protocol violation).(60)

Twenty-five patients completed the study and 12 continued to cycle 3. Six patients remained on maintenance treatment and one patient remained at the date of data cut-off, 28 September 2018.(60)

Baseline characteristics– MOR208C201 DLBCL cohort

Table 10 presents the baseline demographics and disease characteristics of the patients enrolled in MOR208C201.

Table 10. MOR208C201 study: selected demographics and baseline characteristics– DLBCL cohort (FAS)

Characteristics	DLBCL cohort (N=35)
Age, (years)	
Median (range)	71 (35–90)
Sex, n (%)	
Male	24 (69)
Female	11 (31)
Race, n (%)	
Asian	1 (3)
White	33 (94)
Black/African American	0 (0)
Other	1 (2.9)
Median time since first DLBCL diagnosis, months	23 (2–120)
Ann Arbor Disease Staging dichotomised, n (%)	
Stage I and II	4 (11)
Stage III and IV	30 (86)
Unknown	1 (3)
ECOG performance status, n (%)	
0	19 (54)
1	15 (43)
2	1 (3)

Source: Incyte, data on file (MOR208C201 CSR)(61)
Abbreviations: DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group

B.2.6.4. Efficacy outcomes in L-MIND

At the time of writing, the latest data cut available for the L-MIND study is the third planned interim analysis, with follow-up of ≥35 months (data cut-off 30 October

2020). The clinical benefit of TAFA+LEN in patients with R/R DLBCL followed the same trend observed in the early interim analyses.

Primary efficacy outcomes–L-MIND

Nineteen of 22 patients who were receiving ongoing tafasitamab treatment were assessed through new tumour imaging and/or clinical data accumulated between the data cut-offs of 30 November 2019 and 30 October 2020. For 15 patients, the best response did not change. For two patients, the best response changed from PR to CR, and for two additional patients, the best response changed from CR to PR. The best objective response was CR for 32 patients (n=32/80; 40%) and PR for 14 patients (n=14/80; 18%). Based on these data, the best ORR as assessed by independent radiology/clinical review committee (IRC) was 57.5% (95% CI: 45.9%, 68.5%),(57) consistent with analyses at the previous data cut-offs.

Twenty-six patients had stable disease or progressive disease (PD; n=13/80; 16.3% for each group) as their best objective response. As in the initial analysis, eight (n=8/80; 10.0%) patients were not evaluable, as no valid post-baseline radiological examination for response assessment was available, or the baseline scan was inadequate. These patients were included as non-responders in the analysis.(57) The best ORR data at this timepoint are summarised in Table 11.

Table 11. Best ORR (updated analysis data cut-off 30 October 2020; FAS; IRC assessed)

	TAFA+LEN (N=80)
Best objective response, n (%)	
CR [95% CI]	32 (40) [29, 52]
PR [95% CI]	14 (18) [10, 28]
SD	13 (16)
PD	13 (16)
Not evaluable	8 (10)
Best ORR,* n (%) [95% CI]	46 (58) [46, 69]

*CR + PR

Source: Source: Incyte, data on file (L-MIND CSR Addendum 3)(57)

Abbreviations: CI = confidence interval; CR = complete response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; TAFA+LEN = tafasitamab + lenalidomide

Secondary efficacy outcomes–L-MIND

Duration of response

As of the 30 October 2020 data cut-off, the median duration of response (DoR) was 43.9 months (95% CI: 26.1, not reached). Of the 46 responders, 13 (n=13/80; 28.3%) patients progressed, two (n=2/80; 4.3%) patients died, and 31 (n=31/80; 67.4%) patients were censored. Figure 6 shows the Kaplan-Meier (KM) plot for patients in the FAS. A KM probability estimate for DoR at 12 months was 73.7% (95% CI: 57.4%, 84.5%), at 18 months was [redacted], at 24 months was [redacted], and at 30, 36, and 42 months was [redacted].(57) These long-term data further demonstrated that a durable response was achieved in a substantial proportion of patients receiving TAFA+LEN.

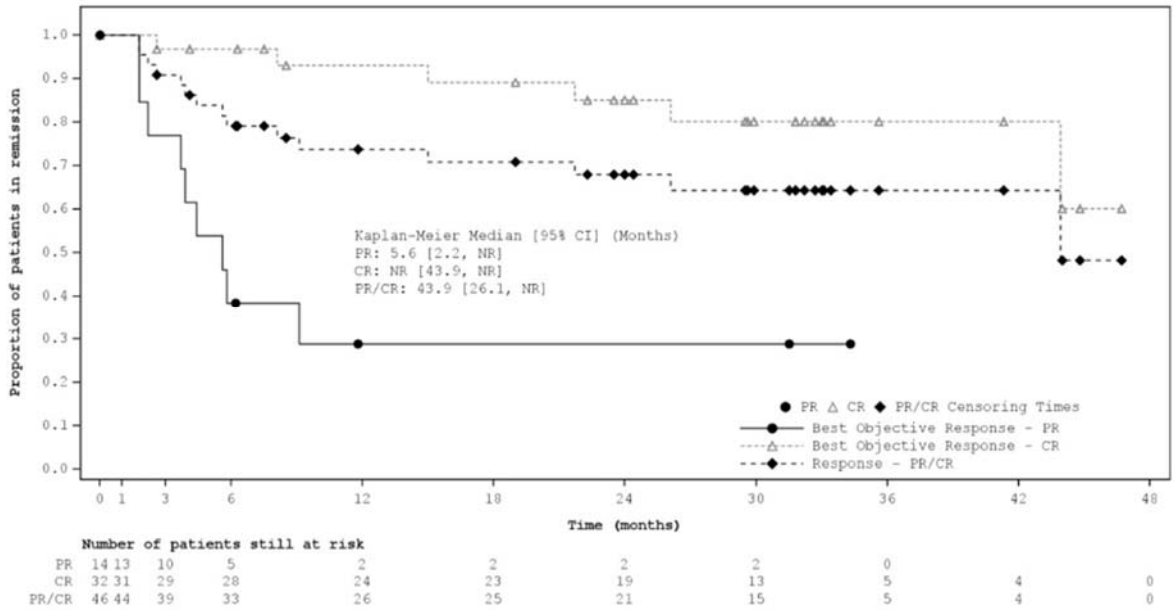
Figure 6. KM plot of DoR (updated analysis data cut-off 30 October 2020; FAS; IRC assessed)

Note: In case the median or the respective confidence limits were not calculable by the KM method, NR is displayed instead.
Source: (57)
Abbreviations: CI = confidence interval; LEN = lenalidomide; NR = not reached

A KM plot of DoR by best objective response CR or PR for patients in the FAS (IRC evaluation) is presented in

Figure 7.(57) Of the [redacted] patients with a best objective response of CR, [redacted] patients progressed ([redacted]), [redacted] patient died ([redacted]), and [redacted] patients were censored ([redacted]).(57) The estimate of the median DoR for patients with a best objective response of CR was not reached. The KM probability estimate for patients with a best objective response of CR was [redacted] at 12 months, [redacted] at 18 months, [redacted] at 24 months, and [redacted] at 30, 36 and 42 months.(57) Of the [redacted] patients ([redacted]) with PR, the median DoR was [redacted]; [redacted] patients progressed ([redacted]), [redacted] patient died ([redacted]), and [redacted] patients were censored ([redacted]).(57)

Figure 7. KM plot of DoR by best objective response (updated analysis data cut-off 30 October 2020; FAS; IRC assessed)



Notes: In case the median or the respective confidence limits were not calculable by the KM method, NR is displayed instead. The 34 patients with best objective response not PR or CR were not included in this subgroup analysis.
Source: (57)

Abbreviations: CI = confidence interval; CR = complete response; NR = not reached; PR = partial response

PFS

PFS data provided additional support for the efficacy and durable responses demonstrated by the ORR and DoR data, with consistent results achieved at each data cut-off.

PFS events were observed in 42 patients (n=42/80; 52.5%). A KM curve of PFS in the FAS is presented in Figure 8. The KM estimate for the median PFS was 11.6 months (95% CI: 6.3, 45.7 months) with a median follow-up time of 33.9 months ([redacted]).(57)

Figure 8. KM plot of PFS (updated analysis data cut-off 30 October 2020; FAS; IRC assessed)

Note: In case the median or the respective confidence limits were not calculable by the KM method, NR is displayed instead.
Source: (57)
Abbreviations: CI = confidence interval; LEN = lenalidomide; NR = not reached

Patients continued to receive a PFS benefit from tafasitamab monotherapy after the combination treatment period had ended and lenalidomide had been discontinued. A

post-hoc analysis at the 30 November 2018 data cut-off (median follow-up 17.3 months [95% CI: 11.5, 21.2 months]) showed that the median PFS was 12.7 months (95% CI: 2.3 months, not reached) after discontinuation of lenalidomide (while still on tafasitamab monotherapy).(38) Furthermore, PFS was longer in patients receiving 2L vs ≥3L treatment: 23.5 months (95% CI: 7.4 months, not reached) and 7.6 months (95% CI: 2.7 months, not reached) respectively.(54)

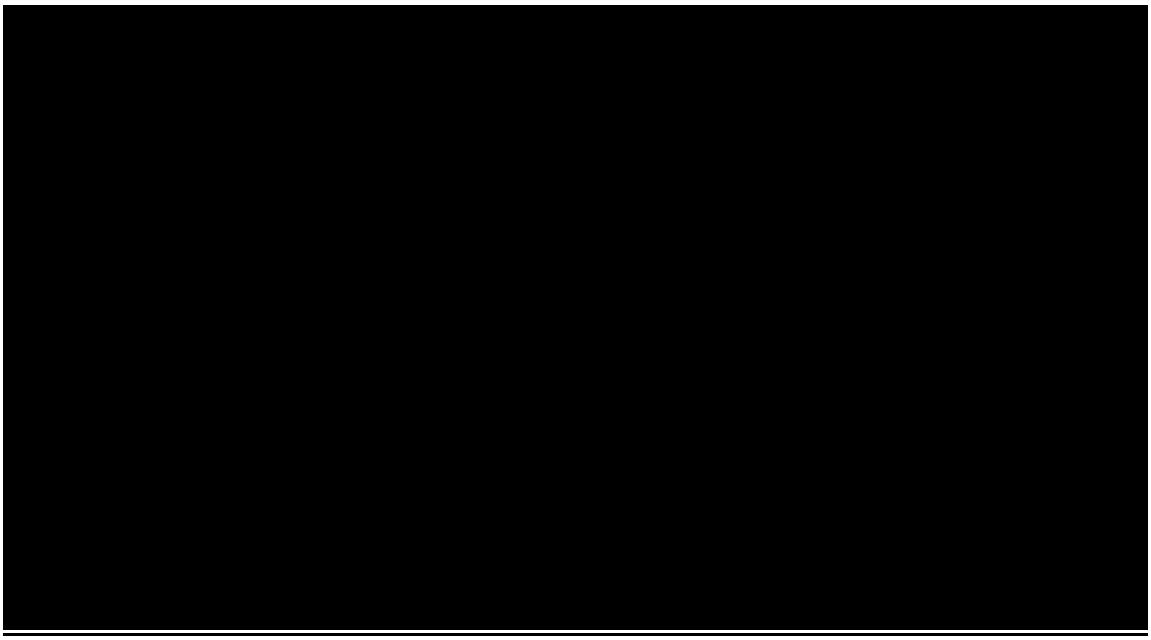
Time to progression and time-to-next treatment

The median time to progression (TTP) was 16.2 months (95% CI: 17.4 months, not reached) and PFS events occurred in 35 of 80 patients (44%). The median time-to-next treatment (TTNT) was 15.4 months (95% CI: 7.6 months, not reached) and 43 of 80 patients (54%) received subsequent treatment. Two patients subsequently received salvage treatment consolidation with stem cell transplant (one patient each with ASCT and allogeneic stem cell transplant). One other patient subsequently received CD19 CAR-T therapy after disease progression, had a CR, and was in remission at the time of data cut-off (30 November 2018).(53)

OS

The KM estimate for median OS was 33.5 months (95% CI: 18.3 months, not reached; FAS; Figure 9) with a median follow-up time of 42.7 months (95% CI: 38.0, 47.2 months).(57) Overall, 41 patients died (n=41/80; 51.3%). Thirty-nine patients were censored in the OS analysis, including one patient censored due to being lost to OS follow-up. The KM probability estimate of OS at 12 months was [redacted], [redacted] at 18 months, [redacted] at 24 months, [redacted] at 30 months, [redacted].(57)

Figure 9. KM plot of OS (updated analysis data cut-off 30 October 2020; FAS; IRC assessed)



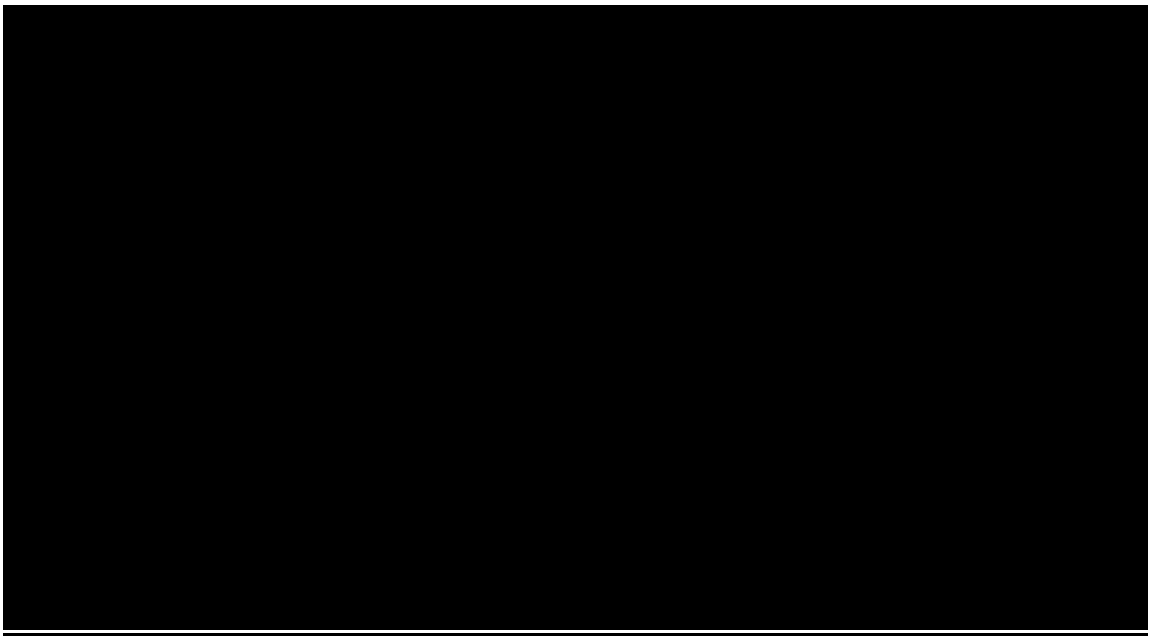
Note: In case the median or the respective confidence limits were not calculable by the KM method, NR is displayed instead.

Source:(57)

Abbreviations: CI = confidence interval; LEN = lenalidomide; NR = not reached

The KM estimate for median OS by best objective response of CR (IRC) was not reached (95% CI: 45.7 months, not reached; FAS; Figure 10) at the 30 October 2020 cut-off date.(57) For this subgroup, the KM probability estimate of OS was 96.9% (95% CI: 79.8%, 99.6%) at 18 months, 90.6% (95% CI: 73.7%, 96.9%) at 24 months, 81.3% (95% CI: 62.9%, 91.1%) at 36 months, and [redacted].(57) The KM estimate for median OS by best objective response of PR was 22.5 months (95% CI: 8.5 months, not reached; FAS; Figure 10).

Figure 10. KM plot of OS by best objective response (updated analysis data cut-off 30 October 2020; FAS; IRC assessed)



Note: In case the median or the respective confidence limits were not calculable by the KM method, NR was displayed instead. Thirty-four patients with best objective response not PR or CR were not included in this subgroup analysis.

Source: (57)

Abbreviations: CI = confidence interval; CR = complete response; NR = not reached; PR = partial response

Additional outcomes–L-MIND

Time to response and time to CR; primary analysis

The depth of the response achieved with TAFA+LEN was supported by the time to response and time to CR data. Time to response was defined as the date of assessment of first documented response of CR or PR minus the date of first administration of any study drug.(57) In the primary analysis, the median time to response was 2.1 months (IQR: [redacted]).(54, 57) Time to CR was defined as the date of assessment of first documented response of CR minus the date of first administration of any study drug.(57) In the primary analysis, the median time to CR was 6.8 months (IQR: [redacted]).(54, 57)

Patients with a c-MYC translocation; primary analysis

A post-hoc evaluation of the 30 November 2018 primary analysis showed that seven patients had a *c-MYC* translocation that was identified during central pathology review: of these patients, three had a CR, one had a PR, and three did not respond to therapy. Another of the seven patients presented with a double-hit translocation and had a PR (lasting 5.8 months); one more had a triple-hit translocation and a CR (ongoing at data cut-off: 20.1 months).(53) c-MYC translocations, particularly in combination with one or more additional mutations (i.e., double- or triple-hit disease), are associated with a high risk of progression and poor outcomes.(27)

Patients with central pathology-confirmed DLBCL

Efficacy analyses based on the data cut-off of [redacted] were evaluated in patients who had both a local pathology and a central pathology histological diagnosis of DLBCL. [redacted] patients were included in the DLBCL primary efficacy SAS and [redacted] patients were included in the DLBCL SAS).(57)

The distribution of patients in subgroups of prognostically important covariates were comparable between the full population and the patients with centrally confirmed DLBCL. Therefore, no imbalance in baseline factors was present that could confound the interpretation of efficacy results between the full population (FAS, n=[redacted] or SAS, n=[redacted]) and the subgroup of patients with centrally confirmed DLBCL (based on DLBCL FAS, n=[redacted] or DLBCL SAS, n=[redacted]).(57)

The following efficacy outcomes were reported for the DLBCL FAS population as of the [redacted] data cut-off date:

- Best objective response was CR for [redacted] patients and PR for [redacted] patients. Based on these data, the IRC-assessed best ORR was [redacted].(57)
- The estimate for the median DoR was [redacted]. Of the [redacted] responders, [redacted] patients progressed, [redacted] patients died, and [redacted] patients were censored.(57)

- The median follow-up time for PFS was [redacted] in the DLBCL FAS. The KM estimate for median PFS was [redacted].(57)

- The median follow-up time for OS was [redacted] The KM estimate for the median OS was [redacted]

Efficacy results between the investigator (INV)-confirmed DLBCL and patients with central pathology-confirmed DLBCL were consistent, and estimates for primary and secondary endpoints (i.e., best ORR, CR rate, median DoR, median PFS and median OS) between patients with DLBCL as per INV and as per central pathology were comparable, supporting the interpretation of efficacy results based on the primary efficacy population (n=[redacted] patients).(57) This reflected routine clinical practice where patients are diagnosed locally without central reassessment. The validity of this approach also confirmed when the EMA approved tafasitamab based on a review of the L-MIND results. [redacted] patients who were still on treatment at the latest data cut-off had their initial DLBCL diagnosis confirmed centrally.

B.2.6.5. Efficacy outcomes in MOR208C201

Primary efficacy outcomes–MOR208C201 DLBCL cohort

The primary efficacy analysis for the DLBCL cohort is summarised in Table 12. The data cut-off for the primary analysis was 28 September 2018. The median duration of exposure to tafasitamab in the DLBCL cohort was 7.1 weeks (range: 0–232 weeks). The ORR was 25.7% (95% CI: 12.5%, 43.3%), demonstrating the efficacy of tafasitamab single-agent treatment in this population.(61)

Table 12. Primary efficacy analysis: MOR208C201 (ITT population)

Outcome	DLBCL cohort (N=35), n (%)
CR	2 (5.7)
PR	7 (20.0)
ORR	9 (25.7)
95% CI, %	12.5–43.3

Outcome	DLBCL cohort (N=35), n (%)
SD	5 (14.3)
DCR	14 (40.0)
95% CI, %	23.9–57.9
PD	11 (31.4)
NE	0
No response assessment	10 (28.6)

Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; ORR = overall response rate; NE = not estimable; PD = progressive disease; PR = partial response; SD = stable disease
Source: Incyte, data on file (MOR208C201 CSR)(61)

B.2.7. Subgroup analysis

Subgroup analyses are presented in Appendix E.

B.2.8. Meta-analysis

A meta-analysis study is not presented as part of the clinical evidence.

B.2.9. Indirect and mixed treatment comparisons

As the pivotal L-MIND study of TAFA+LEN in R/R DLBCL (Section B.2.) was a single-arm trial, the comparative efficacy of TAFA+LEN was assessed via 1:1 nearest-neighbour (NN) matching with external (synthetic) control arms. These data were generated from two generated in two retrospective cohort studies (RE-MIND [MOR208C206] and RE-MIND2 [MOR208C213]),(62, 63) and a matching-adjusted indirect comparison (MAIC) against the published clinical studies of key comparators.(64)

In line with the final decision problem, the comparators considered most relevant to the UK market according to expert clinical opinion are listed below.

- Pola-BR
- Gemcitabine, oxaliplatin (R-GemOx)
- BR

Data for these comparisons were provided by RE-MIND2 and the MAIC (Sections B.2.9.2. and Appendix D), while the RE-MIND comparison of TAFA+LEN vs.

lenalidomide monotherapy provided additional evidence regarding the efficacy and potential synergy of TAFA+LEN compared with lenalidomide monotherapy, and is described briefly for context in Section B.2.9.1.

B.2.9.1. RE-MIND

The RE-MIND study was an estimated propensity-score (ePS)-based 1:1 NN matched comparison, designed to quantify the additional benefit of combining tafasitamab with lenalidomide.(62) Details of the methodology and patient population can be found in Appendix D.

A statistically significant improvement was seen with TAFA+LEN vs. lenalidomide monotherapy in endpoints including: best ORR (67.1% [95% CI, 55.4%, 77.5%] vs. 34.2% [95% CI, 23.7%, 46.0%]; odds ratio [OR]: 3.9 [95% CI: 1.9, 8.1]; p<0.0001); median PFS (12.1 months vs. 4.0 months; hazard ratio [HR]: 0.463 [95% CI: 0.307, 0.698]; p=0.0002); and median OS (not reached vs. 9.3 months; HR: 0.499 [95% CI: 0.317, 0.785]; p=0.0026).(62) Key efficacy endpoints are summarised in Table 13. The best ORR was defined as the proportion of patients with CR or PR as best response achieved at any time within the analysis window (index to 32 months (974 days) or between index date and date of initiation of a new anti-DLBCL medication or death. The denominator was the total number of patients included in the analysis set.

Table 13. RE-MIND study: overview of efficacy outcomes–MAS25

Category/statistic	TAFA+LEN (N=76)	Lenalidomide monotherapy (N=76)
Primary efficacy outcomes		
Best ORR, n (%); [95% CI][1]	51 (67.1); [55.4, 77.5]	26 (34.2); [23.7, 46.0]
CR, n (%); [95% CI][1]	30 (39.5); [28.4, 51.4]	10 (13.2); [6.5, 22.9]
PR, n (%); [95% CI][1]	21 (27.6); [18.0, 39.1]	16 (21.1); [12.5, 31.9]
SD, n (%)	8 (10.5)	11 (14.5)
PD, n (%)	12 (15.8)	34 (44.7)
Deaths before any post-baseline assessment	5 (6.6)	5 (6.6)
Secondary efficacy outcomes		
DCR, n (%); [95% CI][1]	59 (77.6); [66.6, 86.4]	37 (48.7); [37.0, 60.4]
OR(SE); [95% CI], p-value[2]	3.625 (0.3570); [1.719, 7.899], p=0.0004	
Median PFS, months (95% CI)	12.1 (5.9, NE)	4.0 (3.1, 7.4)
HR (95% CI), p-value[3]	0.463 (0.307, 0.698), p=0.0002	

Category/statistic	TAFA+LEN (N=76)	Lenalidomide monotherapy (N=76)
Median OS, m	NR	9.3
Median TTNT, months (95% CI)	16.7 (7.6, NR)	5.1 (4.7, 7.3)
Median EFS, months (95% CI)3	12.1 (5.5, 21.0)	4.0, (3.1, 6.2)
HR (95% CI), p-value2	0.439 (0.296, 0.650), p<0.0001	

Notes:

[1]Clopper-Pearson exact method

[2]Logistic regression for unpaired data; logistic regression model: response=cohort status

[3]Cox proportional hazard model

Source: Incyte, data on file (RE-MIND CSR)(62)

Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; EFS = event-free survival; HR = hazard ratio; LEN = lenalidomide; NR = not reached; OR = odds ratio; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; SE = standard error; TAFA+LEN = tafasitamab + lenalidomide; TTNT = time-to-next treatment

Although L-MIND demonstrated the clear benefit of adding tafasitamab to lenalidomide monotherapy for the management of R/R DLBCL, clinical experts from the UK highlighted{Incyte Corporation, 2020 #316} that, as lenalidomide monotherapy is not frequently used to treat R/R DLBCL in clinical practice, the RE-MIND study was not relevant for assessing comparative efficacy in the UK clinical practice setting. Additional data from RE-MIND, including sensitivity analyses, can be found in Appendix D.1.4.9.

B.2.9.2. RE-MIND2

RE-MIND2 was a large, real-world, retrospective cohort study of patients with R/R DLBCL (N=3,454)), based on a pre-specified design, aimed at characterising the effectiveness and tolerability of TAFA+LEN (in L-MIND; data cut-off 30 October 2020) with a 1:1 NN-matched population treated with systemic regimens administered in routine clinical care as recommended by NCCN/ESMO guidelines.(63) The RE-MIND2 cohort included patients treated with the following regimens: BR, R-GemOx, pola-BR, rituximab (R)+lenalidomide (LEN), CAR-T therapies, and pixantrone; in the second, third, or fourth-line treatment settings.(63)

Based on feedback from UK clinical experts{Incyte Corporation, 2020 #316}, BR, R-GemOx and pola-BR were considered the most relevant comparators for patients with R/R DLBCL who are ineligible for ASCT in the UK; therefore, the RE-MIND2 study provided a relevant and meaningful comparison of outcomes for TAFA+LEN

against therapies used in current UK clinical practice. Overall, there were five UK-based patients enrolled into L-MIND (all of whom received TAFA+LEN) and 115 UK-based patients enrolled into Re-MIND2 (receiving different systemic therapies).(63)

RE-MIND2 methodology overview

A cohort of 3,454 patients was selected from sites in Europe, North America and the Asia-Pacific region according to the inclusion and exclusion criteria outlined in Table 14. Several key eligibility criteria were identical to those employed in L-MIND to enable comparison between populations.(63).

Table 14. Inclusion and exclusion criteria for the RE-MIND2 study

Inclusion criteria	Exclusion criteria

• ≥18 years at initial DLBCL diagnosis
• One of the following histologically-confirmed diagnosis:
  o DLBCL not otherwise specified
  o T-cell/histiocyte rich large B-cell lymphoma
  o EBV-positive DLBCL of the elderly
  o Grade 3b follicular lymphoma
  o Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse (according to REAL/WHO) classification
  o Evidence of histological transformation to DLBCL from an earlier diagnosis of low-grade lymphoma with a subsequent DLBCL relapse
• R/R DLBCL and received at least two systemic regimens for the treatment of DLBCL, including at least one anti-CD20 containing therapy
	• Patients with CNS involvement by lymphoma at initial DLBCL diagnosis
	• Patients who were treated with CD19-targeted therapy or immunomodulatory drugs as a frontline DLBCL therapy
	• Patients who underwent an allogeneic stem cell transplant
	• Patients who had prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥5 years prior to inclusion. Exceptions to this time limit include a history of the following:
	  o Basal cell carcinoma of the skin
	  o Squamous cell carcinoma of the skin
	  o Carcinoma in situ of the cervix
	  o Carcinoma in situ of the breast
	  o Carcinoma in situ of the bladder
	  o Incidental histological finding of prostate cancer (Tumour/Node/Metastasis stage of T1a or T1b)
	• Patients who received tafasitamab.
	• Patients who were human immunodeficiency virus positive (applicable to sites in Taiwan only).

Source: Incyte, data on file (RE-MIND2 CSR)(63)

Abbreviations: CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; REAL = Revised European American Lymphoma; R/R = relapsed or refractory; WHO = World Health Organization

In addition, the non-randomised cohorts were balanced with the L-MIND population on nine baseline covariates using estimated propensity score (ePS; Table 15), with additional sensitivity analyses conducted with matching according to 11 covariates.(63)

Table 15. Baseline covariates used in the ePS for RE-MIND2

Baseline covariates
Age (as categorical variable with subgroups <70 vs. ≥70 years of age)
Ann Arbor stage (I/II vs. III/IV)
Refractoriness status to last therapy line (yes vs. no)
Number of prior lines of therapy (1 vs. 2/3)
History of primary refractoriness (yes vs. no)
Prior ASCT (yes vs. no)
Neutropenia (<1.5×109/L) (yes vs. no)
Anaemia (<10 g/dL [=6.21 mmol/L]*) (yes vs. no)
Elevated LDH (LDH>upper limit of normal [ULN]) (yes vs. no)

*Conversion formula (g/dL×0.621=mmol/L)

Source: Incyte, data on file (RE-MIND2 CSR)(63)

Abbreviations: ASCT = autologous stem cell transplant; LDH = lactate dehydrogenase; ULN = upper limit of normal

Data from the L-MIND study database (data cut-off 30 November 2019; i.e., approximately two years after the last patient was enrolled in the study)(53) were compared with the following observational cohorts in RE-MIND2(63) (key comparators are highlighted in bold):

- Systemic therapies pooled cohort
- **BR cohort**
- **R-GemOx cohort**
- R + LEN (R2) cohort
- CD19 CAR-T cohort (pre-specified sensitivity analysis)
- Pola-BR cohort (pre-specified sensitivity analysis)
- Pixantrone monotherapy cohort

The high degree of cohort-balancing using ePS-based 1:1 matching allowed for a more robust estimation of treatment effect between the TAFA+LEN cohort and the primary analysis cohorts of systemic therapies pooled, BR, and R-GemOx than would have been afforded by other balancing methods.(63).

In the L-MIND study, the administration of TAFA+LEN was followed by tafasitamab monotherapy until disease progression,(53) whereas other comparator therapies in RE-MIND2 were administered for a fixed duration. The analysis window for

observational cohorts was therefore defined as the interval between the index date for the given treatment line plus 44 months (1,338 days).(63) Key study endpoints are listed below; a full list of endpoints and subgroup analyses is provided in Appendix D.5.3. (63)

- Primary endpoint: OS
- Secondary endpoints:
  - ORR
  - CR rate
  - DoR
  - Event-free survival (EFS)
  - PFS
  - TTNT
  - Treatment discontinuation rate due to AEs
  - Duration of treatment exposure

RE-MIND2 primary analysis results

OS

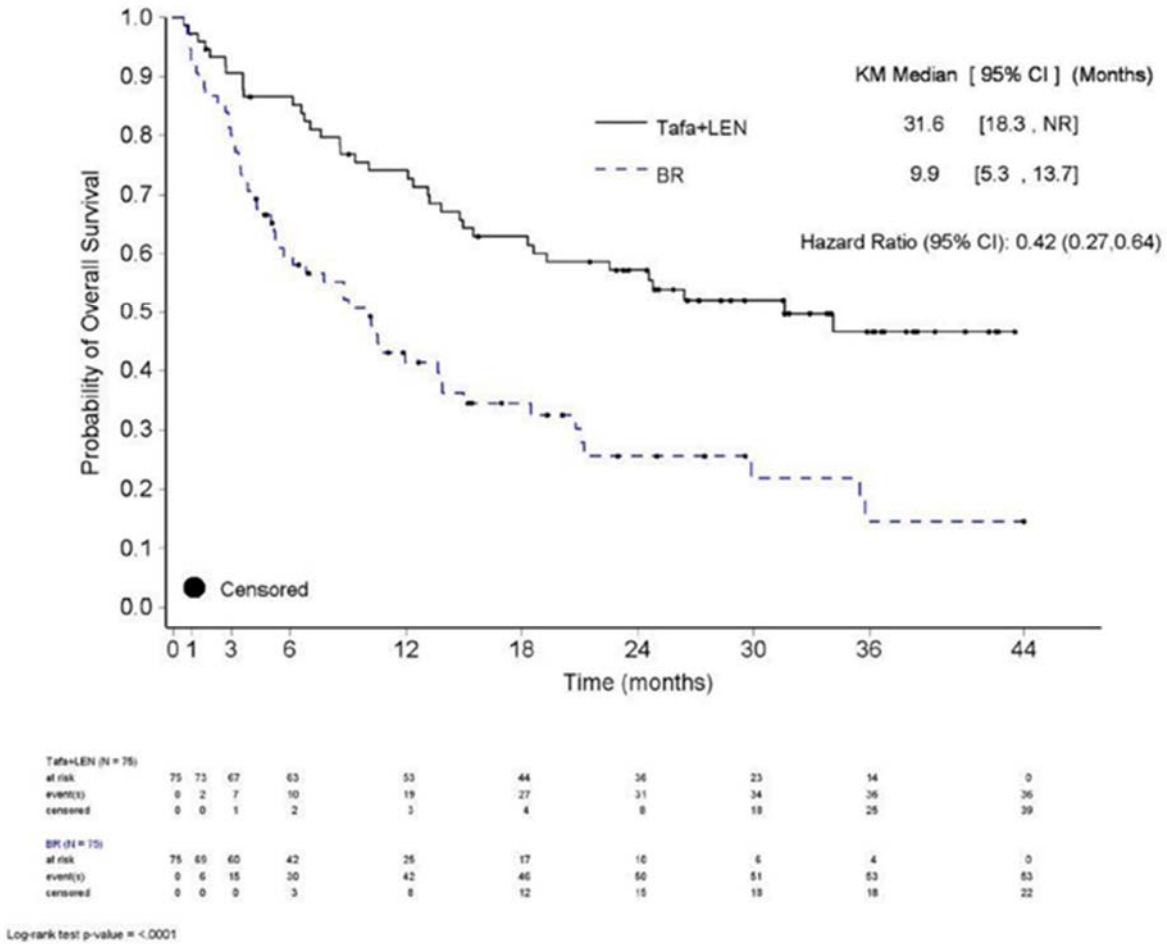
The difference in OS between cohorts was statistically significant in favour of TAFA+LEN vs. BR (HR=0.418 [95% CI: 0.272, 0.644]; Cox proportional hazard model p<0.0001; Figure 11), and R-GemOx (HR=0.467 [95% CI: 0.305, 0.714]; Cox proportional hazard model p=0.0004; Figure 11).(63) Thus, the RE-MIND2 study met its primary endpoint, showing statistically significant improvements in OS for TAFA+LEN vs. BR, R-GemOx and the pooled cohort of all systemic therapies for R/R DLBCL listed in the NCCN/ESMO guidelines.(63) Clinical expert opinion aligned with the OS for the comparators of R-GemOx and BR, although BR was not a commonly used regimen.{Incyte Corporation, 2020 #316}

The proportion of patients who had an OS event in the TAFA+LEN cohort was lower with TAFA+LEN compared with BR (48.0% vs. 70.7%), and R-GemOx (48.6% vs. 74.3%). The main cause of the OS event was DLBCL disease progression in all the cohorts. The median OS (KM estimate) was longer in the TAFA+LEN cohort

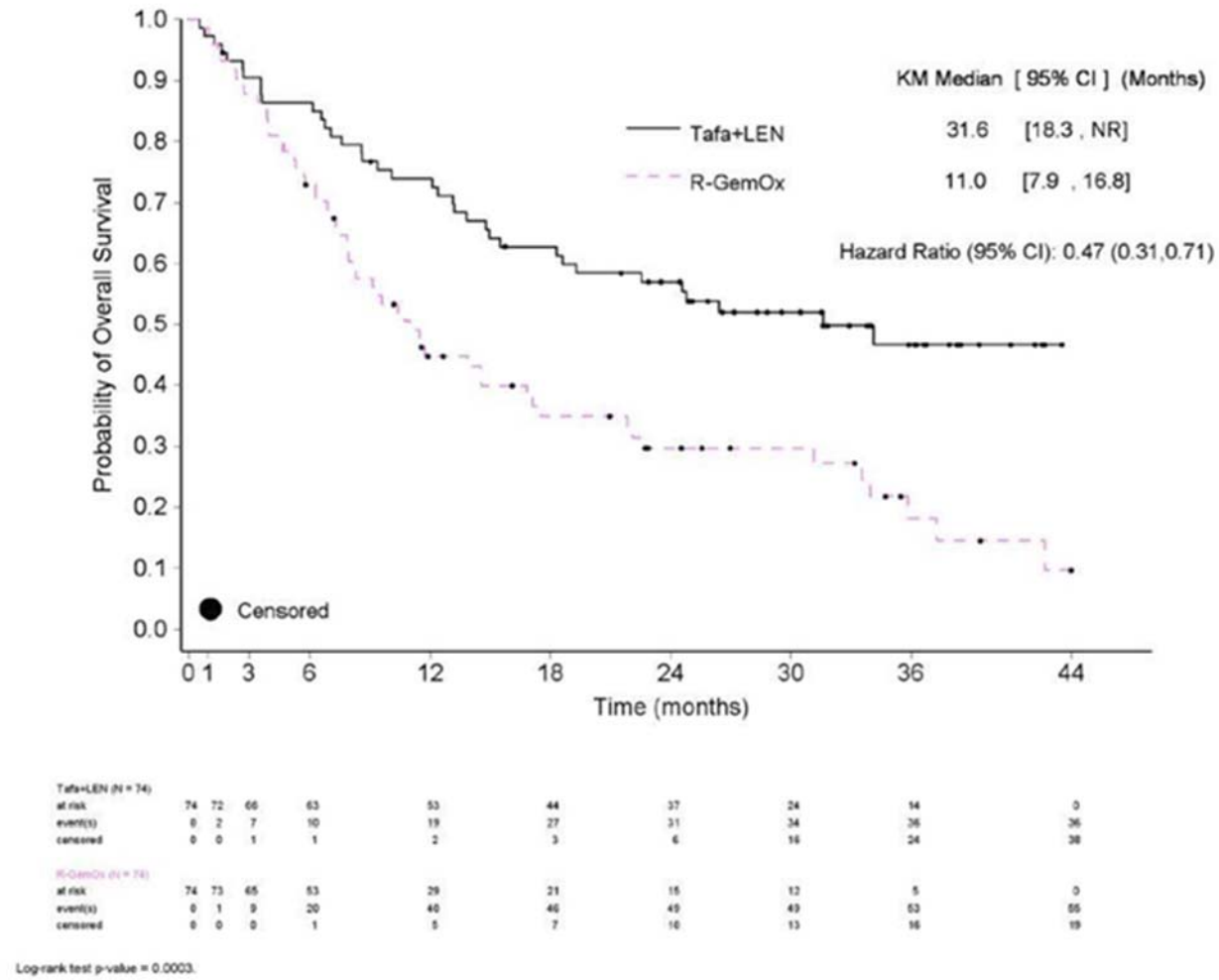
compared with BR (31.6 vs. 9.9 months), and R-GemOx (31.6 vs. 11.0 months). The probability of patients surviving at month 12 was 74.0% in the TAFA+LEN cohorts and was 41.4% and 44.7% in the BR and R-GemOx cohorts, respectively.(63)

Figure 11. KM plot for OS: BR (a) and R-GemOx (b)

(a) BR



(b) R-GemOx



Notes: MAS_Pool included 1:1 matched patients from the L-MIND study and the observational cohort using nine baseline covariates. MAS_BR included 1:1 matched patients from the L-MIND study and BR as pre-specified treatment. MAS_R-GemOx included 1:1 matched patients from the L-MIND study and R GemOx as pre-specified treatment.

The median was calculated with the KM method. The 95% CI was calculated by means of Greenwood formula.

HR was calculated with Cox proportional hazard model.

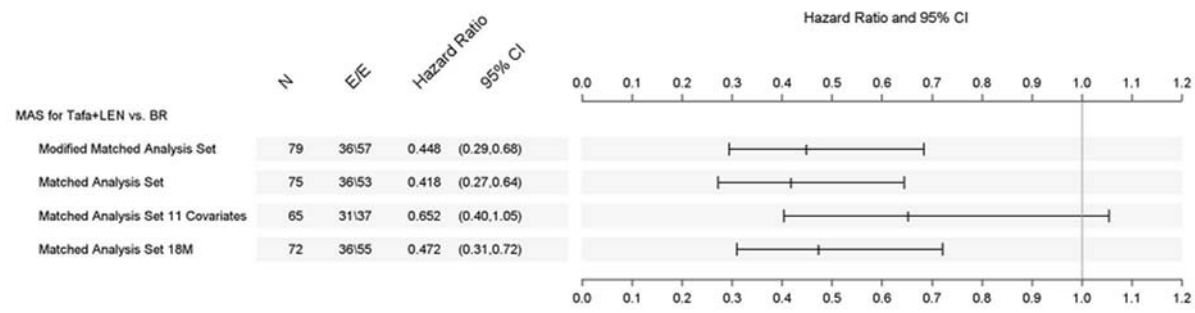
Source: Incyte, data on file (RE-MIND2 CSR)(63)

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; KM = Kaplan-Meier; MAS, matched analysis set; NR = not reached; R-GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

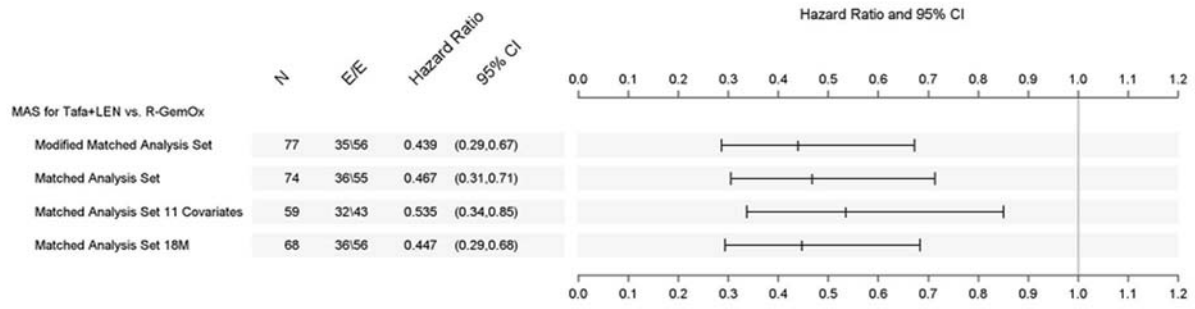
A forest plot of OS HRs with 95% CIs using the Cox proportional hazard model for the different analysis sets is provided in Figure 12.

Figure 12. Forest plot of OS HRs with 95% CIs using Cox proportional hazard model for different analysis sets

(a) Matched analysis set for TAFA+LEN vs. BR



(b) Matched analysis set for TAFA+LEN vs. R-GemOx



Notes: HR was calculated using the observational cohort as reference cohort. HR <1.0 favours TAFA+LEN.
Source: Incyte, data on file (RE-MIND2 CSR)(63)
Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; E/E = number of events in TAFA+LEN/the observational cohort; MAS = matched analysis set; R-GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

The subgroup analysis by age of OS was consistent with the primary matched analysis results (Appendix D). Outcomes were broadly consistent across the different matching analyses for each comparison, with improvements in OS for TAFA+LEN in each case.

Summary of secondary efficacy endpoints

All time-to-event endpoints (PFS, EFS, and TTNT) supported the primary analysis results of OS and aligned with the overall results, with differences between the TAFA+LEN cohort and the BR, and R-GemOx cohorts. The median PFS in the TAFA+LEN cohort was longer compared with the cohorts of systemic therapies pooled (12.1 vs. 4.6 months) and R-GemOx (9.1 vs. 4.0 months). The median (KM estimate) PFS in the BR cohort was longer compared with the TAFA+LEN cohort (11.5 vs. 8.7 months). Moreover, a significantly higher ORR was observed in the

TAFA+LEN cohort compared with the cohorts of systemic therapies pooled and R-GemOx.

A detailed overview of the secondary efficacy endpoints is presented in Appendix D.

Summary of safety endpoints

Treatment discontinuation rate due to AEs

AEs leading to permanent discontinuation of treatment were reported for 156 (4.7%) patients in the Ob-ENR[1] analysis set. Eight patients discontinued due to AEs in the TAFA+LEN cohort compared with BR (14.5%) and R-GemOx (15.1%). In the BR, and R-GemOx cohorts, two (2.8%), and four (5.4%) patients, respectively, had AEs leading to permanent discontinuation of treatment.(63)

The sensitivity analysis confirmed the primary analysis with seven (14.9%), and six (13.6%) patients who discontinued due to the AEs in the TAFA+LEN cohort for BR, and R-GemOx, respectively. The number of patients who discontinued due to the AEs in the BR and R-GemOx cohorts were three (4.8%), and one (1.7%), respectively.(63) The longer exposure in the TAFA+LEN cohort also indicated a favourable tolerability profile of this regimen.(63)

Duration of treatment exposure

The median duration of exposure in the TAFA+LEN cohort was longer ([redacted] months) compared with BR ([redacted] months) and R-GemOx ([redacted] months). This difference can be attributed to the respective treatment regimens. In the L-MIND study, the administration schedule for TAFA+LEN was 12 cycles (approximately 12 months), followed by tafasitamab monotherapy until disease progression. In comparison, most therapies administered in the BR and R-GemOx cohorts were immunochemotherapies, which are typically administered over a fixed, limited treatment duration of approximately two to six months.

[1] The Ob-ENR included all patients enrolled in the observational study.

RE-MIND2 – additional analyses

Sensitivity analyses confirmed the main analyses of the primary (i.e., OS) and secondary endpoints. Details of the sensitivity analyses are provided in Appendix D.

RE-MIND2 included pre-specified exploratory of TAFA+LEN vs. pola-BR and vs. CAR-T therapy. Due to the recent approvals of both therapies, there were insufficient patient numbers with which to conduct the 1:1 NN matching analysis.(63) Instead 1:1 matching was undertaken based on 9 covariates with multiple imputations.

The TAFA+LEN cohort exhibited [redacted] survival time than the pola-BR cohort, with a median survival time of [redacted] compared with [redacted] in the pola-BR cohort. The improvement was statistically significant using propensity score analysis (HR, 0.42 [0.23, 0.78]; [redacted]). [redacted] individuals in each cohort experienced PD [redacted] in the TAFA+LEN cohort, [redacted] in the pola-BR cohort); approximately [redacted] of subjects in both cohorts died [redacted] in TAFA+LEN vs. [redacted] n pola-BR). The median progression event time (KM estimate) was [redacted] for the TAFA+LEN cohort and [redacted] for the pola-BR cohort. [redacted] p-value = [redacted]; HR = [redacted] with Cox proportional hazard model p-value = [redacted]

B.2.9.3. MAIC

In the absence of head-to-head clinical studies of TAFA+LEN vs. comparators, an indirect treatment comparison was designed to evaluate the relative efficacy of TAFA+LEN in L-MIND vs. published comparator studies, including pola-BR, BR and R-GemOx. The population from L-MIND was matched with the published comparator populations via an MAIC.

MAIC methodology overview

Six prospective studies were selected for inclusion in the MAIC (

Table 16). The studies were selected based on an SLR and interviews with clinical experts, to enable a meaningful, population-adjusted comparison to the L-MIND study.{Incyte Corporation, 2020 #316} The MAICs were conducted using the methods described by Signorovitch et al., 2012(65) following current NICE guidelines.(66) For further details on the identification of studies and methodology for the MAIC, and a full list of studies identified in the SLR (and reasons for exclusion where relevant), please see Appendix D.

Three studies reporting data for BR were included in the MAIC: the GO29365 trial of pola-BR vs. BR,(21, 40) the Vacirca et al., 2014 study,(67) and the Ohmachi et al., 2013 study.(68) An MAIC comparing L-MIND with pooled BR cohort data from the three trials was also conducted with further details included in Appendix D.

There were conflicting estimates of response rates observed for the GO29365 trial. The Sehn et al., Journal of Clinical Oncology paper(21) reported 25 patients with CR or PR according to the IRC, while the Sehn et al., paper(21) only mentions 19 patients with IRC-CR or IRC-PR. As the breakdown of patients by response type was not reported in this source, these data were not investigated further.

The United States (US) Food and Drug Administration (FDA) re-analysis of the GO29365 trial explicitly censored PFS records of patients who received a subsequent anti-cancer treatment without a recorded progression events at the time of the last progression assessment available. A similar censoring rules was used in the L-MIND study, and as a result, the PFS reported by the FDA re-analysis appeared more comparable to the L-MIND data than the PFS reported in the Sehn et al., Journal of Clinical Oncology paper. Therefore, the comparative analyses against the data reported in the FDA dossier were used in the base-case analyses. Comparative analyses for PFS-IRC used the Sehn et al., Journal of Clinical Oncology paper as a data source.

Table 16. Studies identified for the MAIC study by the SLR and clinician interviews

Treatment	Study	Data sources
Lenalidomide	DLC-001(69)	Czuczman et al., 2017
Pola-BR	GO29365(21, 40)	OS: Sehn et al., 2018 Blood

		ORR, CRR, PFS-IRC[b]: Sehn et al., 2020 PFS-IRC and DoR: FDA regulatory appraisal[b]
BR	GO29365[a](21, 40)	OS: Sehn et al., 2018 Blood ORR, CRR, PFS-IRC[b]: Sehn et al., 2020 PFS-IRC and DoR: FDA regulatory appraisal[b]
	Ohmachi et al., 2013(68)	Ohmachi et al., 2013(68) (no OS or DoR results)
	Vacirca et al., 2014(67)	Vacirca et al., 2014.(67) (no OS results reported)
R-GemOx	Mounier et al., 2013(70)	Mounier et al., 2013(70) (only median DoR without CI reported)

[a]There were conflicting estimates of response rates observed for the GO29365 trial. The Sehn et al., Journal of Clinical Oncology paper reported 25 patients with CR or PR according to the IRC, while the Sehn et al., Blood paper only mentions 19 patients with IRC-CR or IRC-PR. As the breakdown of patients by response type was not reported in this source, these data were not investigated further.

[b]The FDA re-analysis of the GO29365 trial explicitly censored PFS records of patients who received a subsequent anti-cancer treatment without a recorded progression events at the time of the last progression assessment available. A similar censoring rules was used in the L-MIND study, and as a result, the PFS reported by the FDA re-analysis appeared more comparable to the L-MIND data than the PFS reported in the Sehn et al., Journal of Clinical Oncology paper. Therefore, the comparative analyses against the data reported in the FDA dossier were used in the base-case analyses. Comparative analyses for PFS-IRC used the Sehn et al., Journal of Clinical Oncology paper as a data source.

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; CRR = complete response rate; DoR = duration of response; FDA = Food and Drug Administration; IRC = independent radiology/clinical review committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pola-BR = polatuzumab, bendamustine, and rituximab; R-GemOX = rituximab, gemcitabine, oxaliplatin

MAIC results

Results of the MAIC vs. the key comparator cohorts of pola-BR and BR are presented below; results vs. lenalidomide monotherapy and R-GemOx are presented in Appendix D. An overview of the relative efficacy estimates for TAFA+LEN compared with all comparators (pola-BR, BR) across all efficacy outcomes is also provided in Appendix D. The best response changed for some patients during reassessment between the [redacted] data cuts, which accounts for some small differences in patient numbers.

Matching scenarios and baseline characteristics

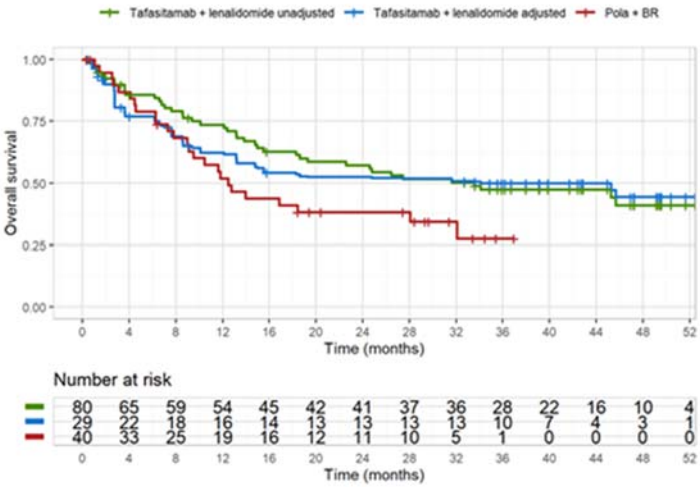
Details of the matching scenarios and baseline characteristics for the key comparators pola-BR and BR, compared with the L-MIND observed and matched populations for each MAIC analysis, are included in Appendix D. Successful matching was achieved for all three comparators, allowing meaningful assessment of the relative efficacy of TAFA+LEN in L-MIND vs. each of the three comparators.

OS

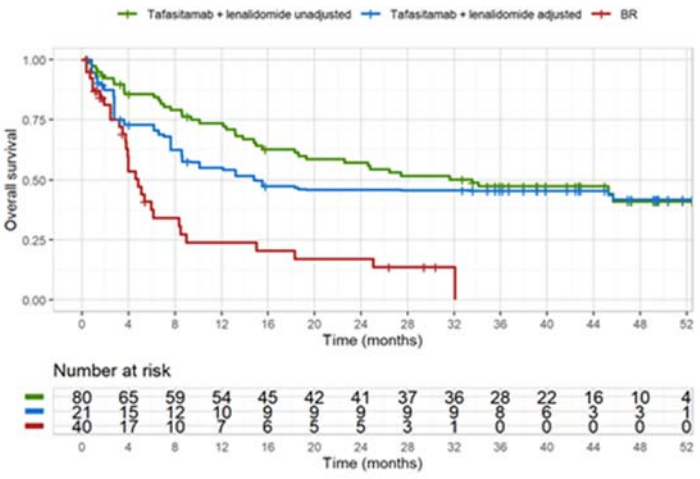
The estimated HRs for TAFA+LEN for the unadjusted and adjusted L-MIND populations vs. comparators are shown in Appendix D. KM curves for the L-MIND adjusted and unadjusted populations vs. comparators are shown in Figure 13.

Figure 13. KM estimates for OS for TAFA+LEN observed (green) and adjusted (blue) compared with reported OS estimates for comparators (red)

MAIC vs. pola-BR



MAIC vs. BR (GO29465 study)



Source: MAIC technical report(64)

Abbreviations: BR = bendamustine and rituximab; MAIC = matching-adjusted indirect comparison; pola-BR = polatuzumab vedotin with bendamustine and rituximab

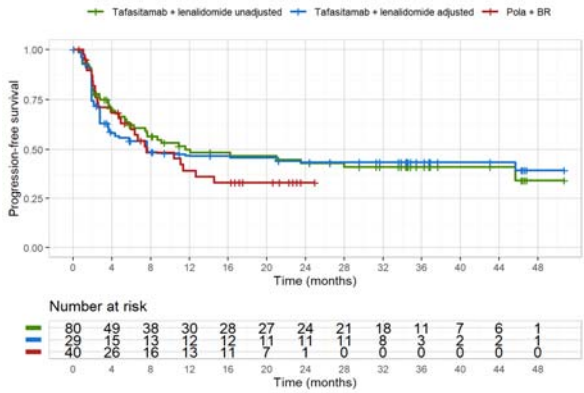
Results for the assessment of the proportionality of hazard assumption for each MAIC are presented in Appendix D. No concerns were raised regarding the assessments for OS vs. R-GemOx. In the MAIC vs. BR (GO29365 study), the distance between the TAFA+LEN and BR curves increased over time, hinting at a potential violation of the proportional hazards assumption.

PFS

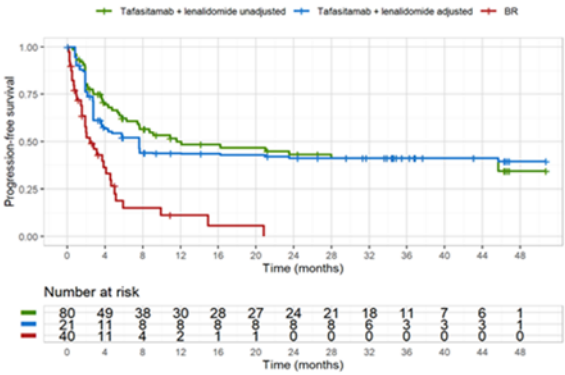
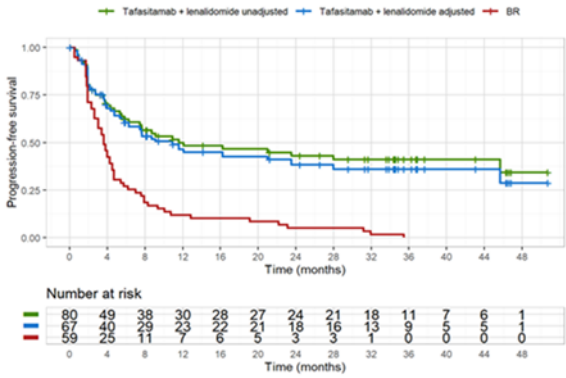
The estimated HRs for PFS with TAFA+LEN in the unadjusted and adjusted L-MIND populations vs. comparators are shown in Appendix D. KM curves for the L-MIND adjusted and unadjusted populations vs. comparators are shown in Figure 14.

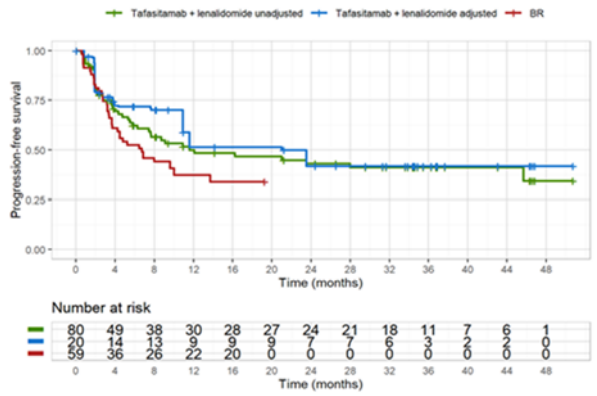
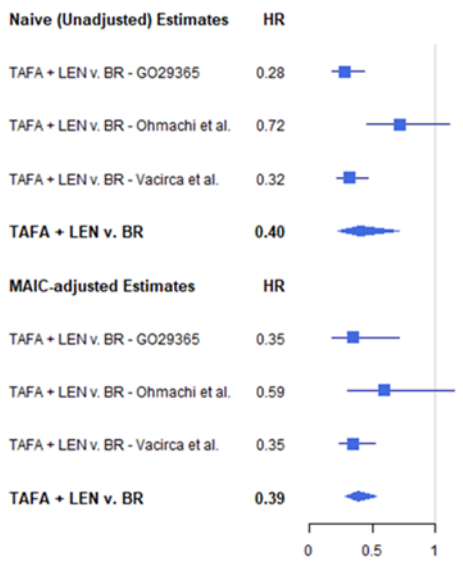
Figure 14. KM estimates for PFS for TAFA+LEN observed (green) and weighted (blue) compared with reported PFS-IRC estimates for comparators (red)

MAIC vs. pola-BR (PFS-IRC)



MAIC vs. BR (PFS-IRC)

GO29365	Vacirca et al., 2014
	

Ohmachi et al., 2013	Pooled naïve and MAIC-adjusted estimates of HRs
	

Source: MAIC technical report(64)

BR = bendamustine and rituximab; INV = investigator-assessed; IRC = independent review committee; KM = Kaplan-Meier; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine, oxaliplatin

In the MAIC vs. BR (GO29365 and Vacirca et al., studies), no major concerns were identified. Although the TAFA+LEN and BR curves were observed to overlap initially for PFS-IRC in GO29365 and Vacirca et al., they quickly separated.

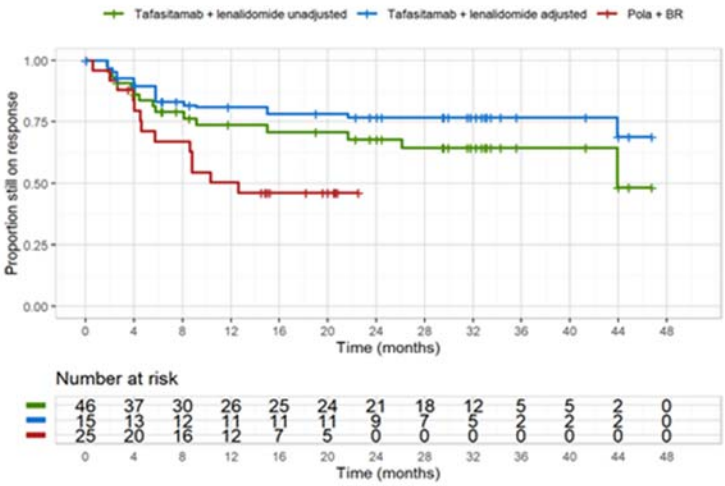
DoR

The estimated HRs for DoR with TAFA+LEN in the unadjusted and adjusted L-MIND populations vs. comparators are shown in Appendix D. KM curves for the L-MIND adjusted and unadjusted populations vs. comparators are shown in

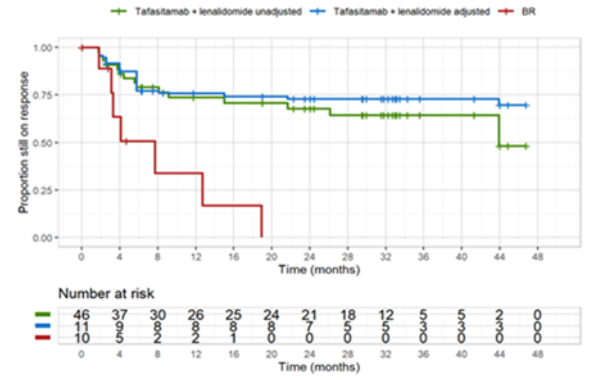
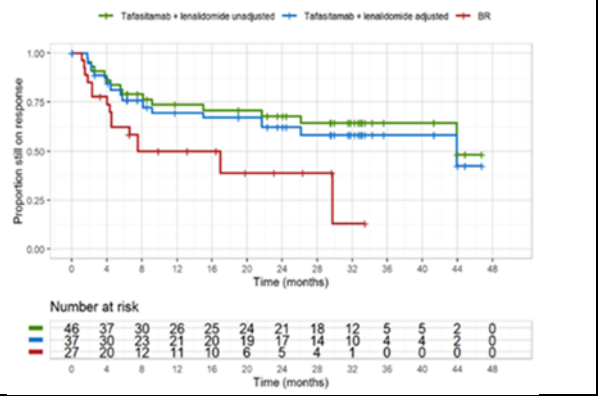
Figure 15.

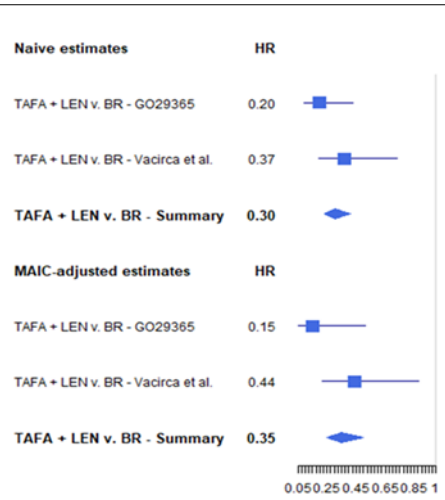
Figure 15. KM estimates for DoR for TAFA+LEN observed (green) and weighted (blue) compared with reported DoR estimates for comparators (red)

Pola-BR (DOR-IRC)



BR (DoR-IRC)

GO29365	Vacirca et al., 2014
	

Ohmachi et al., 2013	Pooled naïve and MAIC-adjusted estimates of HRs
Not available	

Source: MAIC technical report(64)

Abbreviations: BR = bendamustine and rituximab; DoR = duration of response; HR = hazard ratio; IRC = independent review committee assessed; KM = Kaplan-Meier; pola-BR, polatuzumab vedotin with bendamustine and rituximab; TAFA+LEN = tafasitamab + lenalidomide

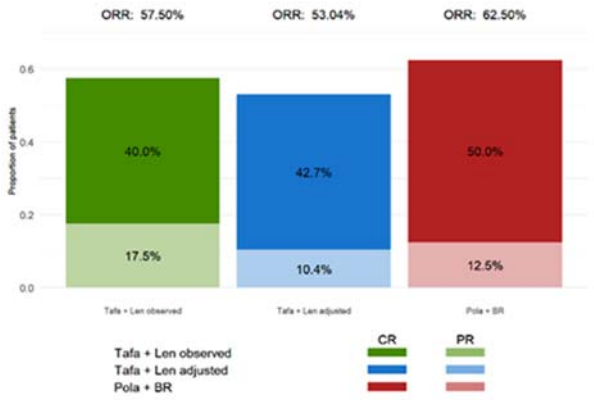
Response rates

The estimated ORs for ORR and complete response rate (CRR) with TAFA+LEN in the unadjusted and adjusted L-MIND populations vs. comparators are shown in Appendix D. Depth of response (ORR and CRR) in the L-MIND adjusted and unadjusted populations vs. comparators are shown in

Figure 16.

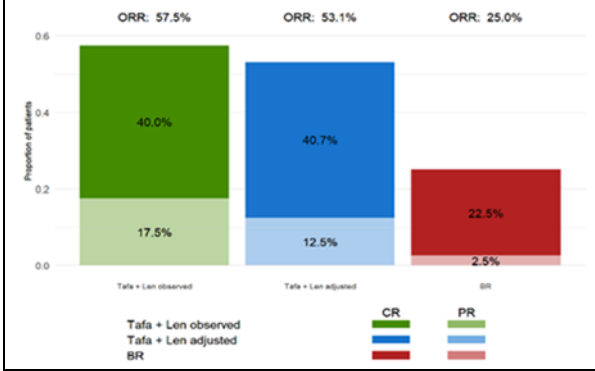
Figure 16. Depth of IRC responses for TAFA+LEN observed (green) and weighted (blue) compared with those reported for comparators (red)

MAIC vs. Pola-BR (IRC assessed)

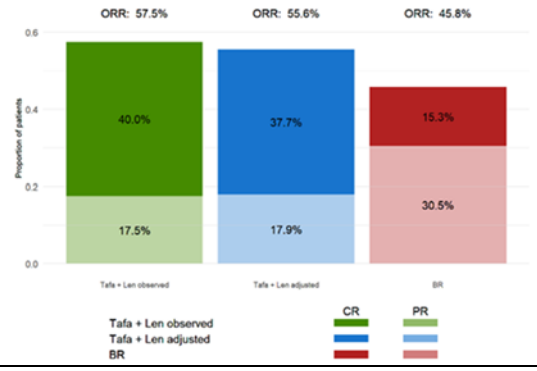


MAIC vs. BR (IRC assessed)

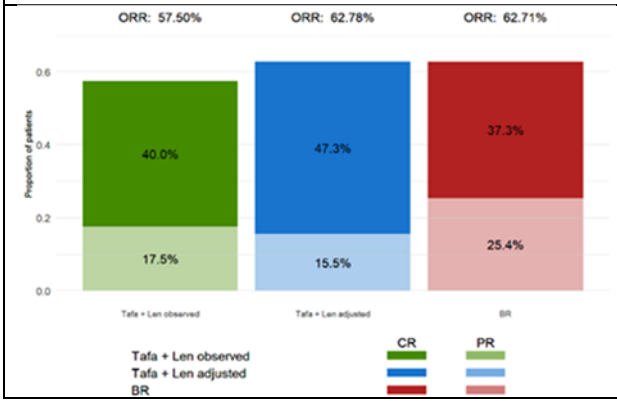
GO29365

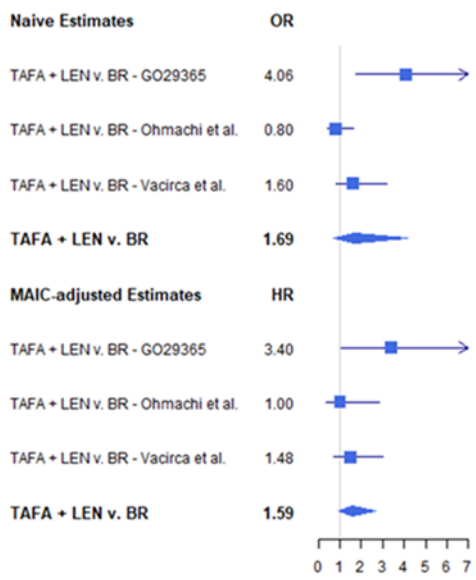
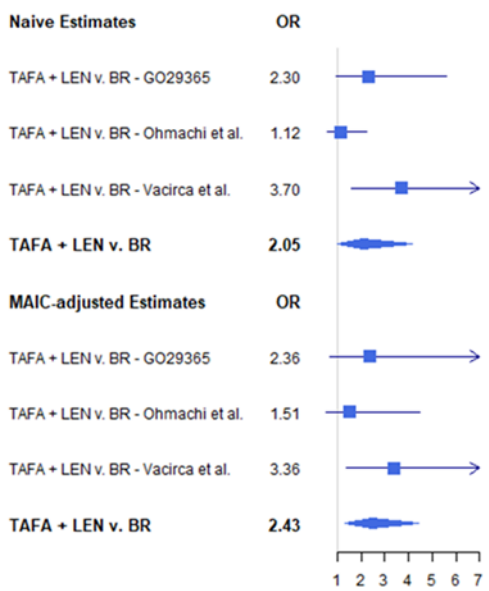


Vacirca et al., 2014



Ohmachi et al., 2013



Odds ratios for ORR for TAFA+LEN vs. BR across sources of evidence (pooled)	Odds ratios for CR for TAFA+LEN vs. BR across sources of evidence (pooled)
	

Source: MAIC technical report.(64)

Abbreviations: BR = bendamustine and rituximab; CR = complete response; HR = hazard ratio; IRC = independent review committee assessed; MAIC = matching-adjusted indirect comparison; OR = odds ratio; ORR = objective response rate; pola-BR, polatuzumab vedotin with bendamustine and rituximab; TAFA+LEN = tafasitamab + lenalidomide

Limitations of the MAIC

The shared-effect modifier assumption states that treatment effect modifiers affect all treatments in a similar way.(66) Some concerns were raised by clinical experts with respect to this assumption{Incyte Corporation, 2020 #316}. Clinical experts noted that sex could have an impact on the clearance of rituximab, and therefore, may have a differentiated effect on the efficacy of rituximab-containing regimens such as BR compared with TAFA+LEN.

Furthermore, rituximab-naïve patients were found to benefit more from R-GemOx than patients with prior rituximab exposure in the Mounier et al., 2013 study.(70) Therefore, it is possible that prior rituximab exposure could have had a differentiated impact on the efficacy of a subsequent TAFA+LEN or R-GemOx line. No population adjustment was possible on prior rituximab exposure as all patients from the L-MIND study were required to have had prior rituximab exposure. It was expected that had the Mounier et al., 2013 study(70) only included anti-CD20–experienced patients, the relative efficacy estimates would have favoured TAFA+LEN.

In the comparison of TAFA + LEN against POLA + BR, no significant treatment benefit was observed for OS, PFS-IRC, ORR-IRC, and CRR-IRC. A numeric advantage in favour of TAFA + LEN could be observed on OS and PFS-IRC, while patients receiving POLA + BR were numerically more likely to achieve a response or a complete response compared to patients receiving TAFA + LEN, although no statistically significant treatment benefit could be estimated either. A significant treatment effect in favour of TAFA + LEN was detected on DoR-IRC both before and after population-adjustment. However this result should be interpreted with caution due to the small sample size supporting this analysis. There were some concerns about the assumption of proportional hazards for the comparison of OS and PFS-IRC, and time-varying hazard ratios (HR) were estimated before and after four months from baseline. For OS and PFS-IRC, an HR initially numerically favoring POLA + BR was estimated for the first four months, followed by an HR numerically favoring TAFA + LEN. Importantly, a significant treatment effect of TAFA + LEN against POLA BR could be estimated on OS after the first four months on treatment. Although a numerical advantage in favour of TAFA + LEN could be observed after the first four months on treatment on PFS, this result was not statistically significant.

B.2.10. Adverse reactions

L-MIND

Overall extent of exposure

Overall, 427 patients received tafasitamab in the clinical study programme (as of 30 June 2019). In the primary safety analysis pool, 222 patients received tafasitamab (141 patients received tafasitamab as monotherapy and 81 as combination therapy in the L-MIND study), with an overall cumulative patient exposure of approximately 155 patient years.(61)

Long-term data from the L-MIND study (30 October 2020 data cut-off) showed that the median duration of exposure to study treatment (either TAFA+LEN or tafasitamab monotherapy) was 9.2 months (range: 0.23–53.67). The median duration of exposure to lenalidomide was [redacted] weeks (range: [redacted]).(57)

Treatment-emergent AEs

In the pivotal L-MIND clinical trial, treatment-emergent AEs (TEAE) of any grade occurred in all 81 patients. Neutropenia was the most common AE (all grades), occurring in 40 patients (49%). Common AEs of grade 3 or worse included thrombocytopenia, febrile neutropenia, leukopenia, anaemia and pneumonia. Most non-haematological AEs were mild (grades 1 or 2; Table 17). Of these, diarrhoea was the most common, with a median duration of 8 days (IQR: 3–24). Rashes were also common; 29 patients (n=29/81; 36%) developed rashes, most of which were grade 2 or lower. Seven patients (n=7/81; 9%) had a non-serious rash of grade 3, which was classified as allergic dermatitis in three patients and as maculopapular rash, erythematous rash, pruritus and psoriasis in one patient each. All patients recovered between two and 40 days after the event onset, but one patient with allergic dermatitis recovered with sequelae 45 days after event onset and both study drugs were discontinued in this patient.(53)

Ten (12%) of 81 patients discontinued the study during the combination therapy because of adverse events (Figure 5. L-MIND study: patient disposition (all patients enrolled)Figure 5). In total, 20 (25%) of 81 patients discontinued treatment with one or both study drugs because of adverse events during the study. LEN was discontinued in one patient with psoriasis and temporarily interrupted in two patients with allergic dermatitis. Infusion-related reactions were observed in five patients (n=5/81; 6%) and were all mild (grade 1). All occurred once during the first infusion and none required discontinuation.(53)

None of the four grade 5 AEs were AEs of special interest (AESI). No cases were suspected to be related to tafasitamab or LEN (see Section B.2.10.1. for details of deaths in the study).(53)

Table 17. TEAEs (SAS)

Adverse events	**Adverse event grades**			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**
Haematological events, n (%)				
Neutropenia	1 (1)	22 (27)	17 (21)	0
Anaemia	22 (27)	6 (7)	0	0

Adverse events	Adverse event grades			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Thrombocytopenia	11 (14)	10 (12)	4 (5)	0
Leukopenia	5 (6)	6 (7)	1 (1)	0
Febrile neutropenia	0	8 (10)	2 (2)	0
Lymphopenia	2 (2)	2 (2)	1 (1)	0
Agranulocytosis	0	0	1 (1)	0
Non-haematological events, n (%)				
All rash*	22 (27)	7 (9)	0	0
Diarrhoea	26 (32)	1 (1)	0	0
Asthenia	17 (21)	2 (2)	0	0
Cough	17 (21)	1 (1)	0	0
Peripheral oedema	18 (22)	0	0	0
Pyrexia	16 (20)	1 (1)	0	0
Decreased appetite	16 (20)	0	0	0
Hypokalaemia	10 (12)	4 (5)	1 (1)	0
Back pain†	11 (14)	2 (2)	0	0
Fatigue	12 (15)	2 (2)	0	0
All urinary tract infection*	9 (11)	3 (4)	1 (1)	0
Constipation	13 (16)	0	0	
Muscle spasms	12 (15)	0	0	0
Nausea	12 (15)	0	0	0
Bronchitis	10 (12)	0	1 (1)	0
Vomiting	11 (14)	0	0	0
Dyspnoea	9 (11)	1 (1)	0	0
Abdominal pain	7 (9)	1 (1)	0	0
Upper respiratory tract infection	6 (7)	2 (2)	0	0
Hypertension	4 (5)	3 (4)	0	0
Increased blood creatinine†	5 (6)	1 (1)	0	0
Mucosal inflammation	5 (6)	1 (1)	0	0
Pneumonia	1 (1)	5 (6)	0	0
Hypocalcaemia	4 (5)	1 (1)	0	0
Hypogammaglobulinemia	4 (5)	1 (1)	0	0
Increased γ-glutamyl transferase	4 (5)	1 (1)	0	0
Atrial fibrillation	1 (1)	2 (2)	1 (1)	0
Pulmonary embolism	0	2 (2)	2 (2)	0
Sinusitis	3 (4)	1 (1)	0	0
Deep vein thrombosis	2 (2)	0	1 (1)	0
Hyperbilirubinemia	2 (2)	1 (1)	0	0
Increased blood bilirubin	2 (2)	1 (1)	0	0

Adverse events	Adverse event grades			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Increased transaminases	1 (1)	2 (2)	0	0
Lower respiratory tract infection	2 (2)	1 (1)	0	0
Renal failure	1 (1)	2 (2)	0	0
Syncope	2 (2)	1 (1)	0	0
Tumour flare	2 (2)	1 (1)	0	0
Cataract	1 (1)	1 (1)	0	0
Congestive cardiac failure	0	2 (2)	0	0
Muscular weakness	1 (1)	1 (1)	0	0
Urinary incontinence	1 (1)	1 (1)	0	0
Arthritis	0	1 (1)	0	0
Atrial flutter	0	1 (1)	0	0
Biliary colic	0	1 (1)	0	0
Bronchopulmonary aspergillosis	0	0	1 (1)	0
Cardiac failure	0	0	1 (1)	0
Cerebrovascular accident	0	0	0	1 (1)
Cervicobrachial syndrome	0	1 (1)	0	0
Cranial nerve infection	0	1 (1)	0	0
Cytomegalovirus infection	0	1 (1)	0	0
Device-related thrombosis	0	1 (1)	0	0
Enterobacter bacteraemia	0	1 (1)	0	0
Febrile infection	0	0	1 (1)	0
Femur fracture	0	1 (1)	0	0
Haematuria	0	1 (1)	0	0
Hyperkalaemia	0	1 (1)	0	0
Hypersensitivity	0	1 (1)	0	0
Hyponatraemia	0	1 (1)	0	0
Infected bite	0	1 (1)	0	0
Klebsiella sepsis	0	1 (1)	0	0
Lower limb fracture	0	1 (1)	0	0
Lung infection	0	1 (1)	0	0
Myocardial ischaemia	0	0	1 (1)	0
Myositis	0	1 (1)	0	0
Nephrolithiasis	0	1 (1)	0	0
Neutropenic sepsis	0	1 (1)	0	0
Osteonecrosis	0	1 (1)	0	0
Peripheral sensorimotor neuropathy	0	1 (1)	0	0
Progressive multifocal leukoencephalopathy	0	0	0	1 (1)

Adverse events	Adverse event grades			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Recurrent marginal zone Lymphoma	0	1 (1)	0	0
Respiratory failure	0	0	0	1 (1)
Respiratory syncytial virus infection	0	1 (1)	0	0
Sepsis	0	0	1 (1)	0
Soft tissue infection	0	1 (1)	0	0
Streptococcal sepsis	0	0	1 (1)	0
Sudden death	0	0	0	1 (1)
Varicella zoster virus Infection	0	0	1 (1)	0
Wound complication	0	0	1 (1)	0

The table shows treatment-emergent AEs of grade 1 or 2 occurring in at least 10% of patients and all grade 3, 4, and 5 events.

*Defined by customised Medical Dictionary for Regulatory Activities query

†One report of back pain and one report of increased blood creatinine had no toxicity grading.

Source: Salles et al., 2020(53)

B.2.10.1. Serious AEs

In the primary analysis (30 November 2018 data cut-off), serious AEs (SAE) occurred in 41 patients (n=41/81; 51%). The most frequent (in two or more patients) were pneumonia (n=5/81;6%), febrile neutropenia (n=5/81;6%), pulmonary embolism (n=3/81; 4%), bronchitis (n=2/81; 2%), atrial fibrillation (n=2/81; 2%), and congestive cardiac failure (n=2/81; 2%).(53)

As of the 30 October 2020 data cut-off, 43 patients (n=43/81; 53.1%) had experienced a treatment-emergent SAE during the L-MIND study. The most frequent treatment-emergent SAEs were similar to those reported in the primary analysis.(57)

Deaths

As of the 30 November 2018 data cut-off, 30 patients died (n=30/81; 37%)—eight patients died during study treatment and 22 died post treatment. Twenty-three of the 30 deaths (77%) were related to lymphoma progression and seven (23%) were unrelated to disease progression. TEAEs leading to death occurred in four (13%) of the 30 patients: sudden death, respiratory failure, cerebrovascular accident and

worsening of progressive multifocal leukoencephalopathy. None were considered related to the study treatment.(53)

As of the 30 October 2020 data cut-off, 42 patients had died (12 additional patients after the primary analysis; n=42/81; 51.9%). As with the primary analysis, no deaths were considered related to the study treatment.(57)

B.2.10.2. MOR208C201

TEAEs

A summary of the TEAEs reported in the DLBCL cohort and total study population of the MOR208C201 study is provided in Table 18.

Table 18. TEAEs (SAS)

	DLBCL, n=35	**Total, N=92**
Any grade ≥3[b], n (%)	19 (54)	37 (40)
Haematological[c], n (%)		
Neutropenia	6 (17)	8 (9)
Thrombocytopenia	2 (6)	4 (4)
Anaemia	3 (9)	3 (3)
Non-haematological[c], n (%)		
Dyspnoea	2 (6)	4 (4)
Pneumonia[d]	3 (9)	3 (3)
Fatigue	1 (3)	2 (2)
Hypokalaemia	1 (3)	2 (2)
Infusion-related reaction,[a] n (%)		
Any, n (%)	4 (11)	11[e] (12)
Grade 1/2	4 (11)	10 (11)
Grade 4	0	1 (1)

Data are number of patients (%).

[a]TEAEs according to the Medical Dictionary for Regulatory Activities preferred term (PT)

[b]TEAEs including PT disease progression

[c]TEAEs reported at grade 3 in two or more patients overall

[d]In two patients, pneumonia started during the extended treatment phase (days 706 and 468, respectively), both patients recovered within two weeks. One patient developed pneumonia with cardiorespiratory failure (unrelated to tafasitamab treatment) in cycle 1 (day 23) with a fatal outcome

[e]No grade 3 or grade 5 infusion-related reactions were reported.

Source: Jurczak W, et al., *Ann Oncol*. 2018;29:1266–72(54)

Abbreviation: DLBCL = diffuse large B-cell lymphoma

B.2.11. Ongoing studies

There are four ongoing clinical studies investigating tafasitamab (in combination with other treatments and as monotherapy) in 1L and 2L+ R/R DLBCL:

- The pivotal L-MIND study: phase II, open-label, multicentre study characterising the safety and efficacy of tafasitamab in combination with lenalidomide in adults with R/R DLBCL(4)
- B-MIND: an open-label, phase II/III randomised, two-arm, multicentre study of tafasitamab + bendamustine vs. rituximab + bendamustine in patients with R/R DLBCL who are receiving 2L or 3L treatment and who are not candidates for high-dose chemotherapy (HDC) and ASCT (thus have exhausted their therapeutic options)(71)
- An expanded access study for tafasitamab: in patients with R/R DLBCL(72)
- FIRST-MIND: a phase Ib study of tafasitamab monotherapy or TAFA+LEN, both in addition to R-CHOP, in the 1L DLBCL setting(73)

As part of the conditional marketing authorisation, Incyte has committed to complete a further clinical study with TAFA+LEN in R/R DLBCL patients not eligible for ASCT. This study is due in 2026 and could further support the evidence already presented. This could support inclusion in the Cancer Drugs Fund to support the decision making for this appraisal.

The international clinical development programme investigating tafasitama+b for the treatment of DLBCL and other cancers is summarised in Table 19.

Table 19. Clinical development programme for tafasitamab

Study	Phase	Therapy	Line of Tx	Cancer type	Recruiting countries	Enrolment (n)	Status
DLBCL							
NCT04134936 MOR208C107 FIRST-MIND	Ib	Tafasitamab or TAFA+LEN in addition to R-CHOP	1L	DLBCL	Austria, Belgium, Czech Republic, Germany, Portugal, US	Estimated: 60	Ongoing, not recruiting
NCT02399085 MOR208C203 L-MIND	II	TAFA+LEN	2L/ 3L	R/R DLBCL	Spain, Poland, Italy, Hungary, Germany, France, Czech Republic, Belgium, UK, US	81	Ongoing, not recruiting
NCT02763319 MOR208C204 B-MIND	II/III	Tafasitamab + bendamustine vs. BR	2L/ 3L	R/R DLBCL	Australia, Austria, Canada, Croatia, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Korea, New Zealand, Poland, Portugal, Romania, Serbia, Singapore, Spain, Taiwan, Turkey, UK, US	Estimated: 450	Ongoing, recruiting
NCT04300803 MOR208N001	Expanded access	Tafasitamab	2L+	R/R DLBCL	US	NA	Approved for marketing
Other therapy R/R DLBCL							
NCT04150328 MOR208C206 RE-MIND	Retrospective	LEN monotherapy vs. TAFA+LEN	2L/ 3L	R/R DLBCL	France, Italy, Spain, US	490	Completed
NCT04697160 MOR208C213 RE-MIND2	Retrospective	Systemic therapies vs. TAFA+LEN	2L+	R/R DLBCL	Australia, Austria, Canada, Denmark, France, Germany, Italy, South Korea, Spain, Taiwan, UK, US	Estimated: 3,729	Ongoing, not recruiting
Other cancers							
NCT01685021 MOR208C202	2a	Tafasitamab	2L+	R/R B-ALL	US	22	Terminated

Study	Phase	Therapy	Line of Tx	Cancer type	Recruiting countries	Enrolment (n)	Status
NCT02639910 MOR208C205 COSMOS	2	Tafasitamab + idelalisib or venetoclax	2L+	R/R CLL/SLL (previously treated with BTKi)	Italy, Poland, Germany, Austria, UK, US	24	Ongoing, not recruiting
NCT01161511 XmAb5574-01	1	Tafasitamab	2L+	R/R CLL/SLL	US	27	Completed
NCT02005289 NCI-2013-02082 OSU-13031	2	TAFA+LEN	1L/ 2L	R/R CLL, SLL or PLL or older pts w/untreated CLL, SLL, or PLL	US	41	Ongoing, not recruiting
NCT01685008 MOR208C201	2a	Tafasitamab	2L+	R/R NHL	Belgium, Germany, Hungary, Italy, Poland, Spain, US	92	Ongoing, not recruiting

Sources: NCT04134936(73); NCT02399085(4); NCT02763319(71); NCT04150328(74); NCT04300803(72); NCT01685021(75); NCT02639910(76); NCT01161511(77); NCT02005289(78); NCT01685008(79); NCT04697160(71)

Abbreviations: B-ALL = B-cell acute lymphoblastic leukaemia; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin lymphoma; PLL = prolymphocytic leukaemia; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; Tx = treatment; UK = United Kingdom; US = United States

B.2.12. Innovation

Tafasitamab an Fc-enhanced mAb directed against CD19, combined with the immunomodulatory agent lenalidomide, is a novel immunological treatment combination and represents a step change in the management of R/R DLBCL. The value of this new therapeutic combination to patients with R/R DLBCL is highlighted by the Promising Innovative Medicines designation awarded by the Medicines and Healthcare products Regulatory Agency in the UK (January 2020 – PIM 2019/0012) and accelerated approval received from the US Food and Drug Administration (FDA) on the 1 July 2020. Additionally tafasitamab maintained orphan designation in R/R DLBCL after EMA and MHRA assessed that DoR could be clinically relevant and supportive of a significant benefit over Pola+BR (based on MAIC analysis).(10)

Combination treatments for patients with R/R DLBCL, including transplant-ineligible patients, commonly include re-targeting of CD20 in combination with chemotherapy, despite evidence that some B-cell malignancies, including DLBCL, lose CD20 expression after exposure to anti-CD20 therapy.(24, 36, 44, 45, 48, 80, 81)

While advances in treatment for R/R DLBCL have improved response rates in second and third line, these treatment options are not providing durable responses in majority of patients. Patients with R/R DLBCL, in particular those with advanced age, associated comorbidities, and CD20-negative transformation after prior treatment with rituximab, may be unsuitable for regimens such as ASCT, CAR-T therapy, or pola-BR.

CD19 is a transmembrane protein and signalling molecule present on B cells that is involved in B-cell development, differentiation, proliferation and signalling via enhancement of B-cell receptor signalling.(82) The protein is expressed throughout the B-cell lineage and across a wider population of B cells than CD20.(82) Tafasitamab triggers malignant B-cell death by binding to CD19 and inducing direct cytotoxicity as well as immune-mediated mechanisms, i.e., NK cell-mediated ADCC and macrophage-mediated antibody-dependent cellular phagocytosis, with ADCC as the primary contributor to the mechanism of action (MOA) for tafasitamab.(8) In

several in vitro studies comprising various leukaemia and lymphoma models, tafasitamab exhibited greater B-cell cytotoxic potential compared with the CD20-targeting antibody rituximab.(8) LEN, an immunomodulatory agent that enhances the activity and recruitment of NK cells, has been shown to enhance NK-cell-mediated ADCC when combined with tafasitamab in vitro.(83)

An analysis of B-cell lymphoma patient biopsies revealed that CD19 expression is preserved even after CD20 is downregulated by anti-CD20 treatment.(45, 84) This allows sequencing of novel CD19 therapies with anti-CD20 treatments such as rituximab. Multiple CD19-targeting therapies have demonstrated clinical efficacy in R/R DLBCL, including adoptive cell therapies (i.e., CAR-T therapies) and antibody-drug conjugates (i.e., loncastuximab tesirine), providing clinical evidence that CD19-targeting therapies deliver a treatment option for patients who progress after anti-CD20 therapy.(85-91) Preclinical and clinical data also suggest that tafasitamab does not impact CD19 expression or the mechanism and viability of CAR-T therapy.(92-95) Introducing the potential for sequencing. Data on CD19 sequencing is currently immature though early research is showing promise.(54)

Finally, in contrast to currently available fixed-duration treatment options, the safety and tolerability of tafasitamab allows administration until disease progression in the majority of patients.(53, 54)

B.2.13. Interpretation of clinical-effectiveness and safety evidence

L-MIND (MOR208C203) demonstrated that TAFA+LEN, followed by tafasitamab monotherapy, resulted in deep and durable clinical responses in patients with R/R DLBCL who failed at least one prior systemic therapy (including an anti-CD20 therapy) and were not eligible for ASCT.

In the primary analysis, TAFA+LEN resulted in a best ORR of 60%, CR rate of 42.5%, PR rate of 17.5% and a median time to CR of 6.80 months. The activity of this combination was consistent across patient subgroups, including those who were refractory to prior therapies. In addition to the positive ORR result, responses were durable (median DoR was 21.7 months), particularly in patients who achieved a CR

(median DoR was not reached). The median PFS was 12.1 months and median OS was not reached (73.7% of patients were alive at 12 months).(53)

An updated analysis of the study was conducted with three years of follow-up for all patients (30 October 2020 data cut-off). The results of the primary analysis, including the durability of response, were confirmed with continued treatment. The median DoR was 43.9 months, median PFS 11.6 months, and median OS 33.5 months. With a median follow-up of 42.7 months for OS.(53)

At ≥35 months of follow-up, 23.5% of patients were still alive and continued to receive treatment at the data cut-off; the median OS was 33.5 months (median survival follow-up of 42.7 months.(54) For context, adults diagnosed with R/R DLBCL in a systematic review of published literature were estimated to have an age-standardised, one-year survival of 41%.(25) For patients who were refractory to 1L therapy, median OS was 6.3 months, with only 22% of patients alive at two years, in a large pooled, retrospective analysis of patients with refractory DLBCL (SCHOLAR-1 study).(26) Table 20 presents the time to event endpoints split by number of prior lines.

Table 20. L-MIND extended follow-up analysis for PFS, DOR and OS by prior lines of therapy (data cut-off 30 October 2020; ≥35 months of follow-up)(54)

	1 prior line of therapy n=40	**≥2 prior lines of therapy n=40**
Median PFS, months (95% CI)	23.5 (7.4, NR)	7.6 (2.7, NR)
Median DoR, months (95% CI)	43.9 (9.1, NR)	NR (15.0, NR)
Median OS, months (95% CI)	45.7 (24.6, NR)	15.5 (8.6, NR)

Abbreviations: CI = confidence interval; DoR = duration of response; NR = not reported; OS = overall survival; PFS = progression-free survival

To appropriately contextualise the data, in the absence of an RCT, two indirect-treatment comparisons using 1:1 NN matching methodology were developed (RE-MIND and RE-MIND2). As well, an MAIC study comparing L-MIND with an SLR-based list of prospective studies of comparators generated results that were consistent with those observed in the RE-MIND studies.

RE-MIND2 estimated the activity of TAFA+LEN in the context of the various therapies administered in routine care. Primary analysis results showed statistically

significant and clinically meaningful improvement of OS in the TAFA+LEN cohort vs. the cohorts of BR (31.6 vs. 9.9 months; HR=0.418 [95% CI: 0.272, 0.644]), and R-GemOx (31.6 vs. 11.0 months; HR=0.467 [95% CI: 0.305, 0.714]). All time-to-event endpoints (PFS, EFS and TTNT) supported the primary analysis results of OS and were in line with the overall results, with numerical but clinically meaningful differences, non-statistically significant differences between the TAFA+LEN cohort and the BR and R-GemOx. TAFA+LEN showed numerical improvement in these comparisons vs. pola-BR.

These results were supported by the findings of the MAIC study, which compared published literature identified by an SLR with the results from L-MIND. The MAIC analyses showed significant improvements for TAFA+LEN vs. LEN monotherapy and vs. BR. In the MAICs of TAFA+LEN vs. LEN and vs. BR, TAFA+LEN was found to significantly improve OS, PFS and CR rate, and have a numeric advantage on ORR. DoR achieved by patients was also significantly longer when receiving TAFA+LEN vs. BR or vs. Pola-BR. For OS applying a time varying hazard ratio provided a statistically significant result from four months to the end of follow-up irrespective of population adjustment for TAFA+LEN vs. Pola+BR.

Tafasitamab was well tolerated in the L-MIND study. The most frequently reported AEs were in line with the MOA for tafasitamab, mild, and managed as part of routine oncology practice.(53) Few patients had to stop tafasitamab due to AEs (12% (n/N=10/81) in the study overall).(53) The safety profile of TAFA+LEN was very similar to that of LEN alone. Comparing the commonly reported AEs to data for LEN monotherapy revealed no major difference in incidence between these two treatments.

While the safety profile of tafasitamab was typical for a B-cell targeting mAb, the incidence and severity of infusion reactions were much lower than seen with other mAbs used in the treatment of B-cell malignancies.(96, 97) Infusion-related reactions were managed with appropriate supportive/prophylactic therapy.

Prolongation of remission has been identified by international and national treatment guidelines as an important goal of therapy.(41) The results of L-MIND demonstrated

that TAFA+LEN can provide lasting remission and overall survival in patients with R/R DLBCL, a population that is known to be difficult to treat.

B.2.13.1. End-of-life criteria

The combination treatment of TAFA+LEN meets the NICE end-of-life criteria as summarised in Table 21.

Table 21. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with R/R DLBCL have a life expectancy of 3–9 months, are limited to palliative care, and therefore represent an important unmet need.(39, 98, 99)	Section B.1.3.5. pg. 25
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The KM estimate for median OS was 33.5 months (95% CI: 18.3 months–NR; FAS; Figure 9).(54) In the SCHOLAR-1 study median overall survival was 6.3 months in patients who are refractory to 1L therapy.(26) In the model, TAFA+LEN was associated with undiscounted life year gains were 3.97 vs Pola-BR, 4.48 vs BR and 4.41 vs R-GemOx	Section B.2.6.4. pg. 50

Abbreviations: 1L = first line; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; FAS = full analysis set; KM = Kaplan-Meier; NHS = National Health Service; NR = not reached; OS = overall survival; R/R = relapsed/refractory

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

In the economic SLR, 40 R/R DLBCL economic publications were identified, of which four were cost-effectiveness analyses assessing the cost-effectiveness of comparators included in the final scope. Table 22 presents an overview of these studies.

One study explored the cost-effectiveness of TAFA+LEN against existing treatment pathways in terms of cost per LYG using a discrete event simulation model, although the exact comparators considered were not clearly stated in the study abstract.

The remaining three cost-effectiveness studies (Betts 2019 and Betts 2020(100), Patel 2020) compared pola-BR against BR from a US payer perspective for a transplant-ineligible R/R DLBCL population. Betts 2019 and Betts 2020(100) both adopted a partitioned survival model approach, whereas Patel 2020(101) used a Markov modelling approach.

Table 22. Overview of cost-effectiveness analysis studies

Study	Perspective	Time horizon	Model design	Model population	Comparators	Base-case effectiveness results	Base-case cost results	Base-case ICERs
Neubauer 2019(102)	US payer	Not stated	Discrete event simulation	L-MIND (transplant-ineligible R/R DLBCL)	TAFA+LEN DLBCL treatment pathway	Not stated	Not stated	Cost per LYG: between $60,000 and $330,000 (depending on a hypothetical drug cost range of $200,000–$600,000)
Betts 2019(100)	US third-party payer	Not stated	Partitioned survival model	Transplant-ineligible R/R DLBCL	Pola-BR BR	Patients treated with pola-BR had increased QALYs vs. BR (incremental: 2.49).	Costs (USD) The total cost of pola-BR ($232,358) was $113,484 higher than BR ($118,874), primarily due to higher drug and administration costs ($170,028 vs. $50,163, respectively). Pola-BR had cost-savings for PD (-$11,914) and end-of-life care (-$2,131) vs. BR. AE costs were higher for pola-BR ($21,989) than BR ($15,505).	Cost per QALY gained: $45,535
Betts 2020(100)	US third-party payer	Lifetime	Partitioned survival model	Adults with R/R DLBCL, after ≥1 prior therapy, who were ineligible for HSCT	Pola-BR BR	pola-BR LYs: 4.04 QALYs: 3.31	Total costs Pola-BR: $210,418 BR: $118,088	Pola-BR vs. BR: Cost per LY gained: $29,881

Study	Perspective	Time horizon	Model design	Model population	Comparators	Base-case effectiveness results	Base-case cost results	Base-case ICERs
				(based on the GO29365 trial)		BR LYs: 0.95 QALYs: 0.73 Incremental LYs: 3.09 QALYs: 2.57	Incremental: $92,329	Cost per QALY gained: $35,864
Patel 2020(101)	US payer	Lifetime	Markov model	Transplant-ineligible R/R DLBCL	Pola-BR BR	Effectiveness, QALYs: Pola-BR: 2.35 BR: 0.59 Incremental: 1.76	Total costs Pola-BR: $200,905 BR: $108,265 Incremental: $92,641	Pola-BR vs. BR: Cost per QALY gained: $52,519

Abbreviations: AE = adverse event; BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; HSCT = haematopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; LY = life year; PD = progressive disease; pola-BR, polatuzumab vedotin with bendamustine, and rituximab; QALY = quality-adjusted life-year; R/R - relapsed or refractory; TAFA+LEN = tafasitamab + lenalidomide; US = United States; USD = United States dollar

Further details on the economic SLR methodology and results are described in Appendix D and Appendix H.

B.3.2. Economic analysis

For the economic analysis, a de novo economic model was constructed to evaluate TAFA+LEN in the transplant-ineligible R/R DLBCL setting. To inform the main model inputs and assumptions, a review of previous health technology assessments (HTA) and relevant guidelines in transplant-ineligible R/R DLBCL was conducted, and expert opinion sought via discussions with key opinion leaders (KOL) in the UK (Table 23 and Appendix M).

B.3.2.1. Patient population

The population included in the economic evaluation were patients with R/R DLBCL ineligible for stem cell transplantation (SCT), in line with the population enrolled in the L-MIND study (Section B.2.2.), the decision problem addressed in this submission (Section B.1.1.), and the marketing authorisation for TAFA+LEN (Appendix C).

Patients in the model were assumed to have an average baseline age of 69.3 years, 54.5% male, a mean weight of [redacted] and a mean height of [redacted], based on the L-MIND population characteristics.

B.3.2.2. Model structure

An economic model was developed in Microsoft Excel® to assess the cost-effectiveness of tafasitamab vs. relevant comparators for the treatment of patients with DLBCL who are ineligible to receive SCT in line with the licensed indication.

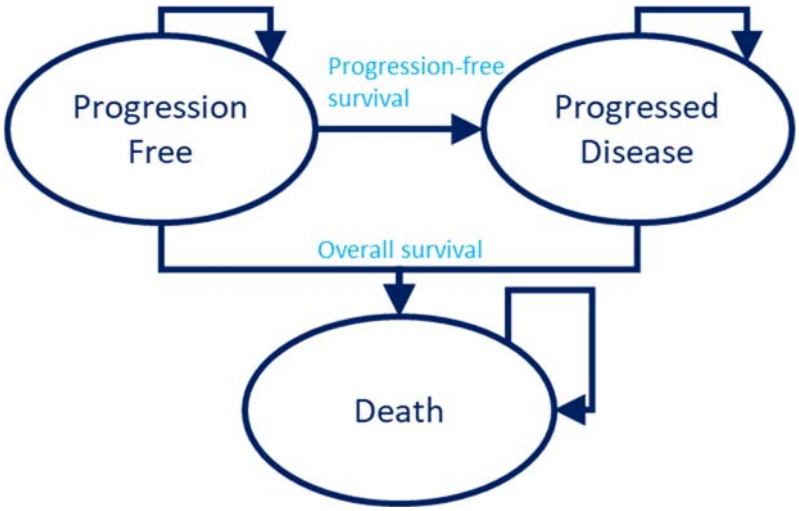
A partitioned survival modelling approach was selected in line with NICE Decision Support Unit (DSU) guidance. Partitioned survival models are one of the most commonly adopted modelling approaches for oncology, particularly for advanced cancer populations.

This approach was also in line with most recent NICE technology appraisals (TA) for R/R DLBCL, including the most recent NICE Ta (TA649(5)) for pola-BR (Table 23).

Partitioned survival model approach

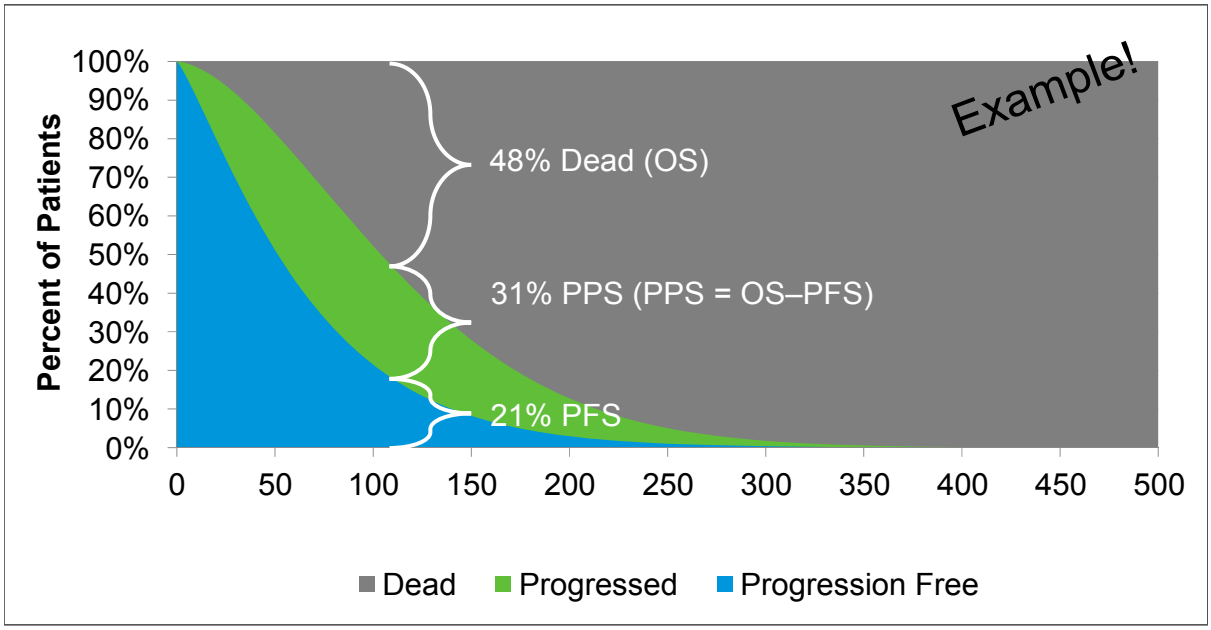
Figure 17 illustrates the partitioned survival model health states, which applies treatment-specific and independent OS and PFS curves for each comparator. These curves are used directly to calculate the proportion of patients in the mutually exclusive health states of pre-progression, post-progression, and death at any given time.

Figure 17. Model Diagram



The survival partition approach does not directly calculate the transitions between health states but partitions the population into groups based on survival outcomes. At any timepoint in the model, patients falling under the PFS curve are in the pre-progression health state, with the proportion of patients between the OS and PFS curves classified as having PD and the remainder above the OS curve in the death health state (Figure 18).

Figure 18. Example survival partition approach



Abbreviations: OS = overall survival; PFS = progression-free survival; PPS = post-progression survival

B.3.2.3. Features of the economic model

Perspective

The economic analysis was performed from a UK National Health Service (NHS) and Personal and Social Services (PSS) perspective and considered only direct medical costs, including drug costs, drug administration costs (e.g., co-medications), monitoring, management of AEs, subsequent treatment costs, and disease management costs, in line with the NICE reference case.(103)

Cycle length

In line with the treatment cycle length for TAFA+LEM, a four-week cycle length was applied. This cycle length was deemed sufficiently short to accurately capture clinical outcomes and differences in treatment administrations between comparators.

Time horizon and discounting

A 45-year time horizon was used in the base case, expected to cover a lifetime horizon for patients in the target population given the median age (69.3 years) of patients in the L-MIND study. This time horizon was considered long enough to

capture the relevant long-term clinical and economic consequences of DLBCL for patients who are ineligible for ASCT, and was also aligned with prior NICE appraisals for R/R DLBCL therapies (Table 23).

Cost and health-related (like quality-adjusted life years [QALY]) outcomes were discounted at a rate of 3.5% in the base case in accordance with the NICE reference case.(103)

Summary of key features of the economic model vs. prior NICE R/R DLBCL TAs

The key features of the economic analysis compared to prior NICE TAs for R/R DLBCL are summarised in Table 23.

Table 23. Key features of the economic analysis

Factor	Previous appraisals				Current appraisal	
	TA649 (pola-BR)(5)	**TA567 (tisa-genlecleucel)(6)**	**TA559 (axicabtagene-ciloleucel)(1)**	**TA306 (pixantrone)(35)**	**Chosen values**	**Justification**
Population	R/R DLBCL patients who are ineligible for SCT	R/R DLBCL after 2 or more systemic therapies	R/R DLBCL and PMBCL after 2 or more systemic therapies	Multiply R/R aggressive non-Hodgkin's B-cell lymphoma	R/R DLBCL patients who are ineligible for SCT	In line with the marketing authorisation for TAFA+LEN, as well as the population of the L-MIND trial
Model structure	Partitioned survival model with three health states (PFS, PD, death) Individual patient modelling used for calculating background mortality risks	Partitioned survival model with 3 health states (PF, PD and death)	Partitioned survival model with 3 health states (pre-progression, post-progression, death)	Semi-Markov model with 3 health states (SD or PF, PD or relapsed disease, death)	Partitioned survival model with three health states (PFS, PD, death)	NICE DSU guidance(104) Consistent with most prior TAs (excluding TA306(35)) and commonly used approach for modelling advanced cancer indications
Time horizon	Lifetime (45 years)	Lifetime (46 years)	Lifetime (44 years)	Lifetime (23 years)	Lifetime (45 years)	Lifetime horizon adopted to capture cost and health benefits of R/R DLBCL treatments over a patient's lifetime Consistent with NICE reference case and prior DLBCL appraisals.
Cycle length	1 week	1 month	1 month	1 week	4 weeks	To match the treatment cycle length for TAFA+LEN Considered sufficiently short to accurately capture clinical outcomes and differences in treatment administrations between comparators
Durable remission/cure assumptions	Mixture-cure parametric models fitted to OS and PFS	Mixture-cure parametric models fitted to OS and PFS	Mixture-cure parametric models fitted to OS	None	No cure assumptions applied for base-case analysis	Uncertainty expressed by clinical experts around cure assumptions for R/R DLBCL patients{Incyte Corporation, 2020 #316}

Factor	Previous appraisals				Current appraisal	
	TA649 (pola-BR)(5)	**TA567 (tisa-genlecleucel)(6)**	**TA559 (axicabtagene-ciloleucel)(1)**	**TA306 (pixantrone)(35)**	**Chosen values**	**Justification**
	HRQoL and mortality of patients in PFS assumed equivalent to age-and sex-matched general population after 2 years	Assumed that patients who are alive at 2 years (in either treatment group) will revert to the same HRQoL and long-term costs as the PF state	After 2 years in the pre-progression state utilities and mortality matched to general population			Hybrid cure modelling approaches (fixed 2-year cure point and cure at crossing of OS and PFS curves) explored in scenario analyses
Perspective and discounting	NHS and PSS perspective; 3.5% discount rate for costs and outcomes	NHS and PSS perspective; 3.5% discount rate for costs and outcomes	NHS and PSS perspective; 3.5% discount rate for costs and outcomes	NHS and PSS perspective; 3.5% discount rate for costs and outcomes	NHS and PSS perspective; 3.5% discount rate for costs and outcomes	NICE reference case(103).
Treatment waning effect?	No	No	No	No	No	No evidence of treatment effect waning observed in the clinical trial data. Assumptions consistent with previous R/R DBLCL appraisals.
Source of utilities	Utility values from TA559 (PFS: 0.72, PD: 0.65)	SF-36 data from pivotal trial (JULIET) mapped to EQ-5D (PF: 0.83, post-progression: 0.71)	EQ-5D-5L data from pivotal trial (ZUMA-1) cross walked to EQ-5D-3L utility estimates (PF: 0.72, post-progression: 0.65)	Utility values from the literature (pre-progression 0.76, post-progression 0.68)	Utility values from TA559	QoL data not collected in the L-MIND study Utilities from TA559 applied in line with TA649, and in absence of alternative utilities from the literature Alternative utilities from TA567 explored in scenario analysis
Source of costs	NHS reference costs, PSSRU and BNF	NHS reference costs, PSSRU, and BNF/eMIT	NHS reference costs, PSSRU, and National Audit Office	BNF and NHS reference costs	NHS reference costs, PSSRU and BNF/eMIT	Consistent with the NICE reference case(103)

Sources: NICE TA649 (5)

Abbreviations: BNF = British National Formulary; DLBCL = diffuse large B-cell lymphoma; DSU = Decision Support Unit; eMIT = electronic market information tool; HRQOL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression-free survival; PMBCL = primary mediastinal B-cell lymphoma; pola-BR = polatuzumab vedotin with bendamustine and rituximab; PSS = Personal and Social Services; PSSRU = Personal and Social Services Research Unit; R/R = relapsed/refractory; SCT = stem cell transplantation; SD = stable disease; SF-36 = 36-item Short Form health survey; TA = technology appraisal; TAFA=LEN = tafasitamab + lenalidomide; UK = United Kingdom

B.3.2.4. Intervention technology and comparators

Intervention – TAFA+LEN

The model intervention is TAFA+LEN, as described in Section B.1.2. Both tafasitamab and LEN are administered in four weekly (28 day) treatment cycles.

Tafasitamab is administered by intravenous (IV) infusion at a dose of 12 mg/kg. For the first three treatment cycles, tafasitamab is administered weekly on days 1, 8, 15 and 22 of each 28-day treatment cycle, with an additional loading dose administered on day 4 of the first treatment cycle. After the first three treatment cycles, tafasitamab is then administered on days 1 and 15 (bi-weekly) of each 28-day treatment cycle.

LEN is administered orally at a dose of 25 mg per day for days 1 to 21 of each 28-day treatment cycle, up to a maximum of 12 treatment cycles.

Comparators – pola-BR, R-GemOx and BR

The comparators included in the economic analysis were pola-BR, R-GemOx and BR. These treatments were considered the most relevant comparator therapies for a R/R DLBCL population ineligible for SCT based on the R/R DLBCL patient pathway and feedback from clinical experts.{Incyte Corporation, 2020 #316} Dosing for pola-BR and BR was based on NICE TA649(5), with dosing for R-GemOx based on Mounier 2013(70) and the maximum number of treatment cycles for R-GemOx based on UK lymphoma guidelines(105):

- R-GemOx:
    - Rituximab 375 mg/m^2 IV on day 1 of every 15-day treatment cycle up to a maximum of six treatment cycles
    - Gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 IV on day 2 of every 15-day treatment cycle up to a maximum of six treatment cycles

- BR
    - Bendamustine 90 mg/m^2 IV on two consecutive days for each three-week treatment cycle (days 2 and 3 of cycle 1, days 1 and 2 of cycles 2-6) up to a maximum of six total treatment cycles
    - Rituximab 375 mg/m^2 IV on day 1 for each three-week treatment cycle up to a maximum of six total treatment cycles
- Pola-BR
    - Polatuzumab vedotin 1.8 mg/kg IV once every three-week treatment cycle (day 2 of cycle 1, day 1 of cycles 2-6) up to a maximum of six total treatment cycles
    - Bendamustine and rituximab dosing as per BR regimen

Relative efficacy estimates for comparators were obtained using results from the RE-MIND2 study or the MAIC (see Section B.2.9. for details).

B.3.3. Summary of base-case analysis inputs and assumptions

B.3.3.1. Summary of selected base case OS and PFS methods for comparator therapies

A summary of the selected data sources and methods for OS and PFS extrapolation for the base case analysis are summarised below in Table 24. RE-MIND2 data were selected for R-GemOx and BR due to the larger sample sizes compared to the clinical trial data used for the MAIC (74 and 75 vs. 49 and 40, respectively), and the availability of patient level data to allow for more robust analyses and exploration of various parametric extrapolations. Standardised mean differences for key baseline patient characteristics showed no substantial imbalances between TAFA+LEN and R-GemOx or BR after 1:1 matching, and UK clinical experts{Incyte Corporation, 2020 #316} indicated that the RE-MIND2 parametric survival extrapolations for R-

GemOx and BR produced plausible estimates in relation to clinical practice. RE-MIND2 results for R-GemOx and BR were also robust with respect to multiple sensitivity analyses, as shown in Appendix M.1.1.

In addition, due to the poor overlap of L-MIND and Mounier 2013(70) patient populations, the population adjustment for the MAIC for TAFA+LEN vs. R-GemOx was limited. No adjustment could be made on refractoriness of patients to their prior therapy, older patients were kept in the L-MIND population while patients above 75 should not have been candidates for inclusion in the Mounier 2013(70) study, and no adjustment on the number of prior lines of therapy received by patients could be made beyond the exclusion of patients treated in the fourth-line setting or beyond in L-MIND. Therefore, the results produced by the MAIC are expected to be biased in favour of R-GemOx.

However, given the smaller sample size for the Pola-BR comparison for RE-MIND2 compared to the MAIC (39 vs. 40) and clinical expert feedback on the plausibility of the Pola-BR data from RE-MIND2, time-varying HRs from the MAIC were used instead.

Table 24. Base case modelling approaches for OS and PFS

Treatment	Base case data source	Comments
R-GemOx	RE-MIND2 unadjusted parametric fits	RE-MIND2 data selected due to larger sample size vs. MAIC data and availability of 1:1 matched patient level data to explore different parametric extrapolations, as well as limitations with MAIC for comparison against R-GemOx. PH assumption not valid for both OS and PFS. Significant overlap between matched and overall L-MIND TAFA+LEN population curves for both OS and PFS, and therefore unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution for OS and PFS. Alternative parametric models and MAIC HR estimates explored in scenario analyses.
BR	RE-MIND2 constant HR (OS) and unadjusted parametric fit (PFS)	RE-MIND2 data selected due to larger sample size vs. MAIC data and availability of 1:1 matched patient level data to explore different parametric extrapolations. PH assumption plausible for OS, and constant HR from RE-MIND2 (2.392) applied to TAFA+LEN curve to estimate BR OS in base case analysis.

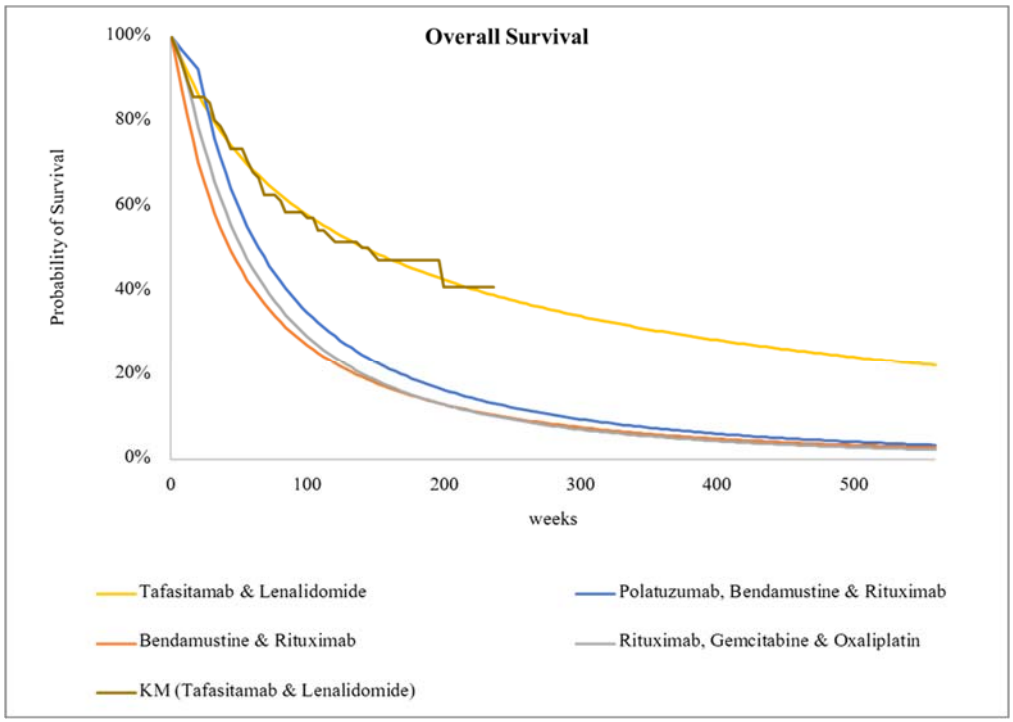
		For PFS, matched and overall L-MIND TAFA+LEN population curves significantly overlap, and therefore unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution. Alternative parametric models and MAIC HR estimates explored in scenario analyses.
Pola-BR	MAIC time-varying HRs with 4-month split	MAIC selected over RE-MIND2 data based on clinical expert feedback and lower sample size for RE-MIND2 matched population for Pola-BR comparison. Time-varying HRs used due to apparent violation of PH assumption, with 4-month split applied for base case analysis. Alternative MAIC HR calculations (11-month HR split, constant HR) and RE-MIND2 data explored in scenario analyses (Appendix D Section D.1.6)

Abbreviations: BR = bendamustine + rituximab; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA+LEN, tafasitamab plus lenalidomide.

Base-case extrapolations for OS are shown in Figure 19, with PFS extrapolations shown in Abbreviation: KM = Kaplan-Meier

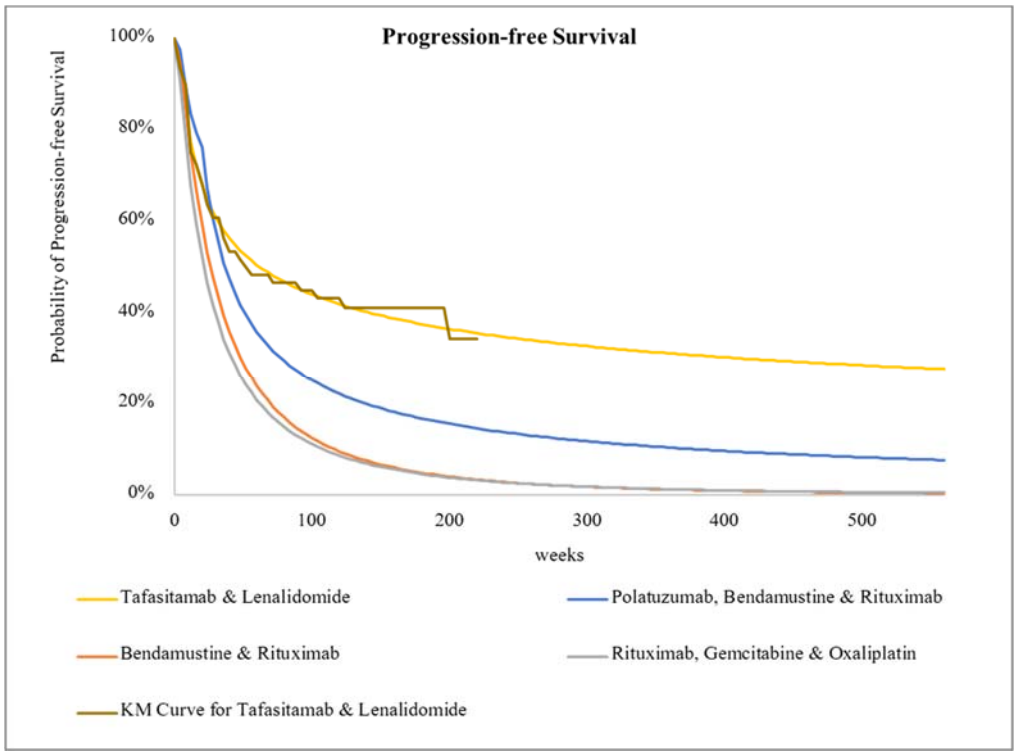
Figure 20.

Figure 19. Base case OS extrapolations



Abbreviation: KM = Kaplan-Meier

Figure 20. Base case PFS extrapolations



Abbreviation: KM = Kaplan-Meier

The following efficacy data scenario analyses were also explored to investigate the impact of choosing different data sources and modelling approaches:

- Alternative RE-MIND2 parametric models
  - R-GemOx
    - Gompertz for OS
    - Generalised gamma for PFS
  - BR
    - Generalised gamma for PFS
- Pola-BR specific scenarios:
  - Apply MAIC HRs with 11-month split
  - Apply constant MAIC HR
  - Apply adjusted parametric models from RE-MIND2 data (generalised gamma for OS, exponential for PFS)

- This scenario utilises TTD data from RE-MIND2 for Pola-BR to align with the data source selection for PFS

- Applying MAIC HR estimates for all comparators (using time-varying HRs with 4-month split for Pola-BR)
  - This scenario utilises exponential models fitted to the median TTD estimates from clinical trial data for R-GemOx and BR to better align with the use of clinical trial data for PFS HR estimates

B.3.3.2. Summary of base-case analysis inputs

A summary of the key inputs for the economic analysis is shown in Table 25. Detailed parameter estimates are available in the sections references in the table or in Appendix M.

Table 25. Summary of base-case inputs

Variable		Reference to section in submission
Model settings		
Discount rate (costs and outcomes)	3.5%	B.3.2.2.
Time horizon, years	45	
Patient characteristics		
Baseline age, years	69.3	B.3.2.1.
% male	54.3%	
Mean weight, kg	[redacted]	
Mean height, cm	[redacted]	
Clinical inputs		
OS	Log-normal distribution for TAFA+LEN based on L-MIND Log-normal distribution for R-GemOx and constant HR for BR based on RE-MIND2 Time-varying HRs with 4-month split for pola-BR based on MAIC (Appendix D Section D.1.6)	B.3.3.1.
PFS	Generalised gamma distribution for TAFA+LEN based on L-MIND Log-normal distribution for R-GemOx and BR based on RE-MIND2 Time-varying HRs with 4-month split for pola-BR based on MAIC	B.3.3.1.
TTD	Log-normal distribution for tafasitamab	Appendix M.1.1.6

Variable		Reference to section in submission
	KM curves for other (fixed duration) treatments	
AE frequency	Various	Appendix M.1.1
AE duration	Various	
Proportion of death events among PFS events	10%	Appendix M.1.2.1
Utilities		
PFS	0.72	B.3.4.
PD	0.65	
Costs		
Drug acquisition costs	Various	B.3.5. B.3.5.1.
Administration costs	Various	B.3.5.3.
Co-medication costs	Various	B.3.5.4.
Subsequent treatment costs	Various	B.3.5.5.
Monitoring costs	Various	B.3.5.6.
Disease management costs	Various	B.3.5.6.
AE costs	Various	B.3.5.7.

Abbreviations: AE = adverse event; BR = bendamustine and rituximab; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PD = progressive disease; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide; TTD = time to treatment discontinuation

B.3.3.3. Assumptions

A summary of the key modelling assumptions made are listed in Table 26.

Table 26. Key Assumptions

Assumption	Rationale	Reference to the section
No treatment waning assumed	No evidence of treatment effect waning in clinical trial and consistent with previous R/R DLBCL appraisals	B.3.2.3. , Appendix M.1.2
No cure assumption for base-case analysis	No cure assumption assumed in base-case analysis based on clinical expert feedback around uncertainty of cure assumptions Various cure assumptions explored in scenario analyses	Appendix M.1.2
No prolonged progression-free patients in base-case analysis	Explored in scenario analysis based on clinical expert feedback	Appendix M.1.1, M.1.2
Assumed hypokalaemia disutility equal to leukopenia	Assumption used in polatuzumab NICE submission	
Multiplicative approach to utility	NICE methods guide update and assumption of overlap in symptoms/outcomes for patients with R/R DLBCL compared to other age-related conditions	B.3.4.5.
Assumed 100% dose intensity where no information about dose intensity was available	Assumed that if no data regarding a reduction in dose intensity was available then there was no reduction	B.3.5.1.
[redacted]	[redacted]	B.3.5.1.
Assumed co-medications received by 100% of patients on tafa+len for the first 4-week model cycle and 0% thereafter	In the L-MIND study, co-medications were given prior to tafasitamab infusion for the first three infusions. In the absence of infusion related reactions and at the discretion of the investigator, co medications were not mandated for subsequent infusions. Simplifying assumption made that all patients receive co-medications for the first 4-week model cycle and no patients thereafter.	B.3.5.4.
Assumed treatment duration for subsequent treatments was equal to use in initial treatment	Lack of data for treatment use specifically as a subsequent treatment	B.3.5.5.

Post-progression resource use for TAFA+LEN assumed equal to pola-BR and BR	Absence of data for pola-BR and TAFA+LEN	B.3.5.6.
Assumed terminal care cost for the last three months of life	In line with NICE TA567	B.3.5.6.

Abbreviations: BR = bendamustine and rituximab; NICE = National Institute for Health and Care Excellence; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R/R = relapsed/refractory; TA = technology appraisal; TAFA+LEN = tafasitamab + lenalidomide; TTD = time to treatment discontinuation

B.3.4. Measurement and valuation of health effects

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

HRQoL data were not collected in the L-MIND trial. As such, HRQoL data were sought from previous NICE appraisals and publications identified as part of the SLR.

B.3.4.2. Mapping

No mapping of HRQoL was performed for the economic analysis.

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

An SLR was also performed to identify studies reporting HRQoL and health state utility data in patients with DLBCL. Further details on the SLR methodology and results are provided in Appendix G and Appendix H.

A total of 30 studies were identified in the review of HRQoL evidence. Of these, only three studies with health state utility estimates for relevant model comparators included in the final scope (Betts 2019 and Betts 2020(100), Patel 2020(101)) were identified. Health state utility values from these studies, alongside previous NICE R/R DLBCL submissions, are summarised below in Table 27.

Generally speaking, health state utility values identified from the published studies from the SLR and prior NICE R/R DLBCL studies were sourced either from older studies for aggressive non-Hodgkin lymphoma (NHL), or from the ZUMA-1 or JULIET trials which included R/R DLBCL populations receiving CAR-T therapy.

Table 27. HRQoL and utility studies in R/R DLBCL identified in the SLR and previous NICE appraisals for R/R DLBCL

Source	Health state utilities		Applicability to current appraisal
	PFS	PD	

Betts 2019	0.83	0.71	Utility values sourced from NICE TA567.
Betts 2020(100)	0.83	0.71	Utility values sourced from NICE TA567.
Patel 2020(70)	0.83	0.39	Health state utility data sourced from Chen 2018, which is based on utility estimates from Best 2005, which in turn derived utility estimates using data from Doorduijn 2001.(70) Underlying utility data appear fairly old and based off estimates from an aggressive NHL population receiving CHOP chemotherapy, which may not be generalisable to an R/R DLBCL population ineligible for SCT.(70)
NICE TA649 (Pola-BR)(5)	0.72	0.65	Utility values sourced from NICE TA559.
NICE TA567 (tisa-genlecleucel)(6)	0.83	0.71	Utilities mapped from SF-36 data collected in the JULIET trial to EQ-5D-3L using Rowen 2009.(70) Utilities derived from a population receiving CAR-T which may not be generalisable to the L-MIND population (e.g. due to differences in age).
NICE TA559 (axicabtagene-ciloleucel)(1)	0.72	0.65	Utility values derived from the ZUMA-1 trial, by applying a cross-walking algorithm to generate EQ-5D-3L utilities from the EQ-5D-5L results from the study. Utilities derived from a population receiving CAR-T which may not be generalisable to the L-MIND population (e.g. due to differences in age).
TA306 (pixantrone)(35)	0.76	0.68	Utility estimates based on two published studies on NHL patients (Doorduijn 2005, van Agthoven 2001). Estimates are sourced from fairly old studies and are less specific to R/R DLBCL than other utility estimates.

Abbreviations: CAR-T = chimeric antigen receptor T-cell; EQ-5D, EuroQol-5 Dimension; NHL = non-Hodgkin lymphoma; PD = progressed disease; PFS = progression-free survival; R/R DLBCL = relapsed/refractory diffuse large B-cell lymphoma.

B.3.4.4. Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values were applied to each health state to capture the quality of life associated with treatment and disease outcomes. Table 28 details the utilities used within the model for patients remaining progression free and alive (PFS) or with progressed disease. Although these utility data were derived from a CAR-T population which may not be generalisable to patients from the L-MIND study, base case utility estimates were sourced from the NICE appraisal for axicabtagene ciloleucel (TA559(1)), which were also applied in the NICE R/R DLBCL technology appraisal for Pola-BR (TA649(70)). In addition, two of the three UK clinical experts,

with whom the base case utility values were discussed with, indicated that these utility values were reasonable given their use in TA649, although one of the two clinical experts noted that progressed disease patients may have a lower health state utility as the population of patients receiving TAFA+LEN and other model comparators may be older and generally less fit than patients receiving CAR-T therapy.

Quality of life loss from subsequent CAR-T therapy was also applied in the base case analysis. A published study identified in the SLR (Lin 2019(70)) included utility lower utility estimates for CAR-T therapies for the first 2 months of therapy relative to chemoimmunotherapy. The difference in utility values between chemoimmunotherapy and tisagenlecleucel for the first 2 months of therapy (0.63 – 0.58 = 0.05) was used to generate a one-off disutility for CAR-T treatment.

Table 28. Summary of utility values for cost-effectiveness analysis

Health state	Utility Value	SE	Source
PFS	0.72	0.03	NICE TA559(1)
PD	0.65	0.06	
Disutility: CAR-T (One-Off)	0.0083	0.0008	Lin 2019 0.05 disutility for CAR-T therapy relative to chemoimmunotherapy applied for a 2-month duration

Abbreviations: PD = progressed disease; PFS = progression-free survival; SE = standard error

A second set of health state utilities from NICE TA567 (0.83 for PFS, 0.71 for PD) was also explored in scenario analysis.(21, 54)

Cure assumptions were not included in the base case analysis. However, assumption of equivalent quality of life to progression-free patients and assumption of equivalent quality of life to the general population were both explored in cure assumption-related scenario analyses.

Quality of life loss related to each adverse event (AE) was applied as a one-off QALY loss to each treatment, with disutilities and AE durations displayed in Table 29. QALY losses associated with each AE were weighted by the probability of the AE occurring for each treatment, with AE probabilities summarised in Section B.3.5.7.

Table 29. AE Disutilities

	Disutility	Duration (days)	Source
Anaemia	0.25	16.00	NICE TA649(5)
Febrile neutropenia	0.15	7.10	NICE TA649(5), NICE TA306(35)
Hypokalaemia	0.09	72.00	Assumed same as leukopenia
Leukopenia	0.09	14.00	NICE TA649(5), NICE TA306(35)
Neutropenia	0.09	15.10	NICE TA649(5), NICE TA306(35)
Pneumonia	0.20	14.90	NICE TA649(5), NICE TA306(35)
Thrombocytopenia	0.11	23.20	NICE TA649(5), NICE TA306(35)
Lymphopenia	0.09	34.00	Bullement et al., 2019(85), NICE TA306(35)

*Assumption - maximum Treatment disutility from TA306(35) (Pixantrone for R/R aggressive NHL) Note this assumption was used in Polatuzumab NICE submission (see p100)

Abbreviations: AE = adverse event; LDH = lactate dehydrogenase

B.3.4.5. Age and sex adjustment of utilities

In order to account for differences in age and sex characteristics between the model population and reference populations for the utility values, as well as account for decreasing quality of life with increasing age, utilities were adjusted for age and sex within the model.

To adjust for age and sex, utility values applied in the model were compared against general population utility estimates for the reference age and sex characteristics of the underlying population used to derive the utility estimates. Depending on the adjustment approach selected (additive or multiplicative), an absolute utility decrement (additive) or a multiplication factor (multiplicative) were derived between the health state utility value and the age and sex-matched general population utility. This utility decrement or multiplication factor was then applied to a general population utility curve derived for the modelled population sex characteristics and age over time in order to generate a utility curve by age for each health state.

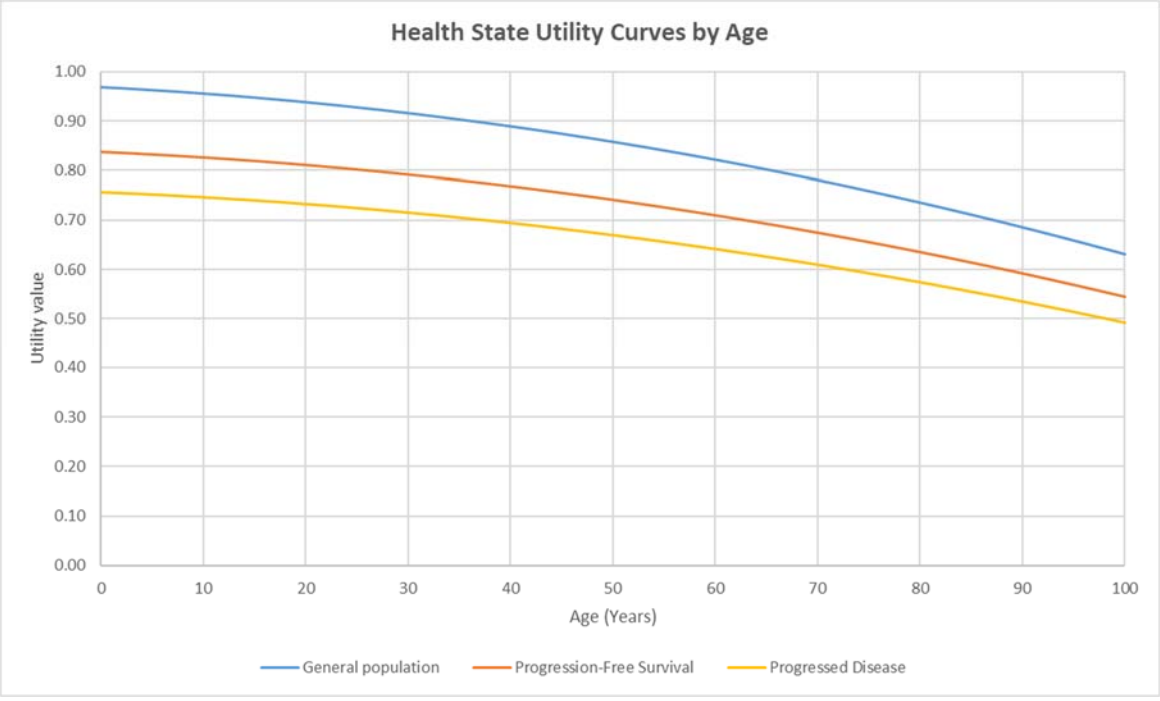
For the base case analysis, the multiplicative approach was applied under the assumption that there may be some overlap in disease symptoms or patient outcomes (such as hospitalisation events) with other age-related conditions, and in line with commentary from NICE regarding the NICE methods guide update. Reference population characteristics used to generate the disutility multiplier vs. the

general population for the progression-free and progressed disease health states were based on the ZUMA-1 trial (median age of 58 years, 67% male), with reference population characteristics for the utility scenario analysis based on the JULIET trial (median age of 56 years, 64.5% male). Reference population characteristics for AE disutilities were based on the original publications used to derive the AE disutilities.

General population utility was modelled according to published UK regression models from Ara/Brazier 2010(106) and Chang-Douglass 2020.(107) Both studies provide general population regression models derived from Health Survey for England (HSE) data, with Chang-Douglass 2020 updating the Ara/Brazier regression model to include additional HSE datasets for 2008, 2010-2012, 2014 and 2017. For the base case analysis, the general population regression model from Chang-Douglass 2020 was applied given the larger sample size of HSE data included in the analysis, and due to the availability of uncertainty data around the regression model coefficients (which were not provided in the Ara/Brazier 2010 study).

General population and health state utility curves applied for the base case analysis are shown in Figure 21.

Figure 21. General population and age/sex adjusted health state utility curves



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

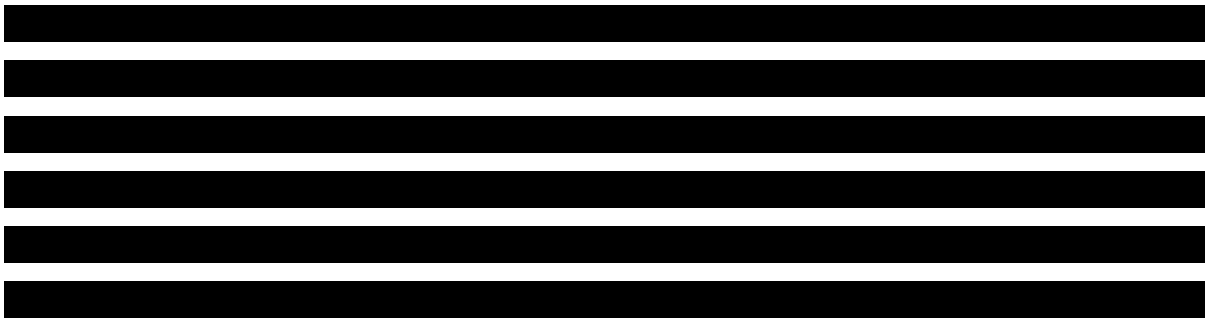
The economic analysis was conducted from the NHS and PSS perspective, with appropriate unit cost sources such as NHS reference costs (2019-2020), PSSRU Unit costs of Health and Social Care 2020, the British National Formulary (BNF) online (October 2021), and the drugs and pharmaceutical electronic market tool (eMIT) (September 2021) used to inform model cost inputs.

Disease- and treatment-related costs were applied to each health state and event in the model. Cost categories included: drug and administration costs applied for the duration of active treatment (determined by dosing regimen and treatment duration); routine follow-up care costs; and unplanned event costs, such as adverse events, progression, and terminal care costs.

B.3.5.1. Drug acquisition costs

Drug acquisition costs for the treatment options included in the model for induction and maintenance are shown in Table 30 and Table 31 respectively.

For TAFA+LEN and R-GemOx, patients who have not discontinued treatment by the end of induction treatment phase could move on to maintenance treatment phase. All tafasitamab patients not discontinuing prior to the end of the induction period were assumed to move on to the maintenance phase of treatment. For R-GemOx, 78% of patients remaining on treatment moved to the maintenance phase of treatment, based on Mounier 2013(70) (where 28 out of the 36 patients completing induction started the consolidation phase of treatment).



[redacted]

Dose intensities are included in the model to adjust the drug costs based on the actual dosage received by the patient, and are shown in Table 30. For the L-MIND study, dose intensity for each treatment cycle for tafasitamab and lenalidomide was calculated as follows:

$$\text{Dose intensity} = \frac{total\ dose\ received}{planned\ total\ dose} * 100$$

Median dose intensity parameters for Pola-BR and BR were sourced from NICE TA649, with dose intensity estimates for Pola-BR based on the overall patient populations of the Phase Ib and Phase II trials. R-GemOx dose intensities were assumed to be 100% in the absence of available data.

For treatments with weight-based dosing, a mean weight of [redacted] was applied based on the patient characteristics of the L-MIND trial. A body surface area (BSA) of [redacted] was also calculated based on the mean weight ([redacted]) and mean height ([redacted]) of patients in L-MIND and used to estimate drug costs for regimens with dosing based on BSA. For both weight- and BSA-based based treatments, a normal distribution around the mean weight or BSA was used to distribute the proportions of patients requiring different numbers of vials, from which a weighted average cost per dose was calculated.

No vial sharing was assumed in the base case analysis, with vial sharing for all IV based treatments explored in scenario analysis.

Table 30. Induction Drug Costs

Treatment	Dependency	Dose	Cost per dose	# of weeks per treatment cycle	Dose intensity	Notes
Tafasitamab & Lenalidomide						
Tafasitamab	Weight	12.0 mg/kg	£3,655.71	4	[redacted]	[redacted]
Lenalidomide	Fixed dose	25.0 mg	[redacted]	4	[redacted]	[redacted]
Polatuzumab, Bendamustine & Rituximab						
Polatuzumab	Weight	1.8 mg/kg	£12,289.42	3	99.5%	NICE TA649(5)
Bendamustine	BSA	90.0 mg/m2	£30.22	3	95.4%	NICE TA649(5)
Rituximab	BSA	375.0 mg/m2	£1,202.25	3	99.4%	NICE TA649(5)
Bendamustine & Rituximab						
Bendamustine	BSA	90.0 mg/m2	£30.22	3	95.6%	NICE TA649(5)
Rituximab	BSA	375.0 mg/m2	£1,202.25	3	96.7%	NICE TA649(5)
Rituximab, Gemcitabine & Oxaliplatin						
Rituximab	BSA	375.0 mg/m2	£1,202.25	2	100.0%	Cycles were repeated every 15 days (Mounier 2013)(70)
Gemcitabine	BSA	1000.0 mg/m2	£22.06	2	100.0%	Cycles were repeated every 15 days (Mounier 2013)

Oxaliplatin	BSA	100.0 mg/m2	£28.21	2	100%	Cycles were repeated every 15 days (Mounier 2013)

*Dose intensity describes the median intensity of dosages. Where dose intensity is not 100%, patients receive a lower dosage after a number of treatment cycles.

Ref 1: Drugs and pharmaceutical electronic market information tool (eMIT)(24) - Pharmex data for the period 01/01/20 - 31/12/20, for Pharmex products shown as Generic in the period 01/07/20 - 31/12/20. Access data: September 2021.

For gemcitabine and dexamethasone 14 different formulations were listed, therefore calculated £/mg (mg per pack) and selected 4 options with lowest £/mg

Ref 2: BNF Access date: September 2021

Abbreviations: BNF = British National Formulary; BSA = body surface area; eMIT = electronic market information tool; IV = intravenous; PAS = Patient Access Scheme; PO = orally

Table 31. Maintenance Drug Costs

Treatment	Dependency	Dose	Cost per dose	# of weeks per treatment cycle	Dose intensity
Tafasitamab & Lenalidomide					
Tafasitamab	Weight	12.0 mg/kg	£3,655.71	4	[redacted]
Rituximab, Gemcitabine & Oxaliplatin					
Rituximab	BSA	375.0 mg/m2	£1,202.25	4	100.0%
Gemcitabine	BSA	1000.0 mg/m2	£22.06	4	100.0%
Oxaliplatin	BSA	100.0 mg/m2	£28.21	4	100.0%

B.3.5.2. Treatment schedule

The treatment schedules for the induction phase for all comparators are summarised in Table 32.

Table 32. Induction Treatment Schedule

Treatment	Treatment Cycle Length	Treatment Cycle Number	Number of Administrations Per Treatment Cycle	Reference
TAFA+LEN				
Tafasitamab	4 weeks	1	5	L-MIND CSR(109)
		2−3	4	
		4−12	2	
Lenalidomide		1−12	21	
Pola-BR				
Polatuzumab	3 weeks	1−6	1	NICE TA649(5)
Bendamustine		1−6	2	
Rituximab		1−6	1	
BR				
Bendamustine	3 weeks	1−6	2	NICE TA649(5)
Rituximab		1−6	1	
R-GemOx				
Rituximab	2 weeks	1−4	1	Mounier 2013(70)
Gemcitabine		1−4	1	
Oxaliplatin		1−4	1	

Abbreviations: BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell; CSR = clinical study report; Pola-BR = polatuzumab + bendamustine + rituximab; R2 = lenalidomide + rituximab; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-GemOx = rituximab + gemcitabine and oxaliplatin

Treatment schedules for the maintenance phase for all comparators are summarised in Table 33. For R-GemOx, 78% of patients received consolidation treatment for cycles 5-8 in Mounier 2013(70). However, as UK guidelines for R-GemOx recommend a maximum of 6 treatment cycles(110), 78% of patients were instead assumed to have up to 6 cycles of treatment.

Table 33. Maintenance Treatment Schedule

Treatment	Treatment Cycle Length	Treatment Cycle number	Number of administrations per treatment cycle	Reference
TAFA+LEN				
Tafasitamab	4 weeks	13+	2	L-MIND CSR(109)
Lenalidomide		---	---	
R-GemOx				
Rituximab	2 weeks	5−6	1	Mounier 2013(70) El Gnaoui 2007(111) NHS lymphoma chemotherapy protocols(110)
Gemcitabine		5−6	1	
Oxaliplatin		5−6	1	

Abbreviations: BSA = body surface area; CSR = clinical study report; R2 = lenalidomide + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

B.3.5.3. Administration costs

Administration costs for IV and subcutaneous (SC) treatments included in the model are presented in Table 34, with the unit cost per resource sourced from NHS reference costs(2).

As the first and subsequent instances had different costs these were both included within the model. A radiotherapy administration unit cost is also included as some patients receive radiotherapy in the subsequent line of treatment.

Table 34. Administration Costs

Mode of Administration	Unit Cost	Reference:
IV/SC admin: first attendance (SB13Z)	£302.53	NHS reference costs 2019/20(2)
IV/SC admin: subsequent (SB15Z)	£253.77	
Radiotherapy (SC25Z)	£367.32	

Abbreviations: IV = intravenous; NHS = National Health Service; SC = subcutaneous

B.3.5.4. Concomitant medications

Table 35 details the drug dosing and cost calculation for the co-medication costs for each of the treatments.

In the L-MIND study, co-medications were given prior to tafasitamab infusion for the first three infusions. In the absence of infusion related reactions and at the discretion of the investigator, co medications were not mandated for subsequent infusions.(9)

Otherwise, co-medications were continued for subsequent infusions. Co-medications were therefore assumed to be received all patients on TAFA+LEN for the first 4-week treatment cycle and then 0% of patients thereafter for the base case analysis. In terms of concomitant treatment with methylprednisolone, doses of between 80-120mg were administered in the L-MIND study, and as such a fixed dose of 100mg was assumed for patients on TAFA+LEN.

All patients on other treatments were assumed to receive co-medications during their fixed duration treatment periods. Inclusion of co-medications was based on NICE TA649(5) for Pola-BR and BR, and El Gnaoui 2007(112) for R-GemOx.

Table 35. Co-medication Drug Dosing and Cost Calculation

Treatment	Dependency	Dose	Cost per Dose	# of Administrations per Tx Cycle	Cost per Tx Cycle	# of Weeks per Tx Cycle	Cost per Model Cycle
TAFA+LEN co-medications (induction)							
Acetaminophen (paracetamol)	Fixed dose	1000.0 mg	£0.01	4	£0.04	4	£0.04
Diphenhydramine	Fixed dose	37.5 mg	£0.24	4	£0.95	4	£0.95
Cimetidine	Fixed dose	300.0 mg	£0.07	4	£0.28	4	£0.28
Methylprednisolone	Fixed dose	100.0 mg	£0.64	4	£2.56	4	£2.56
Meperidine	Fixed dose	25.0 mg	£0.26	4	£1.05	4	£1.05
TAFA+LEN co-medications (maintenance)							
Acetaminophen (paracetamol)	Fixed dose	1000.0 mg	£0.01	2	£0.02	4	£0.02
Diphenhydramine	Fixed dose	37.5 mg	£0.24	2	£0.47	4	£0.47
Cimetidine	Fixed dose	300.0 mg	£0.07	2	£0.14	4	£0.14
Methylprednisolone	Fixed dose	100.0 mg	£0.64	2	£1.28	4	£1.28
Meperidine	Fixed dose	25.0 mg	£0.26	2	£0.52	4	£0.52
Pola-BR co-medications(5)							
Acetaminophen (paracetamol)	Fixed dose	1000.0 mg	£0.01	4	£0.04	3	£0.05
Allopurinol	Fixed dose	300.0 mg	£0.06	5	£-	3	£-
Chlorphenamine	Fixed dose	24.0 mg	£0.32	6	£1.93	3	£2.57
BR co-medications(5)							
Acetaminophen (paracetamol)	Fixed dose	1000.0 mg	£0.01	4	£0.04	3	£0.05
Allopurinol	Fixed dose	300.0 mg	£0.06	5	£-	3	£-
Chlorphenamine	Fixed dose	24.0 mg	£0.32	6	£1.93	3	£2.57
R-GemOx co-medications(112)							

Treatment	Dependency	Dose	Cost per Dose	# of Administrations per Tx Cycle	Cost per Tx Cycle	# of Weeks per Tx Cycle	Cost per Model Cycle
Methylprednisolone	Weight	1.0 mg/kg	£0.50	1	£0.50	2	£1.00
Acetaminophen	Fixed dose	1000.0 mg	£0.01	1	£0.01	2	£0.02
Dexchlorpheniramine	Fixed dose	6.0 mg	£0.08	1	£0.08	2	£0.16

Abbreviations: BR = bendamustine + rituximab; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; NA = not applicable; Tx = treatment

Table 36. Administration Dosing for Co-medications

Treatment	# of Administration per Treatment Cycle	Administration Route
Acetaminophen (paracetamol)	4	PO
Diphenhydramine	4	IV
Cimetidine	4	PO
Methylprednisolone	4	IV
Meperidine	4	PO
Acetaminophen (paracetamol)	2	PO
Diphenhydramine	2	IV
Cimetidine	2	PO
Methylprednisolone	2	IV
Meperidine	2	PO
Acetaminophen (paracetamol)	5.33	PO
Allopurinol	6.67	PO
Chlorphenamine	8	PO
Acetaminophen (paracetamol)	5.33	PO
Allopurinol	6.67	PO
Chlorphenamine	8	PO
Methylprednisolone	2	IV
Acetaminophen	2	PO
Dexchlorpheniramine	2	PO
Chlorphenamine	1	PO
Acetaminophen	1	PO

Abbreviations: IV = intravenous; NA = not available; PO = per oral

Table 37 displays the total co-medication costs for each of the treatments used within the model, which were calculated using the data in Table 35 and Table 36. For TAFA+LEN, co-medication costs are only applied to the proportion of patient receiving these comedications over time (assumed to be 100% in the first cycle, then 0% of patients in subsequent cycles).

For IV co-medications with the same frequency of administration (such as diphenhydramine and methylprednisolone), it was assumed that these co-medications would be administered simultaneously.

Table 37. Co-medication Costs

Treatment	Co-medication Cost per Model Cycle (Induction)	Co-medication Cost per Model Cycle (Maintenance)
TAFA+LEN	£1,019.94	£509.97
Pola-BR	£2.62	-
BR	£2.62	-
R-GemOx	£508.71	-

Abbreviations: BR = bendamustine and rituximab; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

B.3.5.5. Subsequent treatment costs

Drug costs for subsequent treatment options after progression are included in the model. These post-progression costs are a combination of possible SCT and other anti-cancer drug costs, including their administration costs.

The proportions of patients receiving different subsequent treatments upon progression on each induction treatment are listed in Table 38 and are based on the full analysis set for RE-MIND2, with the costs associated with each subsequent treatment being listed in Table 39. A 2% threshold was applied for inclusion of subsequent treatments from RE-MIND2 among any treatment arm, with the exception of CAR-T and SCT.

Table 38. Subsequent Treatment Distributions

Subsequent treatment	Patient Proportions per Initial Line of Treatment (based on RE-MIND2 FAS)			
	TAFA+LEN	Pola-BR	BR	R-GemOx
R-GemOx	5.3%	6.5%	5.6%	0.4%
R2	0.0%	1.1%	2.5%	3.6%
Pixantrone	2.6%	0.0%	1.5%	4.3%
Lenalidomide	0.0%	0.0%	1.9%	2.9%
Pola-BR	1.3%	1.1%	0.8%	4.0%
BR	2.6%	0.0%	0.2%	4.3%
Rituximab	1.3%	0.0%	0.8%	2.0%
Carboplatin, Etoposide, Ifosfamide & Rituximab	2.6%	1.1%	1.7%	1.1%

Subsequent treatment	Patient Proportions per Initial Line of Treatment (based on RE-MIND2 FAS)			
	TAFA+LEN	Pola-BR	BR	R-GemOx
Cyclophosphamide, Etoposide, Prednisone & Procarbazine	0.0%	2.2%	0.2%	2.2%
Cyclophosphamide, Doxorubicin hydroxyl & Rituximab	0.0%	2.2%	1.5%	0.2%
Rituximab, Dexamethasone, Cytarabine & Oxaliplatin	5.3%	0.0%	0.0%	0.0%
R-DHAP	2.6%	0.0%	0.0%	0.0%
CAR-T	0.0%	5.1%	4.0%	4.1%
Cyclophosphamide, Fludarabine Phosphate & Other Antineoplastic agents	0.0%	5.4%	0.2%	0.2%
Methotrexate	0.0%	3.3%	0.0%	0.0%
GemOx	1.3%	3.3%	0.4%	0.0%
Radiotherapy	7.5%	0.0%	0.0%	0.0%
Source	RE-MIND2(63)	RE-MIND2(63)	RE-MIND2(63)	RE-MIND2(63)

Abbreviations: BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell; GemOx = gemcitabine and oxaliplatin; Pola-BR = polatuzumab + bendamustine + rituximab; R2, lenalidomide + rituximab; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-GemOx = rituximab + gemcitabine and oxaliplatin.

For SCT and CAR-T, any % of patients with subsequent treatment were included. However, instead of the full analysis set for RE-MIND2, subsequent CAR-T and SCT proportions were estimated using the matched RE-MIND2 patient populations to ensure balance in the underlying patient populations given the high cost of treatment with these therapies. No patients on TAFA+LEN in the matched populations received subsequent CAR-T. In the matched populations, 5.1%, 4.0% and 4.1% of patients received subsequent CAR-T following treatment with Pola-BR, BR and R-GemOx, respectively. No patients in any of the matched RE-MIND2 cohorts received subsequent SCT.

For subsequent CAR-T, it was assumed that 67% of the population received 1 cycle of Pola-BR bridging therapy between t-cell collection and t-cell re-administration based on UK clinical expert feedback, with the exception of patients receiving subsequent CAR-T therapy after Pola-BR (assuming that patients would be unlikely to receive Pola-BR bridging therapy after previously treatment with Pola-BR).

Dosing for subsequent treatments was based on published trials, NICE technology appraisals or available treatment protocols and summary of product characteristics information.

Table 39. Subsequent Treatment Drug Costs

Subsequent treatments used in the model (cut-off: 2%)	# of admin per treatment cycle	Route of administration	Treatment cost per treatment cycle	Administration cost per treatment cycle	Max treatment duration (treatment cycle)	Total cost	Notes/References
R-GemOx			£1,166.95	£761.30		£13,497.76	Mounier et al. 2013(70)
Rituximab	1	IV	£1,123.64	£253.77	7		
Gemcitabine	1	IV	£19.45	£253.77	7		
Oxaliplatin	1	IV	£23.86	£253.77	7		
R2			[redacted]	£507.53		[redacted]	Zinzani et al. 2011(113)
Lenalidomide	1	IV	[redacted]	£253.77	8		
Rituximab	1	IV	£1,123.64	£253.77	4		
Pixantrone	3	IV	£4,966.88	£761.30	4	£22,912.74	TA306(35, 114)
Lenalidomide	1	IV	[redacted]	£253.77	4	[redacted]	Zinzani et al. 2011(113)
Pola-BR			£12,215.86	£1,015.07		£39,692.78	TA649(5)
Bendamustine	2	IV	£50.08	£507.53	3		
Polatuzumab	1	IV	£11,048.88	£253.77	3		
Rituximab	1	IV	£1,116.90	£253.77	3		
BR			£1,136.75	£761.30		£5,694.15	TA649(5)
Bendamustine	2	IV	£50.19	£507.53	3		
Rituximab	1	IV	£1,086.56	£253.77	3		
Rituximab	1	IV	£1,123.64	£253.77	4	£5,509.63	Zinzani et al. 2011(113)
Carboplatin, Etoposide, Ifosfamide & Rituximab			£2,290.92	£1,776.37		£12,201.89	NHS Chemotherapy Protocol: Carboplatin-Etoposide-

Subsequent treatments used in the model (cut-off: 2%)	# of admin per treatment cycle	Route of administration	Treatment cost per treatment cycle	Administration cost per treatment cycle	Max treatment duration (treatment cycle)	Total cost	Notes/References
							Ifosfamide-Rituximab (RICE), 2016(115)
Carboplatin	1	IV	£24.46	£253.77	3		
Etoposide	3	IV	£18.29	£761.30	3		
Ifosfamide	2	IV	£1,124.54	£507.53	3		
Rituximab	1	IV	£1,123.64	£253.77	3		
Cyclophosphamide, Etoposide, Prednisolone & Procarbazine			£276.58	£-		£829.73	Coleman et al., 2008(116)
Cyclophosphamide	21	Oral	£11.02	£-	3		
Etoposide	21	Oral	£91.59	£-	3		
Prednisolone	21	Oral	£1.20	£-	3		
Procarbazine	21	Oral	£172.77	£-	3		
Cyclophosphamide, Doxorubicin hydrochloride & Rituximab			£1,245.75	£761.30		£12,042.31	NHS England: R-CHOP Regimen, 2006(117)
Cyclophosphamide	1	IV	£19.16	£253.77	6		Induction treatment cycle was daily until leukocyte count declined to less than 3.0 x 10^9/L - median duration of 3 weeks (2 weeks-2months) - treatment then stopped for mean of 2-3 weeks followed by maintenance phase where dosage frequency was switched (daily, 5/7 days, every other day, twice weekly, weekly) - no reference to the length of treatment for

Subsequent treatments used in the model (cut-off: 2%)	# of admin per treatment cycle	Route of administration	Treatment cost per treatment cycle	Administration cost per treatment cycle	Max treatment duration (treatment cycle)	Total cost	Notes/References
							maintenance (potentially indefinite)
Doxorubicin hydrochloride	1	IV	£102.95	£253.77	6		Maximum treatment duration was based on the maximum time of 2 months for induction therapy (2.7 cycles rounded up to 3)
Rituximab	1	IV	£1,123.64	£253.77	6		
R-DHAP			£1,201.50	£2,030.14		£25,853.09	Machover et al., 2010(118)
Rituximab	1	IV	£1,123.64	£253.77	8		
Dexamethasone	4	Oral	£4.28	£1,015.07	8		
Cytarabine	2	IV	£42.55	£507.53	8		
Oxaliplatin	1	IV	£31.02	£253.77	8		
CAR-T (excluding bridging therapy)	1	IV	£282,000.00	£253.77	1	£282,253.77	Applied to patients receiving CAR-T after pola-BR
CAR-T (including bridging therapy)	1	IV	£290,825.03	£253.77	1	£291,078.79	67% of population assumed to receive 1 cycle of pola-BR if not receiving pola-BR as prior therapy
Cyclophosphamide & Fludarabine phosphate			£159.10	£2,030.14		£13,135.41	Fludarabine with or without cyclophosphamide clinical trial (NCT00276848)(119)
Cyclophosphamide	3	IV	£57.48	£761.30	6		
Fludarabine phosphate	5	IV	£101.62	£1,268.84	6		
Methotrexate	5	Oral	£2.47	£-	1	£4.27	Methotrexate summary of product characteristics.(120)

Subsequent treatments used in the model (cut-off: 2%)	# of admin per treatment cycle	Route of administration	Treatment cost per treatment cycle	Administration cost per treatment cycle	Max treatment duration (treatment cycle)	Total cost	Notes/References
GemOx			£43.31	£507.53		£3,855.91	Demols et al., 2006(121)
Gemcitabine	1	IV	£19.45	£253.77	7		Maximum treatment duration assumed to be the same as R-GemOx
Oxaliplatin	1	IV	£23.86	£253.77	7		Dosage was given in a study of pancreatic cancer, R-GemOx for R/R DLBCL used same dosage, number of administrations and cycle length for 8 cycles
Radiotherapy	10	Radiotherapy	£-	£3,673.17	1	£3,673.17	

Abbreviations: BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell; GemOx = gemcitabine and oxaliplatin; IV = intravenous; Pola-BR = polatuzumab + bendamustine + rituximab; R2, lenalidomide + rituximab; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-GemOx = rituximab + gemcitabine and oxaliplatin.

Total subsequent treatment costs for each therapy are summarised in Table 40.

Table 40. Total Subsequent Treatment Costs

Treatments	Total Cost
TAFA+LEN	£4,239.86
Pola-BR	£17,042.23
BR	£13,765.76
R-GemOx	£15,445.21

Abbreviations: BR = bendamustine and rituximab; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin.

B.3.5.6. Health-state unit costs and resource use

Monitoring costs

Costs related to monitoring the treatment and the progression status of the patient were included in the model. These resources are used by patients up to the progression point. The list of disease monitoring resource items was selected based on previous NICE submissions in R/R DLBCL. The types and frequencies of healthcare resource and laboratory tests included for TAFA+LEN were based on those used in the L-MIND trial.

Table 41 presents the unit costs for each monitoring test included in the model, with costs taken from NHS reference costs and the literature. All costs were sourced from NHS reference cost or PSSRU data.

Table 41. Unit Costs for Monitoring Tests

Monitoring Test	Unit Cost	Reference
Anti-MOR00208 antibodies	£7.40	NHS reference costs 2019/20.(2) PSSRU Unit Costs of Health and Social Care 2020.(122)
B-, T- and NK cell flow cytometry (blood)	£7.40	
Blood sampling	£2.53	
Bone marrow biopsy	£36.58	
Calcium phosphate	£1.20	
Chemistry panel (including liver function test)	£8.40	
Coagulation panel	£2.53	
CT scan	£185.15	
ECG: electrocardiogram	£85.13	

Monitoring Test	Unit Cost	Reference
Full blood counts	£2.53	
Haematology panel	£2.53	
Immunoglobulin	£1.20	
Lactate dehydrogenase	£1.20	
Liver function test	£8.40	
MRI	£306.54	
PET/CT	£958.49	
Pregnancy test (serum and urine)	£1.20	
Renal function	£12.00	
Serology parameters (Hepatitis B: HbsAg, anti-HBc; anti-HBs; HBV-DNA)	£7.40	
Urinalysis	£1.20	
Comprehensive metabolic panel	£1.20	
Uric acid	£1.20	
Serum lactate dehydrogenase	£1.20	

Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; HBc = hepatitis B core; HBs = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NHS = National Health Service; PET = positron emission tomography; PSSRU = Personal and Social Services Research Unit; UK = United Kingdom

The level of resource use by patients could depend on the time spent in progression-free survival. As such, monitoring frequencies were separated according to the selected point at which patients would be considered to have prolonged PFS (e.g., ≤2 years and >2 years). Frequencies and costs per cycle for these two patients groups are provided in the following sections.

Monitoring Costs: PFHS patients without prolonged PFS

Table 42 presents the frequency of each monitoring test for each comparator, for patients in the progression-free health state (PFHS) who are not considered to have prolonged PFS.

The schedule of assessments within the clinical study report (CSR) for the L-MIND trial was used to inform model assumptions regarding monitoring test frequency for TAFA+LEN. For the other treatment comparators, data was taken from relevant NICE submissions.

Table 42. Monitoring Tests: Frequency of Use per Cycle (PFS patients without prolonged PFS)

Monitoring Test	TAFA+LEN	Pola-BR	BR	R-GemOx
Anti-MOR00208 antibodies	0.50			
Blood sampling	1.00			
Bone marrow biopsy	0.38			
Calcium phosphate		0.67	0.67	
Chemistry panel (including liver function test)				0.40
Coagulation panel				0.40
CT scan	0.17	0.31	0.31	
Full blood counts		3.33	3.33	
Haematology panel				0.40
Immunoglobulin		0.67	0.67	
Lactate dehydrogenase		2.00	2.00	
Liver function test		3.33	3.33	
MRI	0.17			
Pregnancy test (serum and urine)	1.13			
Renal function		3.33	3.33	
Serology parameters (Hepatitis B: HbsAg, anti-HBc; anti-HBs; HBV-DNA)	0.96			
Urinalysis	1.00			
Comprehensive metabolic panel				0.40
Uric acid				0.40
Serum lactate dehydrogenase				0.40
Source	L-MIND CSR	NICE TA649(5)	NICE TA649(5)	NICE TA567(6)

Abbreviations: BR = bendamustine and rituximab; CSR = clinical study report; CT = computed tomography; ECG = electrocardiogram; HBc = hepatitis B core; HBs = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; MRI = magnetic resonance imaging; PET = positron emission tomography; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

In addition to the per cycle monitoring costs, a one-off monitoring cost was also applied for some of the comparators. This is to ensure that the resources which are used for a limited period of time are not accounted for to the whole duration of PFS. Table 43 details the one-off costs used within the model.

For TAFA+LEN, three examples of the reported resource use from the L-MIND trial did not continue up to two years. These exams included B, T and NK cell flow cytometry (up to cycle 8), electrocardiogram (ECG [up to cycle 12]) and positron emission tomography (PET) computed tomography (CT [occurred only once at cycle 12]). Therefore, these were included as a one-off cost as the sum product of their frequency with the cost of each exam.

For R-GemOx, additional resource use from months 1 through 5 was captured in a one-off monitoring cost as per NICE TA567(6).

Table 43. One-off Monitoring Cost

Comparator	One-off Monitoring Costs	Source
TAFA+LEN	£1,359.59	L-MIND CSR, NHS reference costs(2)
Pola-BR	£-	-
BR	£-	-
R-GemOx	£452.22	NICE TA567(6)

Abbreviations: BR = bendamustine and rituximab; Pola-BR = polatuzumab + bendamustine + rituximab; R2 = lenalidomide + rituximab; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 44 summarises monitoring cost for each comparator that is applied per model cycle. Monitoring cost per cycle data was calculated was calculated using the cost data in Table 41 and the frequency data in Table 42.

Table 44. Monitoring Cost per Cycle (PFS patients without Prolonged PFS)

Treatment	Cost per Model Cycle
TAFA+LEN	£111.55
Pola-BR	£137.08
BR	£137.08
R-GemOx	£6.83

Abbreviations: BR = bendamustine and rituximab; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

Monitoring Costs: Prolonged PFS patients

Table 45 presents the frequency of each monitoring test for each comparator, for patients classified as having a prolonged progression-free status. Due to a lack of data specific tor R/R DLBCL patients, DLBCL guidelines(24) are used as a source of resource use in these patients.

Table 45. Monitoring Costs: Frequency of Use per Model Cycle (by year of Prolonged PFS status)

Monitoring test	Frequency per cycle (Year 1)	Frequency per cycle (Year 2)	Frequency per cycle (Year 3+)
CT scan	0.17	0.08	-
Full blood counts	0.25	0.08	-
Source	Tilly 2015(24)(23)	Tilly 2015(24)	Assumption

Abbreviations: CT = computed tomography; PFS = progression-free survival

Table 46 summarises monitoring cost per cycle that is applied each year for prolonged progression-free patients. Costs were calculated using the cost data Table 41 and the frequencies in Table 45.

Table 46. Monitoring Cost per Cycle: Prolonged PFS patients

Cost per cycle (prolonged PFS patients)	
Year 1 of prolonged PFS	£31.49
Year 2 of prolonged PFS	£15.64
Year 3+ of prolonged PFS	£-

Abbreviation: PFS = progression-free survival

Disease management costs

Costs related to disease management are included in the model. These resources are used by patients on or off the initial treatment. The list of disease management resources is based on previous NICE submissions in R/R DLBCL. Table 47 lists the unit costs for each of the possible disease management resource use items.

Table 47. Disease Management Resource Unit Cost

Disease Management Resource	Unit Cost	Source
Consultant visit	£200.20	NHS reference costs 2019/20.(2) PSSRU Unit Costs of Health and Social Care 2020.(122)
Day care	£65.41	
District nurse (visit)	£43.46	
GP (visit)	£39.23	

Disease Management Resource	Unit Cost	Source
Haematologist (visit)[1]	£171.18	
Home care (day)	£24.00	
Hospice (day)	£161.65	
Hospitalisation	£1,158.18	
ICU stay (day)	£1,689.08	
Inpatient (day)	£1,158.18	
Nurse (visit)	£42.00	
Oncologist (visit)[1]	£200.20	
Palliative care team[1]	£356.73	
Radiologist (visit) [1+]	£153.41	
Residential care (day)	£109.00	
Specialist nurse (visit)	£99.30	
Terminal care cost[2]	£2,712.38	NICE TA567(6)

Abbreviations: GP = general practitioner; ICU = intensive care unit; NHS = National Health Service; PSSRU = Personal and Social Services Research Unit; UK = United Kingdom

[1] Assumed follow-up cost in base case

[2] In the Tisagenlecleucel NICE submission (ID1166), terminal care cost of £2,653.73 was applied for the last three months of life, therefore this value is applied as a one-off cost.

The level of resource use for disease management was also set to be dependent on both progression status (PFS and PD) as well as prolonged PFS status, and split accordingly. Frequencies and costs per cycle for these three patients groups are summarised in the following sections.

Disease Management Costs: PFS patients without prolonged PFS

Table 48 presents the frequency of use for each disease management resource for each comparator for PFS patients not considered to have a prolonged progression-free status.

The assessments schedule for the L-MIND trial was used to inform the model assumptions regarding disease management resource frequency for TAFA+LEN. Routine assessments were assumed to be performed by specialist nurses, with physical exams and more complex assessments assumed to be performed by a consultant. The total number of these assessments over the trial period was then used to inform the average number of consultant visits and specialist nurse visits per 4-week model cycle.

Frequency of resource use in the comparators was taken from prior NICE submissions.

Table 48. Disease Management: Frequency of Use per Model Cycle (PFS without prolonged PFS)

Disease Management Resource	TAFA+LEN	Pola-BR	BR	R-GemOx
Consultant visit	0.42			0.4
Day care		1.1	1.1	
District nurse (visit)		1.5	1.5	
GP (visit)		2.0	2.0	
Haematologist (visit)		1.0	1.0	
Home care (day)		4.7	4.7	
Hospice (day)		0.1	0.1	
Inpatient (day)		0.2	0.2	
Nurse (visit)		4.0	4.0	
Oncologist (visit)		1.7	1.7	
Radiologist (visit)		1.7	1.7	
Residential care (day)		3.0	3.0	
Specialist nurse (visit)	2.29	0.7	0.7	
Source:	L-MIND CSR	NICE TA649(5)	NICE TA649(5)	NICE TA567(6)

Abbreviations: BR = bendamustine and rituximab; CSR = clinical study report; GP = general practitioner; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 49 summarises the disease management costs for each comparator that were applied per cycle for PFS patients without prolonged PFS status, and was calculated using data in Table 47 and Table 48.

Table 49. Disease Management Cost per Cycle for PFS patients without prolonged PFS

Treatment	Cost per Model Cycle for (PFS without prolonged PFS)
TAFA+LEN	£311.49
Pola-BR	£1,958.59
BR	£1,958.59
R-GemOx	£80.08

Abbreviations: BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

Disease Management Costs: Prolonged PFS patients

Table 50 presents the frequency of each disease management resource for each comparator for patients with prolonged PFS. Similar to monitoring costs, disease management resource use for these patients was based on DLBCL guidelines(24)in the absence of data for patients with R/R DLBCL.

Table 50. Disease Management: Frequency of Use Per Cycle (Prolonged PFS)

Disease Management Resource	Year 3	Year 4	Year 5	Year 6	Year 7+
Consultant visit	0.33	0.17	0.17	0.08	0.08
Source	Tilly 2015(24)				

Abbreviation: PFS = progression-free survival

Table 51 summarises disease management resource costs per cycle that are applied each year for patients with prolonged PFS, which was calculated using the costs in Table 47 and the frequency of use data in Table 50.

Table 51. Disease Management Cost per Cycle: Prolonged PFS

Cost per Year (prolonged PFS)	
Year 3	£66.73
Year 4	£33.37
Year 5	£33.37
Year 6	£16.68
Year 7+	£16.68

Abbreviation: PFS = progression-free survival

Disease Management Costs: Post-progression

Post-progression resource use frequencies for Pola-BR and BR were based on NICE TA649.(5) As disease management frequencies for post-progression were not captured in the L-MIND study, TAFA+LEN resource use was assumed to have been the same as that which was reported in the Pola-BR NICE submission.

Table 52 presents the frequency of use for each disease management resource for each comparator for patients who have progressed.

Table 52. Disease Management: Frequency of Use (Progressed)

Disease Management Resource	TAFA+LEN	Pola-BR	BR	R-GemOx
Day care	1.9	1.9	1.9	Aggregated total disease management costs per month were directly used from NICE TA567 and inflated from 2017 to 2020 costs.
District nurse (visit)	4.0	4.0	4.0	
GP (visit)	3.3	3.3	3.3	
Haematologist (visit)	1.2	1.2	1.2	
Home care (day)	9.3	9.3	9.3	
Hospice (day)	0.9	0.9	0.9	
Inpatient (day)	0.2	0.2	0.2	
Nurse (visit)	0.2	0.2	0.2	
Oncologist (visit)	0.4	0.4	0.4	
Radiologist (visit)	0.0	0.0	0.0	
Specialist nurse (visit)	2.5	2.5	2.5	
Source	Assumption[1]	NICE TA649(5)	NICE TA649(5)	NICE TA567(6)

[1] No information captured in the L-MIND CSR, therefore assumed to be the same as Pola-BR.

Abbreviations: BR = bendamustine and rituximab; CSR = clinical study report; GP = general practitioner; ICU = intensive care unit; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

An aggregated cost per month was directly used for R-GemOx. A summary of post-progression disease management costs is displayed in Table 53. For TAFA+LEN, Pola-BR and BR, costs were calculated using the data in Table 47 and Table 52, with the same progressed costs applied for each of these treatments.

Table 53. Disease Management Cost per Cycle: Post Progression

Treatment	Progressed
TAFA+LEN	£1,571.25
Pola-BR	£1,571.25
BR	£1,571.25
R-GemOx	£3,550.65

Abbreviations: BR = bendamustine and rituximab; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

<u>One-off Disease Management Costs</u>

Table 54 details the one-off costs applied within the model.

The annual frequency of palliative care team use was taken from the Polatuzumab NICE submission (17.3), adjusted by the cycle length and then multiplied by the cost of the Palliative Medicine – Multi-professional, Follow-up cost (£356.73) from NHS reference costs(2) to give a one-off cost for progression.

In addition, a one-off cost for mortality was also applied. In the tisagenlecleucel NICE submission, a terminal care cost of £2,712.38 was applied for the last three months of life, therefore it was assumed this value would be applied as a one-off cost in our model.

Table 54. One-off Costs

Event	Cost per Model Cycle	Source
Progression	£473.10	NHS reference costs 2019/20(2)
Mortality	£2,712.38	NICE TA649(5)

Abbreviations: NHS = National Health Service; NICE = National Institute of Health and Care Excellence

B.3.5.7. Adverse reaction unit costs and resource use

Only grade ≥3 AEs occurring in ≥5% of study subjects in the L-MIND population or comparator trials are used in the model.

In the model, AEs affect both costs and utilities of patients receiving treatment and are assumed to occur only in the first year of treatment. Therefore, patients who remain 'on treatment' for subsequent years do not incur further AE-related costs.

The model uses the cumulative probabilities of AE occurrence during the treatment period. To account for differences in exposure time, treatment-specific cumulative probabilities for the intent to treat population over the entire trial duration are used to calculate an overall cost of AEs. A per-patient overall AE cost and utility decrement is applied as a one-off lump sum at the start of treatment. The cumulative probability of each AE during the treatment period for each therapy is shown in Table 55.

Table 55. Cumulative Probability of AEs during the Treatment Period

AE	TAFA+LEN	Pola-BR	BR	R-GemOx
Anaemia	7.4%	28.20%	17.90%	33.00%
Febrile neutropenia	12.3%	10.30%	12.80%	
Hypokalaemia	6.2%			
Leukopenia	11.1%			
Neutropenia	49.4%	46.20%	33.30%	73.00%
Pneumonia	9.9%			
Thrombocytopenia	17.3%	41.00%	23.10%	23.00%
Lymphopenia		12.80%		
Source	L-MIND CSR	GO29365 Trial(85)	GO29365 Trial(85)	NICE TA649(5)

Abbreviations: AE = adverse event; BR = bendamustine and rituximab; CSR = clinical study report; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

The costs of managing the AEs that were considered in the model are presented in Table 56 below, and are based on NHS reference costs.

Table 56. Cost of Managing AEs per Event

AE	Cost per Event	Source
Anaemia	£1,238.06	NHS reference costs 2019-20(2)
Febrile neutropenia	£1,785.62	
Hypokalaemia	£1,456.44	
Leukopenia	£1,533.37	
Neutropenia	£1,785.62	
Pneumonia	£1,908.15	
Thrombocytopenia	£1,915.08	
Lymphopenia	£1,533.37	

Abbreviations: AE = adverse event; NHS = National Health Service

Total AE management costs per treatment used in the model are displayed in Table 57 below. Costs were calculated using the cost data in Table 56 and the cumulative probabilities of requiring treatment for each of the comparators in Table 55.

Table 57. AE Management Costs per Treatment

Treatment	Total AE costs
TAFA+LEN	£1,974.06
Pola-BR	£2,339.46
BR	£1,487.16
R-GemOx	£2,152.53

Abbreviations: AE = adverse event; BR = bendamustine and rituximab; Pola-BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

B.3.5.8. Miscellaneous unit costs and resource use

No other miscellaneous unit costs and resource data were applied in the model.

B.3.6. Base-case results

B.3.6.1. Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness results for TAFA+LEN and each model comparator (pola-BR, BR and R-GemOx) are presented in Table 58. While TAFA+LEN generated increased total costs against each model comparator, it also produced substantial increases in total life years (2.88-3.32) and QALYs ([redacted]). Undiscounted life year gains for TAFA+LEN were 3.97, 4.46 and 4.41 vs Pola-BR, BR and R-GemOx, respectively.

The ICERs for TAFA+LEN against Pola-BR, BR and R-GemOx were [redacted], [redacted] and [redacted] per QALY, respectively.

Table 58. Base-case results

Intervention	Total costs (£)	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	[redacted]	5.08	[redacted]	-	-	-	-
Pola-BR	[redacted]	2.20	1.45	[redacted]	2.88	[redacted]	[redacted]
BR	[redacted]	1.76	1.13	[redacted]	3.32	[redacted]	[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]	3.26	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; LYG = life year gained; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

Incremental analysis results are shown below in Table 59. [redacted]

Table 59: Base case results – full incremental analysis

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs previous non-dominated alternative
BR	[redacted]	1.13	[redacted]	[redacted]	-
R-GemOx	[redacted]	1.16	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	1.45	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Tafa+Len, tafasitamab + lenalidomide; Pola-BR, polatuzumab + bendamustine + rituximab; BR, bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaplatin; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

B.3.7. Sensitivity Analyses

B.3.7.1. Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was conducted with a Monte-Carlo simulation using 1,000 iterations in which parameter values were randomly drawn from probability distributions assigned to each relevant model parameter, defined using the parameter value and associated uncertainty data. The parameter inputs used in PSA are shown in Appendix L. Broadly speaking, the following probability distributions were adopted in the PSA for each input type:

- Beta distributions for inputs confined by the interval 0 to 1 (such as proportions) and health state utility values
- Gamma distributions for costs and resource use frequencies
- Log-normal distributions for HRs

- Multivariate normal distributions for time-to-event parameters and general population utility regression model parameters (based on applying Cholesky decompositions to covariance matrices)

- Normal distributions for all other parameters

Standard errors (SE) were used to inform the distributions of input parameters where available. Where SEs or 95% confidence intervals were not available for parameters (or not estimable from other measures of uncertainty), a variation of ±20% in the mean was used to estimate the 95% CI.

The mean probabilistic results are presented in Table 60 alongside the deterministic base-case results. Mean PSA total costs were fairly similar to the deterministic results from the base-case analysis for each model comparator with values within 2.5% of the base-case estimates. Mean PSA total QALYs were similar to the base case analysis for TAFA+LEN and R-GemOx, with mean PSA total QALYs slightly higher for pola-BR and BR than the deterministic base-case results (6.9% and 4.3%, respectively).

Table 60. Mean PSA results

Intervention	Deterministic results		Mean PSA results	
	Total costs	Total QALYs	Total costs (95% CI)	Total QALYs (95% CI)
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	1.45	[redacted]	1.55 (0.63, 3.25)
BR	[redacted]	1.13	[redacted]	1.18 (0.56, 2.13)
R-GemOx	[redacted]	1.16	[redacted]	1.18 (0.88, 1.56)

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; ICER = incremental cost-effectiveness ratio; LYG = life year gained; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

The distribution of incremental costs and QALYs for TAFA+LEN vs. pola-BR, BR and R-GemOx is shown in Figure 22, Figure 23, Figure 24, respectively.

Figure 22. PSA cost-effectiveness plane for TAFA+LEN vs. pola-BR

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 23. PSA cost-effectiveness plane for TAFA+LEN vs. BR

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 24. PSA cost-effectiveness plane for TAFA+LEN vs. R-GemOx

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The cost-effectiveness acceptability curve (CEAC) for TAFA+LEN vs. pola-BR, BR and R-GemOx is shown in **xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxx**

Figure 25 for willingness to pay (WTP) thresholds between £0 and £200,000 per QALY, in increments of £4,000 per QALY. The CEAC indicates that

Figure 25. CEAC

B.3.7.2. Deterministic Sensitivity Analysis

The parameters in the model with single input values were varied individually in deterministic sensitivity analysis (DSA). Upper and lower values were based on the confidence intervals or estimated confidence intervals based on other uncertainty data. In the absence of appropriate uncertainty data to inform the confidence intervals, the upper and lower values for the DSA were calculated as ±20% of the mean base-case value. Each parameter was set to the upper and lower bounds to test the impact of each individual parameter on the results.

Tornado diagrams illustrating the key drivers of ICER values in the comparison are shown in **xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xx**

[redacted]

Figure 26, Figure 27 and Figure 28. [redacted]

[redacted]

Figure 26. Tornado diagram of ICER results for TAFA+LEN vs. pola-BR


[redacted]

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 27. Tornado diagram of ICER results for TAFA+LEN vs. BR


[redacted]

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 28. Tornado diagram of ICER results for TAFA+LEN vs. R-GemOx

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

B.3.7.3. Scenario Analysis

Scenarios exploring alternative long-term extrapolations and data source of survival parameters, cure assumptions, utilities and vial sharing, along with shorter model time horizons and lower discount rates, are summarised in Table 61.

Scenarios with the largest increases in the ICER were shorter time horizons (to and to for five and 10-year time horizons, respectively), use of the Weibull model for TAFA+LEN OS (to for each comparator), use of the log-normal model for TAFA+LEN PFS (to), use of MAIC constant HRs for pola-BR (increase in ICER vs. pola-BR) and applying MAIC HRs and median TTD data for R-GemOx (increase in ICER vs. R-GemOx). Cure scenarios 18 and 19 also generated slight increases in the ICER vs. pola-BR (and respectively).

Scenarios generating the largest decreases in the ICER were the cure assumption scenarios (excluding comparisons against pola-BR for scenarios 18 and 19) with scenarios 16 and 17 generating the largest ICER decreases of between to across comparators, as well as use of RE-MIND2 data for pola-BR ( ), health state utilities from NICE TA567 (to) and assuming vial-sharing for all IV therapies (to).

Table 61. Scenario analysis results

Scenario #	Scenario	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
-	**Base-Case**	[redacted]	[redacted]	[redacted]
1	5-year time horizon	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	[redacted]	[redacted]
3	1.5% discount rate for costs and outcomes	[redacted]	[redacted]	[redacted]
4	TAFA+LEN OS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
5	TAFA+LEN OS parametric model: Weibull	[redacted]	[redacted]	[redacted]
6	TAFA+LEN PFS parametric model: log-normal	[redacted]	[redacted]	[redacted]
7	Pola-BR: apply MAIC HRs with 11-month split for OS and PFS	[redacted]	[redacted]	[redacted]
8	Pola-BR: apply constant MAIC HRs for OS and PFS	[redacted]	[redacted]	[redacted]
9	Pola-BR: apply RE-MIND2 survival data (generalised gamma for OS, exponential for PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
10	BR PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
11	R-GemOx OS parametric model: Gompertz	[redacted]	[redacted]	[redacted]
12	R-GemOx PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
13	Applying MAIC HR estimates for OS/PFS and median TTD durations for BR and R-GemOx	[redacted]	[redacted]	[redacted]
14	Fixed 2-year cure point with 78.6% of PFS patients at 2 year achieving cure: general population mortality only	[redacted]	[redacted]	[redacted]
15	Scenario 14 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
16	Scenario 15 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
17	Scenario 16 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
18	Cure point at crossing of OS and PFS curves: general population mortality only	[redacted]	[redacted]	[redacted]

Scenario #	Scenario	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
19	Scenario 18 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
20	Scenario 19 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
21	Scenario 20 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
22	Utility of 0.83 for PFS and 0.71 for PD based on NICE TA567	[redacted]	[redacted]	[redacted]
23	Vial sharing for all IV administered treatments	[redacted]	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R=GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = Tafasitamab + lenalidomide; TTD = time to treatment discontinuation

B.3.7.4. Summary of sensitivity analysis results

Probabilistic mean total costs and total QALYs were broadly consistent with the base-case estimates, albeit with slight variations in total QALYs for pola-BR and BR. Some variation in incremental costs and QALYs was observed across PSA simulations, likely driven by variations in underlying survival-related parameters.

[redacted] Several scenarios resulted in [redacted] increases or decreases in the ICER. However, these scenarios may be associated with some uncertainty or may not be plausible given the available data.

Shorter time horizons resulted in the largest decreases in the ICERs, but did not reflect the lifetime benefits associated with TAFA+LEN treatment and anticipated long-term gains in LYs and QALYs.

Although the use of the Weibull model for TAFA+LEN OS resulted in an increase in the ICERs of [redacted] to [redacted] and was highlighted by UK clinical experts as a potentially reasonable extrapolation, the Weibull model appeared to be a worse visual fit to the observed data than the log-normal, log-logistic and generalised gamma models and the Weibull model hazard profile (continuously decreasing) did not align with the short-term increasing then decreasing hazards anticipated by UK clinical experts.{Incyte Corporation, 2020 #316}[redacted]Furthermore, while clinical experts indicated that the log-normal model may be plausible in terms of long-term extrapolations for PFS, all models outside the generalised gamma produced either an implausible plateau (Gompertz) or a poor relative statistical and visual fit to the observed data.

Though use of constant MAIC HRs increased the ICER vs pola-BR by [redacted], it should be noted that inspection of the log-cumulative hazard plots displays a kink in the plots at approximately 4 months after which the hazard plots crossed, suggesting that assumption of proportional hazards between TAFA+LEN and pola-BR was not appropriate. A change in hazard profile at around 4 months was also considered plausible given the maximum treatment duration of Pola-BR is ~4 months, the delay between median time to first response (2.1 months) and complete response (6.8 months) for TAFA+LEN and the difference in mechanisms of action between treatments.

In addition, although the use of pola-BR RE-MIND2 efficacy data reduced the ICER for TAFA+LEN compared to pola-BR, clinical experts viewed the underlying data as pessimistic, which may reflect the recent entry of pola-BR onto the market and limited experience with its use in clinical practice at the time of RE-MIND2 data collection.

The base-case analysis was conservative in relation to long-term assumptions of durable remission. Inclusion of cure assumptions appeared to generate some substantial reductions in the ICERs. There was some uncertainty around appropriate long-term assumptions for mortality, utility and costs for cured patients given the current lack of long-term data and different treatment stopping rules for tafasitamab

compared to existing therapies (treat to progression rather than fixed treatment duration).

Overall, the results of the sensitivity and scenario analyses indicated that the model results were fairly robust, with variation in ICERs associated with parameter uncertainty or alternative data sources and assumptions either relatively limited or predictable, albeit it with some uncertainty around cure assumptions and sensitivity to survival parameters.

B.3.8. Subgroup analysis

No subgroups were evaluated as part of the cost-effectiveness analysis.

B.3.9. Validation

The economic analysis was designed to align with the NICE reference case and NICE guidance, as well as modeling approaches and discussion from prior R/R DLBCL TAs. The model time horizon, perspective and discount rates, as well as data inputs and QoL inputs, were aligned with the NICE reference case, with comparators selected based on the NICE scope and UK clinical experts.{Incyte Corporation, 2020 #316}

Extensive validation of parametric survival extrapolations for L-MIND and RE-MIND2 was performed through discussion of model predictions and hazard profiles for OS and PFS with three UK clinical experts.{Incyte Corporation, 2020 #316} UK clinical experts also provided feedback on model comparators, cure assumptions, subsequent treatment usage and base-case utility values. Elicited clinical expert feedback was then used to help inform the base-case analysis as well as scenario analyses, with various parametric extrapolations and cure assumptions explored.

B.3.10. Interpretation and conclusions of economic evidence

An evaluation of the cost-effectiveness of TAFA+LEN against pola-BR, BR and R-GemOx for the treatment of transplant-ineligible patients with R/R DLBCL in the UK

was conducted using a partitioned survival model. The analysis was conducted in the line with the NICE reference case and the NICE final scope in terms of population and comparators, with the L-MIND and RE-MIND2 trial populations expected to be generalisable to the UK.

Limitations of the economic analysis included the limited availability of data for performing direct or indirect comparisons between comparators, limited long term data and different stopping rules related to the cure assumption and the lack of quality of life data directly applicable to the modelled population (with most utility data identified derived from older studies for aggressive NHL patients or for R/R DLBCL patients receiving CAR-T therapies). However, extensive analyses were conducted to explore alternative statistical methods and datasets for comparing TAFA+LEN against existing therapies, as well as the impact of various cure assumptions. In addition, health state utility data were adjusted to account for differences in age and sex characteristics between the original population used to derive the utility estimates and the modelled population.

Sensitivity analysis and a variety of scenario analyses were performed to explore uncertainty relating to parameter values, data sources and assumptions in the model.

[redacted]

Overall, the cost-effectiveness analysis demonstrated that TAFA+LEN represents a highly effective therapy for R/R DLBCL patients ineligible for SCT, with substantial benefit in terms of both life years and QALYs relative to existing therapies as well as the potential to offer durable remission and prolonged survival.

[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Clarification questions

May 2022

File name	Version	Contains confidential information	Date
ID3795 tafasitamab ERG Clarification responses_19 May 2022 redacted.docx	1.0	no	19.05.2022

Notes for company

Highlighting in the template

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Please note:

Some documents were only received by the ERG when the clarification questions were being finalised. If you feel that any of the questions below have been sufficiently answered by these documents, please refer to the pertinent document when responding to the question.

Section A: Literature searches

A1. Priority question: No details of any systematic literature review (SLR) search strategies are provided in the company submission (CS). Please provide full details of all the searches conducted for the clinical effectiveness, cost-effectiveness, health related quality of life (HRQoL) and resource use SLRs. Full strategies, including details of databases searched, dates of searches and complete details of all search terms used and numbers of records found should be provided for all resources used for each of the above sections. These are normally included in full in Appendices D, G, H and I. These were requested by the Evidence Review Group (ERG) in an email to NICE on 1st December 2021.

Response: We thank the ERG for this question. Please see the documents shared on 06 December 2021 that provide this information:

- Clinical SLR Search Strategy
- Economic and HRQoL SLR Search Strategy
- SLR Content Locations document, which outlines where the relevant information for each SLR can be found within the submission

Section B: Clarification on clinical effectiveness data

Decision problem

B1. Priority question: In the National Institute for Health and Care Excellence (NICE) Final Scope, several comparators are listed including R-GemOx (rituximab, gemcitabine oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine), (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (bendamustine, rituximab), Pixantrone, Pola-BR (polatuzumab vedotin in combination with bendamustine and rituximab) and best supportive care.

a. **As solely Pola-BR, BR and R-GemOx have been included in this CS as being relevant to United Kingdom (UK) clinical practice, please provide justification as to why each of the other final scope comparators have been omitted from this CS.**

b. **Please discuss how the comparators selected align with UK clinical practice. Please provide supporting evidence.**

c. **Please report on the methods used to gather the clinical experts' opinions as part of the UK advisory board that recommended Pola-BR, BR, and R-GemOx as the relevant comparators. Please provide both results and references in the form of reference #50 from the CS (this is missing from the submitted reference pack) or other documentation. Reference #50 was requested by the ERG in an email to NICE on 3rd December 2021.**

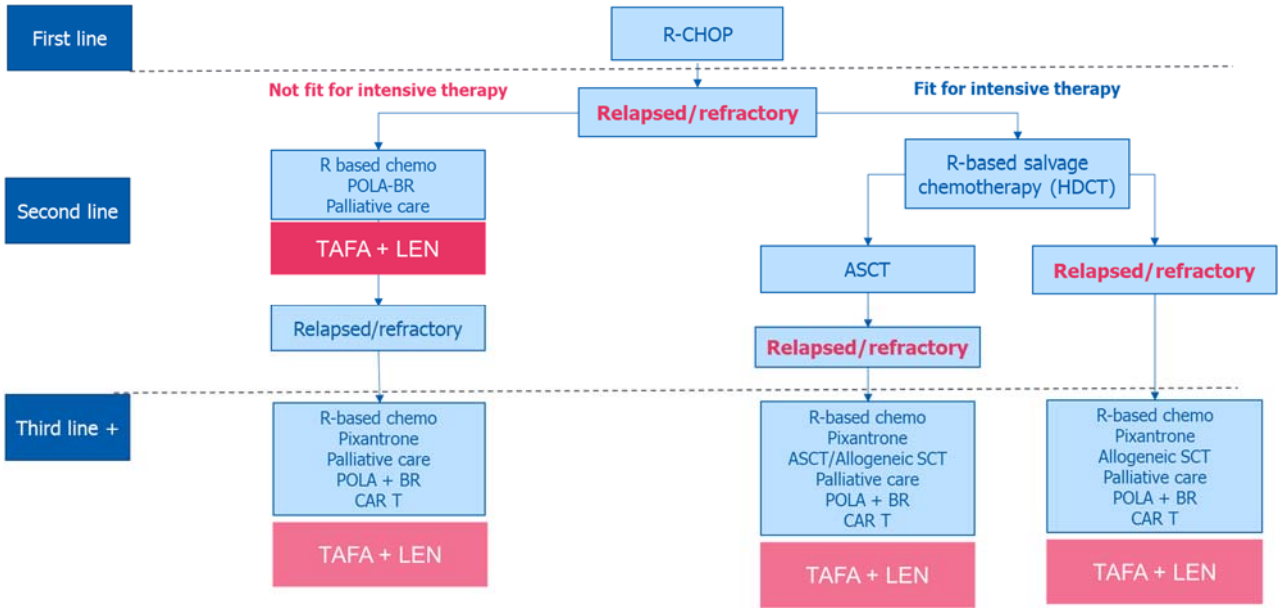
d. **Please update analyses with all relevant comparators.**

Response: We thank the ERG for these questions. A discussion of relevant comparators in UK clinical practice is provided below.

Tafasitamab in combination with lenalidomide (TAFA+LEN) followed by tafasitamab monotherapy is indicated for use in patients with relapsed or refractory (R/R) diffuse B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).[1] Options for management of R/R DLBCL in the second- and third-line plus settings according to available NICE guidance are shown in Figure 1, along with the anticipated positioning of TAFA+LEN.

As noted in the final scope (background section), there is no established standard of care for the population who are ineligible for transplant in the 2L or 3L+ settings. The latest ESMO treatment guidelines (2015) broadly recommend platinum and/or gemcitabine-based regimens, or participation in a clinical trial.[2] NICE guidance published in 2016 provides no clear recommendations for this population.[3] However, polatuzumab vedotin (POLA) in combination with bendamustine and rituximab (BR; POLA+BR) has since become available for second-line-plus management of R/R DLBCL in patients ineligible for transplant (TA649).[4] Pixantrone monotherapy is indicated for this population in the third or fourth-line settings only (TA306).[5]

Figure 1. NICE-recommended treatment pathway for R/R DLBCL – updated to reflect current UK clinical practice and anticipated positioning of TAFA+LEN



Sources: NICE guidance NG52;[3] NICE technology appraisal (TA)649;[4] NICE TA567;[6] NICE TA559;[7] NICE TA306;[5] Tilly 2015[2]

Abbreviations: ASCT = autologous stem cell transplant; BR = bendamustine with rituximab; CAR-T = chimeric antigen receptor T-cell; HDCT = high-dose chemotherapy; POLA+BR, polatuzumab vedotin, bendamustine, and rituximab; R = rituximab; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine,

and prednisone; R/R = relapsed/refractory; SCT = stem cell transplant; TAFA+LEN = tafasitamab and lenalidomide.

Due to the lack of standard of care and the wide range of chemoimmunotherapy regimens, expert opinion was sought regarding the treatments most frequently used in the UK. Three virtual interviews were held on Microsoft Teams in September 2021 with UK clinical experts. The aims of the interviews included seeking advice on the relevant comparators for the population with transplant-ineligible R/R DLBCL in the UK.[8] During the interviews, either a list of treatments or a schematic of the treatment pathway similar to Figure 1 was presented to the experts for comment. Minutes of the three interviews were provided to NICE on 06 December 2021 and contain further information regarding the interviews and key discussion points, including advice provided by the experts on the relevant comparators in the UK.[8]

The three experts all advised that POLA+BR, R-GemOx and BR would be the most relevant comparators for the UK for TAFA+LEN in transplant-ineligible R/R DLBCL:[8]

- POLA+BR has relatively recently become available for this population, and all experts agreed that POLA+BR is a key comparator
- All three experts also advised that R-GemOx is a relevant comparator in the UK, and is frequently used in clinical trials internationally
- All three experts agreed that, while BR is relevant as a comparator for POLA+BR, BR is not frequently used in the UK following introduction of POLA+BR
- Pixantrone is available for use in the 3L and 4L treatment settings; however, the experts all advised that pixantrone is rarely used in the UK and is not a relevant comparator

Neither R-Gem, R-DECC or R-P-Mit-CEBO were referred to by the UK Experts during the interviews as being used in UK clinical practice for the population who would be eligible for TAFA+LEN.[8] These variations of chemoimmunotherapy are therefore not considered to be relevant comparators for TAFA+LEN in England/the UK. Furthermore, given the use of POLA+BR and chemoimmunotherapy for R/R DLBCL in patients ineligible for transplant, best supportive care/palliative care was not considered a suitable option. Based on the clinical expert advice, the submission focusses on the comparisons versus POLA+BR, R-GemOx and BR.

Systematic literature review

B2. Please provide the eligibility criteria used for study screening and selection for the SLR to identify clinical evidence.

Response: The criteria for selecting clinical studies in the SLR are shown in Table 1.

Table 1. Criteria for inclusion and exclusion of studies identified in the clinical SLR, including PICOS (population, intervention, comparator, outcomes, study design) criteria

P (Patient population)	Adult patients with transplant-ineligible, R/R DLBCL. Notes: Refractory is defined as disease that does not respond to initial treatment or that gets worse/stays the same within 6 months after the end of initial treatment. Relapsed is disease that responds to treatment but then returns. Patients must be on at least 2L treatment. Studies that contain only transplant-eligible or salvage therapy including ASCT-eligible patients will be excluded. Studies that contain a mix of transplant-eligible and -ineligible patients and did not report their results separately will be excluded. If a publication evaluates multiple indications, results of a separate DLBCL cohort/group must be available and reported, in detail. Transformed lymphoma with DLBCL component, mixed presentation with either indolent and aggressive lymphoma or DLBCL, will be included. Studies including patients with a history of double-hit or triple-hit lymphoma will be excluded. Testicular lymphoma, bone lymphoma, primary CNS lymphoma, primary breast lymphoma, primary breast DLBCL, primary cutaneous DLBCL, DLBCL with CNS involvement, BL- and EBV-positive aggressive lymphoma, etc, will be excluded. A common scenario is HIV-associated lymphoma and DLBCL in HIV patients. A similar scenario is hepatitis B and C in patients with DLBCL, where the lines between the treatment for lymphoma and associated infection are blurred. These will be excluded. Studies including only patients with prior history of malignancies other than DLBCL will be excluded.
I (Intervention)	Tafasitamab + lenalidomide (TAFA+LEN) as in the L-MIND study
C (Comparator)	To be included, the interventions must comprise at least one of the following regimens in any study arm(s) of the publication (e.g., in single-arm study; either in treatment or control arm, if the study is randomised). Individual agents from within regimens are not acceptable unless specifically listed as a monotherapy below. Regimens derived from NCCN and ESMO guidelines, approved for use in either the US or EU, including: • ASHAP, ASHAP + rituximab (R-ASHAP) • ACVBP, ACVBP + rituximab (R-ACVBP) • Bendamustine, bendamustine + rituximab (R-BENDA) • Bendamustine + rituximab + polatuzumab vedotin (POLA+BR) • Brentuximab vedotin • CEOP, CEOP + rituximab (R-CEOP) • CEPP, CEPP + rituximab (R-CEPP) • CHOP, CHOP + rituximab (R-CHOP), lenalidomide + R-CHOP (R2-CHOP) • DHAOx, DHAOx + rituximab (R-DHAOX) • DHAP, DHAP + rituximab (R-DHAP) • EPOCH, EPOCH + rituximab (R-EPOCH)

	• DA-EPOCH, DA-EPOCH + rituximab (DA-EPOCH-R) • ESHAP, ESHAP + rituximab (R-ESHAP) • GDP, GDP + rituximab (R-GDP) • Gemcitabine • Gemcitabine + rituximab • Gemcitabine + dexamethasone + carboplatin • Gemcitabine + dexamethasone + carboplatin + rituximab • Gemcitabine + vinorelbine • Gemcitabine + vinorelbine + rituximab • GemOx, GemOx + rituximab (R-GemOx) • Ibrutinib, ibrutinib + rituximab • ICE, ICE + rituximab (R-ICE) • IEV, IEV + rituximab (R-IEV) • Ifosfamide, ifosfamide + rituximab • IGEV, IGEV + rituximab (R-IGEV) • Lenalidomide • Lenalidomide + rituximab • Lenalidomide + obinutuzumab • Methylprednisolone, methylprednisolone + rituximab • MINE, MINE + rituximab (R-MINE) • BEAM, BEAM + rituximab (R-BEAM) • Pixantrone, pixantrone + rituximab • Polatuzumab vedotin + rituximab (R-POLA)* • Rituximab • Vinorelbine, vinorelbine + rituximab • Axicabtagene ciloleucel (axi-cel) • Lisocabtagene maraleucel • Tisangenlecleucel • Best supportive care
O (Outcomes)	**Efficacy** • Best overall response rate • End of treatment response rate • Duration of response • Progression-free survival • Event-free survival • Time to progression • Time to next treatment • Overall survival **Safety** • AEs, including SAEs • Laboratory findings
S (Study design)	• RCTs and non-RCTs • Open-label extensions • Observational studies (prospective, cross-sectional, and retrospective, including chart reviews, registries, surveys, etc.) • Single-arm trials • SLRs for hand-search
Setting	Any setting relevant to the population of interest.
S (Study types)	All study types will be included.

Clarification questions

Country	Any
Date range	9 February 2021 to 28/29 June 2021†
Languages	English, French
Exclusions	As noted above, and: • Animal subjects • Non-adult populations (<18 years of age) • Studies indexed as case reports, case series, case study, editorials, letters, comments, opinions, news

Abbreviations: 2L = second line; ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; AE = adverse event; ASCT = autologous stem-cell transplantation; ASHAP = doxorubicin, methylprednisolone, cytarabine, and cisplatin; BEAM = carmustine, etoposide, cytarabine, and melphalan; BL = Burkitt's lymphoma; CEOP = cyclophosphamide, etoposide, prednisolone, and vincristine; CEPP = cyclophosphamide, etoposide, procarbazine, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; CNS = central nervous system; DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DHAOx = dexamethasone, high-dose cytarabine, and oxaliplatin; DHAP = dexamethasone, high-dose cytarabine and cisplatin; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein–Barr virus; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ESHAP = etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; ESMO = European Society for Medical Oncology; GDP = gemcitabine, dexamethasone, and cisplatin; GemOx = gemcitabine and oxaliplatin; HIV = human immunodeficiency virus; ICE = ifosfamide, carboplatin, and etoposide; IEV = ifosfamide, epirubicin, and etoposide; IGEV = ifosfamide, gemcitabine, vinorelbine, and prednisone; MINE = mesna, ifosfamide, mitoxantrone, and etoposide; NCCN = National Comprehensive Care Network; PICOS = population, intervention, comparison, outcome, and setting; R-GemOx = rituximab, gemcitabine, and oxaliplatin; R/R = relapsed or refractory; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review.

Note: *In studies described in this report, polatuzumab vedotin + rituximab is referred to by the alternative abbreviation, POLA-R.

B3. Please describe the processes used for study selection, data extraction, and methodological quality assessment of included studies, i.e., clarify how many reviewers were involved at each stage, how discrepancies were solved and whether a third reviewer was involved in resolving disagreements.

Response: Two independent researchers [redacted] examined all titles and abstracts to determine potential relevance. Full-text screening was conducted for articles that were not definitively categorised via title/abstract. Discrepancies were addressed through discussion; detailed reasons for study inclusion/exclusion were documented in a Microsoft Excel® workbook.

Population, intervention, comparators, outcomes, and study design (PICOS) criteria used to determine the relevance of each article are summarised above in Table 1.

Data extraction

The studies identified in the SLR were transferred to a data extraction template. Data were extracted by a single investigator [redacted] and validated by a second [redacted]. Any disagreements were resolved by a third investigator [redacted].

Data elements for extraction included:

- Study characteristics and design
  - Study design, geography, and enrolment criteria
  - Study years and duration
  - Number of patients included
  - Treatment administration and duration of treatment
  - Study objectives
- Patient baseline characteristics
  - Age
  - Age at onset or diagnosis
  - Gender
  - Disease duration
  - Genetic mutations
  - Eastern Cooperative Oncology Group performance status score (ECOG PSS)
  - Histologic subtype
  - Risk score (including classification system)
  - Ann Arbor stage
  - Bone marrow involvement
  - Extranodal (EN) site involvement
  - Bulky disease
  - Elevated lactate dehydrogenase (LDH)
  - Prior lines of systemic therapy
  - Duration of response (DoR)
  - Prior treatment, including prior ASCT
  - Cell of origin
- Outcomes
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Event-free survival (EFS)
  - Time to progression
  - Best objective response rate (ORR)

- End of treatment (EOT) response rate
- Complete response (CR) rate
- Partial response (PR) rate
- Stable disease rate and time
- Progressive disease rate and time
- DoR
- Percentage of patients in remission at 6/12/18/24 months
- AEs

All available data for each publication were included in the extraction sheet. Where applicable, the definition used for an outcome was also noted.

Quality assessment

Quality assessments of randomised controlled trials (RCTs) and observational studies identified by the SLR were performed. For RCTs, an adapted checklist from the CRD was used (Table 2).[9] For observational studies, a quality assessment tool was adapted from a checklist from the Critical Appraisal Skills Programme (CASP,Table 3).[10] In the case of single-intervention trials and open-label extensions, the application of the adapted CRD tool would have resulted in the majority of questions having a "not applicable" response. Therefore, the adapted CASP tool was considered more informative and was used to evaluate these study designs. One quality assessment per unique study was performed.

Table 2. Adapted CRD checklist for quality assessment of randomised controlled trials

Study question	**Response**	**How is question addressed in the study?**
	(yes/no/partially/ not clear/NA)	
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors (e.g., disease severity)?		
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not		

Study question	Response (yes/no/partially/ not clear/NA)	How is question addressed in the study?
blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		

Abbreviations: CRD = Centre for Reviews and Dissemination; ITT = intention-to-treat; NA = not applicable.

Adapted from: "Systematic reviews: CRD's guidance for undertaking reviews in health care." York: Centre for Reviews and Dissemination, 2009.[9]

Table 3. Adapted CASP checklist for quality assessment of observational studies

Study question	Response (yes/no/partially/not clear/NA)	How is question addressed in the study?
Was the cohort recruited in an acceptable way?		
Was the exposure accurately measured to minimise bias?		
Was the outcome accurately measured to minimise bias?		
Have the authors identified all important confounding factors?		
Have the authors taken account of the confounding factors in the design and/or analysis?		
Was the follow-up of patients complete?		
How precise (e.g., in terms of CI and p values) are the results?		

Abbreviations: CASP = Critical Appraisal Skills Programme; CI = confidence interval; NA = not applicable.

Adapted from: Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.[10]

B4. Information in Figures 1 and 2 of Appendix D (study flow diagrams for initial and updated searches, respectively) indicate that 91 records were included in the SLR. These 91 records are then presented as a reference list (Section D.1.1.1, Reference

list for included studies). Please provide tabulation of these records showing details of participant characteristics, treatment comparisons, outcomes assessed and study designs.

Response: We thank the ERG for this question. The 91 records included in the SLR represent 47 discrete studies. We have provided an accompanying Excel sheet with the tabulated studies showing details of participant characteristics, treatment comparisons, outcomes, and study designs. As well, these details were presented in tabular format within the reports for the SLR and SLR updates (in the sections on 'Study Characteristics' and 'Baseline Characteristics').

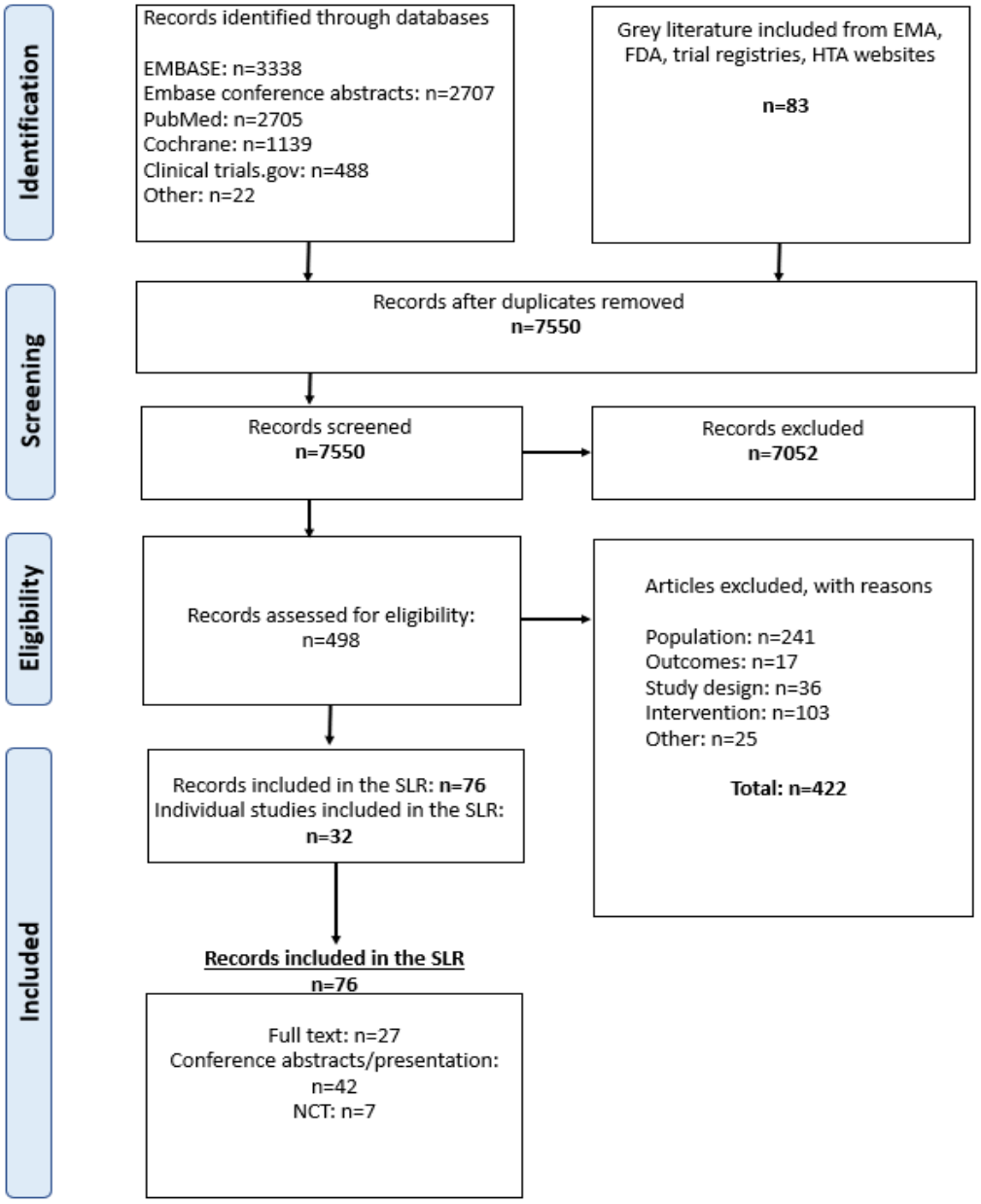
B5. The information about the number of excluded studies is discrepant between different parts of Appendix D. Details in Figures 1 and 2 suggest that 8,128 records were excluded at the title and abstract screening stage and a further 485 after full-text eligibility assessment. However, 398 records are listed in Section D.1.1.2 (Reference list for excluded studies). Please clarify the numbers of records excluded during title and abstract screening and full-text eligibility assessment.

Response: We thank the ERG for this question and apologise that older versions of the PRISMA diagrams were included in the submission. The correct versions of the PRISMAs are presented below in Figure 2 and Figure 3. The initial SLR resulted in a total of 7,474 excluded studies (7,052 after first screening and 422 after full-text assessment). Due to the magnitude of the resulting reference list, only the papers excluded after the second screening (422) were listed in Appendix D. We have updated the list of excluded references to include all 7,474 citations in document *'ID3795_List of excluded studies – Original SLR"*. The SLR update resulted in a smaller number of excluded studies (total number of 1,073 including first and second screening). We have provided the complete list of excluded studies for the SLR update in document *'ID3795_List of excluded studies – SLR update'*.

Finally, for clarity, a formatting error in Appendix D of the CS resulted in the excluded studies from the SLR and the grey literature being combined. References 1 to 398 are the excluded studies after second screening and reference 399 to 422 are the grey literature excluded after the second screening. Please refer to the updated documents provided for numbers and details of the excluded studies in the original

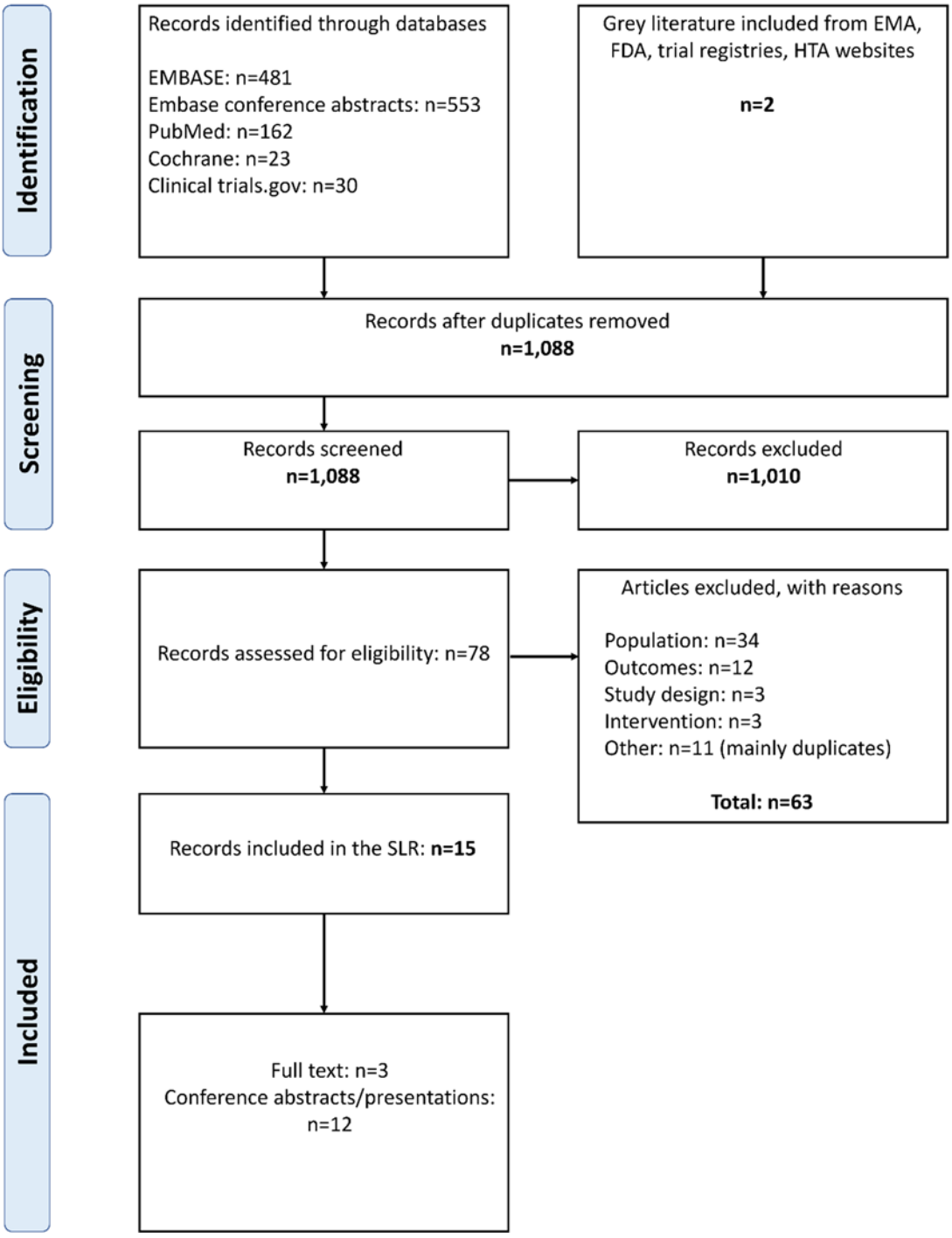
SLR (*'ID3795_List of excluded studies – Original SLR"*) and the SLR update *('ID3795_List of excluded studies – SLR update')*.

Figure 2. PRISMA diagram of the original SLR



Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration; HTA = health technology assessment; NCT = National Clinical Trial; SLR = systematic literature review.

Figure 3. PRISMA diagram of the SLR update



Abbreviations: EMA = European Medicines Agency; FDA, Food and Drug Administration; HTA = health technology assessment; SLR = systematic literature review.

B6. Reasons for exclusion at the full-text eligibility assessment stage are not provided per record but we note some aggregated information in Figures 1 and 2 of Appendix D.

a. Please provide details per individual record for those excluded because of 'outcomes' (n = 9 in Figure 1 and n = 12 in Figure 2).

Response: We have provided the details of the individual records for the studies excluded due to outcomes in the primary SLR report in Table 4 and the SLR update report in Table 5. We also apologise for submitting an older version of the PRISMA diagrams. The correct versions are provided in Figure 2 and Figure 3 of this document and show the number of studies excluded for outcomes as n=17.

Table 4. List of reason for exclusion associated with outcomes in the primary SLR report (PRISMA shown in Figure 2)

Authors	Title	Reason for exclusion
Awasthi, R., Pacaud, L., Waldron, E., Tam, C. S., Jäger, U., Borchmann, P., Jaglowski, S., Foley, S. R., van Besien, K., Wagner-Johnston, N. D., Kersten, M. J., Schuster, S. J., Salles, G., Maziarz, R. T., Anak, Ö, Del Corral, C., Chu, J., Gershgorin, I., Pruteanu-Malinici, I., Chakraborty, A., Mueller, K. T. and Waller, E. K., 2020	Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL	Cellular kinetic
Georgiev, P. G., Belada, D., Dakhil, S., Inhorn, L. F., Andorsky, D., Liberati, A. M., Beck, J. T., Quick, D., Patti, C., Sivcheva, L., Zaucha, J. M., Pettengell, R., Devries, T., Dean, J. P., Pavlyuk, M., Failloux, N. and Hübel, K.	Phase 3 trial of pixantrone plus rituximab versus gemcitabine plus rituximab in treating relapsed/refractory transplant-ineligible aggressive non-Hodgkin's lymphoma	No results
Gleeson, M., Chau, I., Peckitt, C., Patel, B., Wotherspoon, A., Attygalle, A., Du, Y., Sharma, B. and Cunningham, D.	LEGEND: a randomised phase II study comparing lenalidomide plus rituximab, gemcitabine, and methylprednisolone (R-GEM-L) to rituximab, gemcitabine, methylprednisolone, and cisplatin (R-GEM-P) in second-line treatment of diffuse large B-cell lymphoma (DLBCL)	No results
https://clinicaltrials.gov/show/NCT04404283	Brentuximab Vedotin Plus Lenalidomide and Rituximab for the Treatment of Relapsed/Refractory DLBCL	No results
https://clinicaltrials.gov/show/NCT04236141	A Study to Evaluate the Efficacy and Safety of Polatuzumab Vedotin in Combination With Bendamustine and Rituximab Compared With Bendamustine and Rituximab Alone in Chinese Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (R/R DLBCL)	No results

Authors	Title	Reason for exclusion
Cummin TE., Caddy J.	ARGO: A randomised phase II study of atezolizumab with rituximab, gemcitabine and oxaliplatin in patients with relapsed or refractory diffuse large B-cell lymphoma who are not candidates for high-dose therapy	No results
Gerhard Held, MD, Roch Houot, MD PhD, Abraham Avigdor, MD, Marc André, Anna Dabrowska-Iwanicka, Ulrich Jaeger, MD, Sanne Tonino, MD PhD, Marek Trneny, MD prof, Gomes da Silva Maria, MD PhD, Philippe Gaulard, MD PhD, Thierry Jo Molina, MD PhD, Andreas Rosenwald, MD, Grzegorz Rymkiewicz, Thierry Fest, Karin Tarte, PhD, Markus Loeffler, MD, Marita Ziepert, PhD, Bettina Altmann, PhD, Viola Poeschel, MD, Corinne Haioun, MD PhD	Niveau, a phase 3 study for pts with B- or T-cell aggressive non-hodgkin lymphoma in first relapse or progression not eligible for high-dose chemotherapy (HDT), testing nivolumab in combination with gemcitabine, oxaliplatin (GemOx), plus rituximab (R) in case of B-cell lymphoma	First relapse
https://ClinicalTrials.gov/show/NCT04404283	Brentuximab Vedotin Plus Lenalidomide and Rituximab for the Treatment of Relapsed/Refractory DLBCL	No results
https://ClinicalTrials.gov/show/NCT02086604	Brentuximab Vedotin and Lenalidomide for Relapsed or Refractory Diffuse Large B-cell Lymphoma	No results
https://ClinicalTrials.gov/show/NCT02624492	To Determine the Dose of BI 836826-GemOx and the Efficacy of BI 836826-GemOx Versus R-GemOx in Patients With Relapsed/Refractory DLBCL	Trial stopped
https://ClinicalTrials.gov/show/NCT04049825	A Phase 1 Trial of OPB-111077 in Combination With Bendamustine and Rituximab in Patients With r/r DLBCL	No results
https://ClinicalTrials.gov/show/NCT03630159	Study of Tisagenlecleucel in Combination With Pembrolizumab in r/r Diffuse Large B-cell Lymphoma Patients	No results
https://ClinicalTrials.gov/show/NCT03876028	Study of Tisagenlecleucel in Combination With Ibrutinib in r/r Diffuse Large B-cell Lymphoma Patients	No results
https://ClinicalTrials.gov/show/NCT04456023	Study of Tisagenlecleucel in Chinese Adult Patients With Relapsed or Refractory Diffuse Large B-cell Non-Hodgkin Lymphoma (DLBCL)	No results
https://ClinicalTrials.gov/show/NCT04236141	A Study to Evaluate the Efficacy and Safety of Polatuzumab Vedotin in Combination With Bendamustine and Rituximab Compared With Bendamustine and Rituximab Alone in Chinese Patients With Relapsed or	No results

Authors	Title	Reason for exclusion
	Refractory Diffuse Large B-cell Lymphoma (R/R DLBCL)	
https://ClinicalTrials.gov/show/NCT04408638	A Phase III Study Evaluating Glofitamab in Combination With Gemcitabine + Oxaliplatin vs Rituximab in Combination With Gemcitabine + Oxaliplatin in Participants With Relapsed/Refractory Diffuse Large B-Cell Lymphoma	No results
https://ClinicalTrials.gov/show/NCT04285268	Rituximab, Venetoclax, and Bortezomib for the Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma	No results

Abbreviations: DLBCL = diffuse large B-cell lymphoma; r/r = relapsed/refractory.

Table 5. List of reason for exclusion associated with outcomes in the updated report (Figure 3)

Authors	Title	Reason for exclusion
Bartlett, N. L., Yasenchak, C. A., Ashraf, K. K., Harwin, W. N., Sims, R. B. and Nowakowski, G. S.	Brentuximab vedotin in combination with lenalidomide and rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (trial in progress)	No results
Carlo-Stella, C., Linhares, Y., Gandhi, M. D., Chung, M., Adamis, H., Ungar, D. and Hamadani, M.	Phase 3 randomized study of loncastuximab tesirine plus rituximab versus immunochemotherapy in patients with relapsed/refractory diffuse large bcell lymphoma-lotis-5	No results
Hertzberg, M., Ku, M., Catalani, O., Althaus, B., Simko, S. and Gregory, G. P.	A phase III trial of glofitamab plus gemcitabine and oxaliplatin (GEMOX) vs rituximab plus gemox for relapsed/refractory diffuse large B-cell lymphoma	No results
Kenderian, S. S., Oluwole, O. O., McCarthy, P. L., Reshef, R., Shiraz, P., Ahmed, O., Gall, J. L., Nahas, M., Tang, L. and Neelapu, S. S.	ZUMA-19: A phase 1/2 multicenter study of lenzilumab use with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed orrefractory large b cell lymphoma (r/r LBCL)	No results

Authors	Title	Reason for exclusion
Hübel, K., Scholz, C. W., Luminari, S., Salar, A., Wahlin, B. E., Gopal, A. K., Bonnet, C., Trneny, M., Paneesha, S., Manzke, O., Seguy, F., Li, D. and Sehn, L. H.	Inmind: A phase 3 study of tafasitamab + lenalidomide and rituximab vs placebo + lenalidomide and rituximab for relapsed/refractory follicular or marginal zone lymphoma	No results
Novo, M., Castellino, A., Chiappella, A., Ciccone, G., Balzarotti, M., Di Rocco, A., Spina, M. and Vitolo, U.	Copanlisib in combination with rituximab bendamustine in patients with relapsed-refractory DLBCL: A multicentric phase ii trial of the fondazione italiana linfomi	No results
Smith, S. D., Fromm, J. R., Fang, M., Till, B. G., Shadman, M., Lynch, R. C., Cowan, A. J., Vicky Wu, Q., Voutsinas, J., Rasmussen, H. A., Blue, K., Ujjani, C. S., Shustov, A. R., Cassaday, R. D. and Gopal, A. K.	Pembrolizumab with R-CHOP in previously untreated diffuse largeb-cell lymphoma: Long term follow up and analysis of themechanism of pdl-1 tumor expression	Prognosis
Baird, J. H., Epstein, D. J., Tamaresis, J. S., Ehlinger, Z., Spiegel, J. Y., Craig, J., Claire, G. K., Frank, M. J., Muffly, L., Shiraz, P., Meyer, E., Arai, S., Brown, J., Johnston, L., Lowsky, R., Negrin, R. S., Rezvani, A. R., Weng, W. K., Latchford, T., Sahaf, B., Mackall, C. L., Miklos, D. B. and Sidana, S.	Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma	Immune Response
Jiao, C., Zvonkov, E., Lai, X., Zhang, R., Liu, Y., Qin, Y., Savchenko, V., Gabeeva, N., Chung, T. H., Sheng, L. and Chang, L. J.	4SCAR2.0: a multi-CAR-T therapy regimen for the treatment of relapsed/refractory B cell lymphomas	Kinetic and Scan images
http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00023793	A prospective, multicenter randomized phase II trial investigating Gemcitabine/Oxaliplatin/Rituximab with or without Tafasitamab (MOR208) for patients with relapsed/refractory aggressive Lymphoma	No results

Authors	Title	Reason for exclusion
Rejeski, K., Perez Perez, A., Sesques, P., Hoster, E., Berger, C. S., Jentzsch, L., Mougiakakos, D., Frölich, L., Ackermann, J., Buecklein, V., Blumenberg, V., Schmidt, C., Jallades, L., Fehse, B., Faul, C., Karschnia, P., Weigert, O., Dreyling, M., Locke, F. L., von Bergwelt-Baildon, M., Mackensen, A., Bethge, W. A., Ayuk, F., Bachy, E., Salles, G. A., Jain, M. D. and Subklewe, M.	CAR-HEMATOTOX: A model for CAR T-cell related hematological toxicity in relapsed/refractory large B-cell lymphoma	Predictive biomarkers/Prognostic value
Zhu, L., Meng, Y., Guo, L., Zhao, H., Shi, Y., Li, S., Wang, A., Zhang, X., Shi, J., Zhu, J. and Xu, K.	Predictive value of baseline (18)F-FDG PET/CT and interim treatment response for the prognosis of patients with diffuse large B-cell lymphoma receiving R-CHOP chemotherapy	Prognosis

Abbreviations: CAR-T = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; F-FDG PET/CT = positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

b. Please provide details per individual record for those excluded for 'other' reasons (n = 17 in Figure 1 and n = 11 in Figure 2) and please explain the nature of the 'other' reasons in each instance.

Response: In the primary SLR, (PRISMA in Figure 2 of this document), all references excluded for 'other' reasons were duplicates of included studies or of studies already excluded. In the SLR update (PRISMA in Figure 3 of this document), all references excluded for 'other' reasons were also duplicates, the majority of which were duplicates of records identified in the primary SLR.

c. In Figure 2, the reasons for exclusion at full-text eligibility assessment are missing for two of the 63 records indicated (the list of numbers per reason sums to 61). Please provide the individual reasons for exclusion for the two additional records.

Response: We apologise for the oversight in which an older version of the PRISMA was submitted. The updated PRISMA diagram for the SLR update is provided in Figure 3.

B7. Appendix D (starting on page 43) lists 1,022 references under the subheading 'Grey literature'. This number of references does not tally with Figures 1 and 2 (total number of grey literature hits n = 151). It is also not clear whether these references are included or excluded.

a. Please clarify the numbers of records retrieved from the grey literature searches and explain how many were included and excluded.

Response: The total number of grey literature publications found were 85 (83 in the initial report and 2 in the updated report) as shown in the updated PRISMA diagrams in Figure 2 and Figure 3 of this document. Among the 83 grey literature publications identified in the initial report, 59 were not retained after the first screening. The other 24 were excluded after the second screening. The two grey literature publications identified in the updated report were excluded during the first screening.

The excluded reference list for 'Grey literature' included a formatting error that caused it to be combined with the next category of excluded studies totalling 1,022. We have provided updated excluded study lists for the grey literature in the documents 'ID3795_List of excluded studies – Original SLR" and "ID3795_List of excluded studies – SLR update".

b. For grey literature records excluded at the full-text eligibility assessment stage, please provide reasons for exclusion, with details per individual record for those excluded because of 'outcomes' or 'other' reasons.

Response: Most of the grey literature records retained for 2nd screening consisted of agency reports including literature reviews. The reports themselves were excluded but the relevant references included in the reports were verified to make sure that important studies were included.

Table 6. List of reasons for exclusion of grey literature after full text assessment

NICE	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Study Design	Literature review – Relevant literature have been reviewed
NICE	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Study Design	Review - relevant literature have been reviewed
NICE	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Study Design	Not only transplant ineligible + review
NICE	Non-Hodgkin's lymphoma: diagnosis and management	Study Design	Guidelines - not R/R
NICE	Non-Hodgkin's lymphoma: rituximab subcutaneous injection	Population	Non R/R
NICE	Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma	Study Design	Review
SMC	Rituximab (MabThera®)	Study Design	Advice

SMC	tisagenlecleucel (Kymriah)	Study Design	Review
SMC	axicabtagene ciloleucel (Yescarta)	Study Design	Review
SMC	tisagenlecleucel (Kymriah)	Study Design	Review
SMC	polatuzumab vedotin (Polivy)	Study Design	Review
SMC	rituximab subcutaneous (Mabthera)	Study Design	Review
AWMSG	rituximab (MabThera®)	Study Design	Review
CADTH	Rituximab for Non-Hodgkin's Lymphoma: A Review of the Clinical and Cost-Effectiveness and Guidelines	Study Design	Cost Effectiveness + Review
CADTH	Tisagenlecleucel (Kymriah) Pediatric Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma	Population	Paediatrics
CADTH	Polatuzumab Vedotin (Polivy) for DLBCL	Study Design	Review
CADTH	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Study Design	Review + Not transplant ineligible only
CADTH	Axicabtagene Ciloleucel for Non-Hodgkin Lymphoma: Health Technology Assessment Introduction and Clinical Review Protocol	Study Design	Protocol
IQWiG	Polatuzumab vedotin (diffuse large B-cell lymphoma) -	Language	German
IQWiG	Tisagenlecleucel (diffuse large B-cell lymphoma) - Assessment according to §35a (para. 1., sentence 11) Social Code Book V	Language	German
IQWiG	Axicabtagene ciloleucel (B-cell lymphoma DLBCL) - Assessment according to §35a (para. 1., sentence 11) Social Code Book V	Language	German
IQWiG	Pixantrone - Benefit assessment according to § 35a Social Code Book V	Study design	Benefit assessment
IQWiG	[G20-05] Tisagenlecleucel (diffuse large-cell B-cell lymphoma) - assessment according to Section 35a, Paragraph 1, Clause 11 of Social Code Book V (expiry of time limit)	Language	German
HAS	MABTHERA - LDGCB / LB / LA-B / LB-like pédiatriques	Population	Paediatrics

Abbreviations: AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; DLBCL, diffuse large B-cell lymphoma; HAS = Haute Autorité de Santé; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; R/R, relapsed/refractory; LA-B, une leucémie de Burkitt (leucémie aiguë à cellules B matures); LB, un lymphome de Burkitt; LDGCB, un lymphome diffus à grandes cellules; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Compendium.

Clinical effectiveness evidence

B8. Priority question: The patient population for the main source of clinical effectiveness evidence, the single-arm Phase II 'Lenalidomide Combined with

MOR00208 in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma' (L-MIND, MOR208C203, NCT02399085) study appears to be narrower than the NICE final scope i.e., adults with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who were ineligible for a stem cell transplant and high-dose chemotherapy, and had received at least one but no more than three prior lines of therapy, including an anti-CD20 agent.

a. **Please confirm that the population of the main source of clinical effectiveness evidence for this CS is narrower than the population defined in the NICE Final Scope.**

b. **If the above is confirmed, please explain how the narrower population in L-MIND relates to the population defined in the NICE Final Scope, e.g., in relation to treatment response, and provide supporting evidence.**

Response: We thank the ERG for these comments. The population in L-MIND is aligned with the final NICE scope, which specifies the population as adults with relapsed or refractory diffuse large B-cell lymphoma who are not eligible for ASCT,[11] and with the licensed indication for tafasitamab in combination with lenalidomide in patients with relapsed or refractory DLBCL who are not eligible for transplant.[1]

The L-MIND study, which forms the basis of regulatory approval and this submission, also enrolled patients with R/R DLBCL who were ineligible for ASCT. A comparison is provided below for ease (Table 7). L-MIND enrolled adults with R/R DLBCL who were ineligible for HDCT and ASCT.[12] This included patients who had received 1 to 3 prior lines of therapy (i.e., treated in the second to fourth-line setting).[12] In addition, all patients (n=81; 100%) had received prior anti-CD20 treatment during earlier lines of therapy,[12] in line with standard-of-care treatment with R-CHOP-based regimens in the first-line setting for DLBCL. Therefore the population in L-MIND is not narrower than the population specified in the final scope or in the licensed indication for tafasitamab.[12]

Table 7. L-MIND population in comparison with the NICE Final Scope

NICE scope	L-MIND population	Notes
Relapsed or refractory DLBCL	Relapsed or refractory DLBCL	This aspect of the population is aligned

NICE scope	L-MIND population	Notes
Ineligible for stem cell transplant and high-dose chemotherapy	Ineligible for high-dose chemotherapy and a stem cell transplant	This aspect of the population is aligned. High-dose chemotherapy is used as salvage therapy prior to stem cell transplant (ASCT or allogeneic SCT; Figure 1, question B.1).[3]
Received at least one, but no more than 4, prior lines of therapy	Patients in L-MIND had received a median (range) of 2 (1-4) prior lines of systemic therapy. One (second-line tx): n=40 (50%) Two (third-line tx): n = 35 (43%) Three (fourth-line tx): n=5 (6%) Four (fifth-line tx): n=1 (1%)	This aspect of the population is aligned.

Abbreviations: ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma; SCT = stem cell transplant; tx = treatment.

B9. Priority question: The L-MIND study lists the UK as one of the locations for its study centres.

a. Please provide the number of UK patients randomised and provide the baseline characteristics of these patients.

Response: [redacted] from the UK were included in the full analysis set (FAS) in L-MIND and [redacted] was included in the safety analysis set (SAF).

Demographics and baseline characteristics of these patients are provided in Table 8.

Table 8. Demographics and baseline characteristics of patients enrolled in L-MIND from the UK.

Characteristics	L-MIND full population (N=81)[12]	L-MIND UK population: FAS ([redacted])	L-MIND UK population: SAF ([redacted])
Age (years)			
Median (range)	72 (62–76)	[redacted]	[redacted]
Sex, n (%)			
Male	44 (54)	[redacted]	[redacted]
Female	37 (46)	[redacted]	[redacted]
Race, n (%)			
Asian	2 (2)	[redacted]	[redacted]
White	72 (89)	[redacted]	[redacted]
Other	1 (1)	[redacted]	[redacted]
Data missing	6 (7)	[redacted]	[redacted]
Median time since first DLBCL diagnosis, months	26·9 (17–51) IQR: 16.9, 50.0	[redacted] IQR:[redacted]	[redacted] IQR:[redacted]

Characteristics	**L-MIND full population (N=81)**[12]	**L-MIND UK population: FAS ([redacted])**	**L-MIND UK population: SAF ([redacted])**
	Range: 7.8, 189.3	Range: [redacted]	Range: [redacted]
Previous lines of systemic therapy n (%)			
1	40 (50)	[redacted]	[redacted]
2	35 (43)	[redacted]	[redacted]
3	5 (6)	[redacted]	[redacted]
4	1 (1)	[redacted]	[redacted]
Previous anti-CD20 therapy, n (%)			
Yes	81 (100)	[redacted]	[redacted]
No	0 (0)	[redacted]	[redacted]
Primary refractory, n (%)*			
Yes	15 (19)	[redacted]	[redacted]
No	66 (81)	[redacted]	[redacted]
Rituximab refractory, n (%)			
Yes	34 (42)	[redacted]	[redacted]
No	46 (57)	[redacted]	[redacted]
Unknown	1 (1)	[redacted]	[redacted]
Refractory to most recent previous therapy, n (%)			
Yes	36 (44)	[redacted]	[redacted]
No	45 (56)	[redacted]	[redacted]
Prior ASCT n (%)			
Yes	9 (11)	[redacted]	[redacted]
No	72 (89)	[redacted]	[redacted]
Ann Arbor Disease Staging dichotomised, n (%)			
Stage I and II	20 (25)	[redacted]	[redacted]
Stage III and IV	61 (75)	[redacted]	[redacted]
ECOG performance status, n (%)			
0	29 (36)	[redacted]	[redacted]
1	45 (56)	[redacted]	[redacted]
2	7 (9)	[redacted]	[redacted]
IPI category, n (%)			
Low and low-intermediate risk (IPI score 0–2)	40 (49)	[redacted]	[redacted]
High and intermediate-high risk (IPI score 3–5)	41 (51)	[redacted]	[redacted]
LDH levels at baseline, n (%)			
Elevated	45 (56)	[redacted]	[redacted]
Within reference range	36 (44)	[redacted]	[redacted]
Cell of origin by immunohistochemistry, n (%)			
GCB	38 (47)	[redacted]	[redacted]

Characteristics	L-MIND full population (N=81)[12]	L-MIND UK population: FAS ([redacted])	L-MIND UK population: SAF ([redacted])
Non-GCB	21 (26)	[redacted]	[redacted]
Missing	22 (27)	[redacted]	[redacted]
Cell of origin by gene expression profiling, n (%)			
GCB	7 (9)	[redacted]	[redacted]
Non-GCB	19 (24)	[redacted]	[redacted]
Unclassified	6 (7)	[redacted]	[redacted]
Unknown	49 (60)	[redacted]	[redacted]

*Patients who were defined as primary refractory were excluded from the study. After a protocol revision, primary refractory disease was defined as disease progressing in the course of the 1L treatment as per International Working Group response criteria, and/or showing a response of less than a PR to 1L treatment or disease recurrence/progression within <6 months from the completion of 1L therapy. Note that an initial definition of primary refractory DLBCL led to exclusion of relapses within three months of a prior anti-CD20 therapy. After revision, 15 patients in the L-MIND study (18.5%) were classified as having primary refractory disease.

Source: Salles et al., 2020.[12]

Abbreviations: ASCT = autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; GCB = germinal centre B-cell; IHC = immunohistochemistry; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PR = partial response; SAF = safety analysis set; TAFA+LEN = tafasitamab + lenalidomide.

b. Please elaborate on the generalisability of the study baseline characteristics (e.g., age, gender, bodyweight, clinical characteristics) to the general UK population, and explain whether the baseline characteristics in L-MIND are consistent with people seen in UK clinical practice. If possible, please provide supporting evidence.

Response: There is a lack of data regarding the clinical characteristics of people with R/R DLBCL in the UK who are not eligible for transplant; therefore it is difficult to assess the generalisability of L-MIND to the UK population. However, clinical expert feedback indicated that the L-MIND population is largely comparable to the UK population with R/R DLBCL and ineligible for SCT.[8] The exception is that there was a lower proportion of patients with primary refractory disease in L-MIND compared with routine clinical practice, indicating an overall lower-risk population in L-MIND.[8] There were no patients in L-MIND who had relapsed within three months; however, 19% of patients had relapsed within 3 to 6 months of first-line treatment, meeting the definition for primary refractory disease.

The L-MIND population also included a substantial proportion of patients with other high-risk factors representative of patients with R/R DLBCL ineligible for SCT and with a particularly high unmet need in UK clinical practice.[12] For example: 44% of

patients in L-MIND were refractory to their last therapy; 42% of patients were refractory to rituximab, 56% had elevated LDH, 75% had advanced disease (Ann Arbor stage III or IV), and approximately 50% of the population had a high-risk score on the International prognostic index (IPI; score 3-5).[12]

Additionally, we have reviewed the L-MIND population characteristics against the population in a real-world, retrospective multicentre cohort study assessing efficacy of pixantrone monotherapy (N=90).[13] However, it is important to note that this observational cohort study and L-MIND are not directly comparable: pixantrone is reimbursed for third- or fourth-line treatment only in the UK, as reflected in the observational study population.[5,13] By contrast, 50% of the L-MIND population were treated in the second-line setting.[12] Therefore some differences in the patient and disease characteristics are expected (e.g., a higher proportion of patients with high-risk factors for worse outcomes may be expected in the 3L+ vs 2L+ setting).

A brief comparison of the two populations is provided below for information:

- **Patient characteristics:** Median age was similar between studies with a slightly higher median age in L-MIND (median 66 years in the observational study vs 72 years in L-MIND). A slightly higher proportion of patients in the observational cohort study was male (66% vs 54% in L-MIND). Body weight was not reported in the observational cohort study so cannot be compared. More patients in the observational study had higher ECOG PS scores (2–4 vs 1–2, indicating worse prognosis), as would be expected in a later therapy line and in the real-world vs clinical trial setting.[12,13]
- **Clinical/disease characteristics:** The majority of patients in both the observational study and L-MIND had advanced Ann Arbor stage III or IV disease, with a higher proportion of patients with advanced disease in the observational cohort study (90% in the observational cohort study vs 75% in L-MIND).[12,13]
- **Prior therapy:** As noted above, 50% of patients in L-MIND received TAFA+LEN as second-line therapy, while most patients in the observational study received pixantrone at third-line or later. However, all patients had received prior anti-CD20 therapy in both studies, reflecting first-line standard-of-care treatment with R-CHOP and related regimens. A similar proportion of patients (16% in the observational study vs 11% in L-MIND) had received prior SCT.[12,13]

- **Refractory disease:** It is difficult to compare the proportion of patients with refractory disease between studies, due to differing definitions and limited baseline characteristics data available in the observational cohort study. In the retrospective observational cohort study, refractory disease was defined as stable disease (SD) or progressive disease (PD) to the immediate prior line of treatment, or disease that relapsed within 8 months following a previous documented response (PR/CR).[13] Baseline tumour assessment in the observational cohort study indicated 85% of the population had refractory disease.[13] In L-MIND, 44% of patients were refractory to their last prior therapy,[12] indicating a lower proportion of patients with refractory disease for L-MIND than in the observational cohort study. This is in alignment with clinical expert feedback regarding the population in routine clinical practice.

Given the difference in treatment settings, this comparison along with the clinical expert feedback indicates that the L-MIND population is broadly reflective of patients with R/R DLBCL ineligible for transplant in the UK, although with some differences in the proportion of patients with refractory disease in line with feedback from UK clinical experts.

B10. In the L-MIND Phase II study, only patients with stable disease or better were eligible to continue with tafasitamab monotherapy (following 12 cycles, 28 days each of tafasitamab + lenalidomide therapy).

a. During cycles 1 to 12, 4 patients (5%) discontinued lenalidomide only due to adverse events and continued on with tafasitamab monotherapy from cycle 13 onwards. Please discuss the implications of this on the clinical effectiveness results.

Response: 6 patients (7.5%) enrolled in the full efficacy set of the L-MIND study discontinued lenalidomide due to adverse events (AEs) during the first 12 cycles of therapy went on to receive tafasitamab for more than 30 days after discontinuation of lenalidomide. Of these 6 patients, 2 patients also discontinued tafasitamab within the first 12 cycles of therapy. The remaining 4 patients received tafasitamab for 15.2, 39.1, 42.1 and 46.9 months, respectively. 2 of these patients were still alive and receiving tafasitamab monotherapy at the end of follow-up, while the other 2 patients

died after discontinuing tafasitamab because of withdrawal from the study and disease progression.

Of the 4 patients who received tafasitamab beyond the first 12 cycles of therapy after discontinuation of lenalidomide due to AE(s), 2 achieved a centrally confirmed response (1 PR and 1 CR) while receiving lenalidomide. The patient with PR subsequently improved to a centrally confirmed CR while receiving tafasitamab monotherapy. The other two patients achieved a centrally confirmed response (1 PR and 1 CR) after lenalidomide discontinuation.

Of note, the two patients who discontinued tafasitamab monotherapy within the first 12 cycles of treatment after discontinuing lenalidomide due to AE received tafasitamab monotherapy for 5.1 months and 6.5 months, and discontinued therapy because of PD or onset of a new adverse event. 1 of these patients was in centrally confirmed PR at the time of lenalidomide discontinuation, while the other patient achieved centrally confirmed PR after lenalidomide discontinuation.

Based on the outcomes observed, it appears that early discontinuation of lenalidomide due to AEs did not appear to have a substantial impact on the achievement of response or OS for these 6 patients.

b. Please provide the definition of ‘stable disease’.

Response: In L-MIND, disease response assessments were made according to the revised response criteria based on the 2007 guidelines of the International Working Group (IWG) reported by Cheson et al. 2007.[14] Stable disease was defined as not meeting the criteria for a CR or PR, while also not fulfilling the criteria for PD.[14] At presentation, DLBCL is fluorodeoxyglucose (FDG)-avid on positron emission tomography (PET) imaging.[15] The IWG criteria specify that, to confirm SD for FDG-avid lymphomas such as DLBCL, PET imaging should be positive at prior sites of disease, with no new areas of involvement on the post-treatment PET or computed tomography (CT).[14]

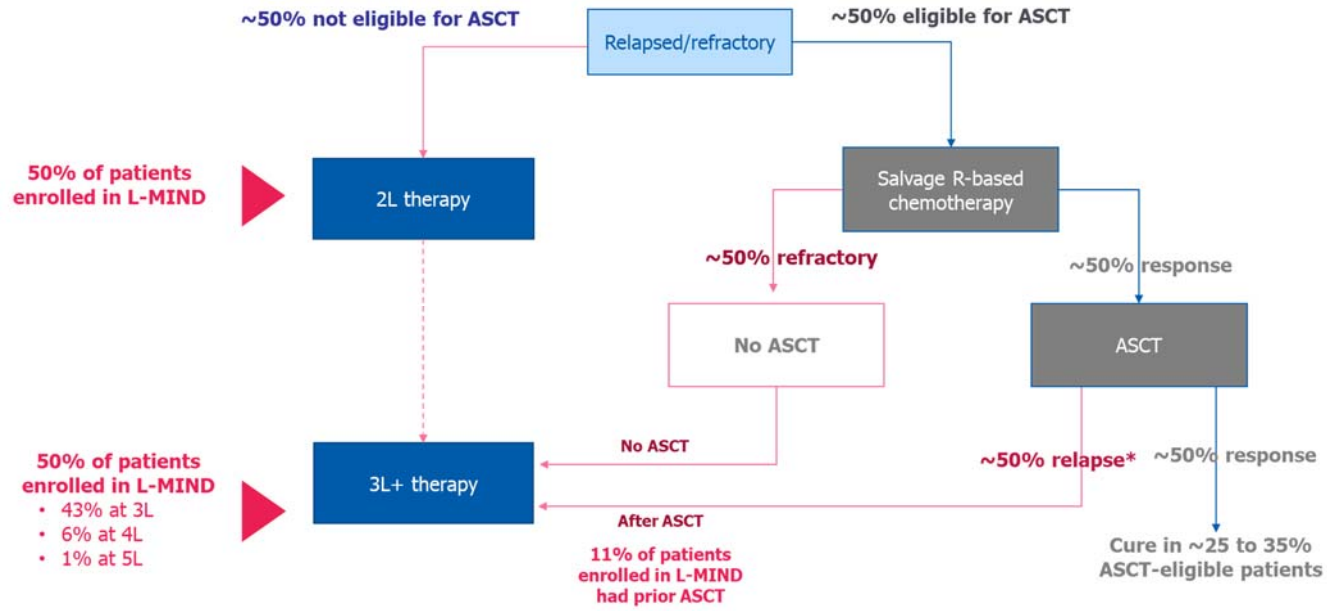
B11. In Figure 4 of the CS, Tafasitamab + Lenalidomide is positioned for 2L and 3L+ relapsed/ refractory DLBCL patients who are transplant ineligible.

a. As 50% of patients (40/81) in the L-MIND study population had failed on one previous line of systemic therapy (1L), please discuss the generalisability of the L-MIND population to the expected population in the clinical pathway.

Response: Tafasitamab is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma who are not eligible for ASCT (i.e., second-line or later [2L+] therapy).[1] The indication is based on, and aligned with, the population enrolled in the L-MIND study. L-MIND enrolled patients who had received at least one prior therapy (i.e., 2L therapy), but no more than three previous therapies (i.e., fourth-line [4L] therapy).[12] No patients in L-MIND were treated in the 1L setting.

The proportion of patients in L-MIND treated at each therapy line is shown in Table 8 of this document (baseline characteristics in full L-MIND population and UK population). The L-MIND population included 50% of patients treated at 2L and approximately 40% of patients treated at 3L. This is in line with the proportions of patients treated in these settings in clinical practice (Figure 4).[16,17] Therefore, the positioning of TAFA+LEN in Figure 4 of the CS (and Figure 1 of this document) is in alignment line with the population enrolled in L-MIND and those treated in UK clinical practice, and captures a high proportion of the patients with the greatest unmet need in the clinical pathway in the UK.

Figure 4. Patient journey in R/R DLBCL



Adapted from Sehn and Salles 2021,[16] with L-MIND data from Salles 2020[12]
2L = second line; 3L = third-line; 3L+ = third-line or more; 4L = fourth-line; 5L = fifth-line; ASCT = autologous stem cell transplant; DLBCL = diffuse B-cell lymphoma

b. Please provide results separately for participants who failed or did not fail on 1L treatment.

Response: OS and PFS results by number of prior lines of therapy are shown below in Figure 5 and Figure 6. No patients in L-MIND were treated in the 1L setting; all patients were refractory to, or had relapsed following, 1L treatment and were ineligible to receive SCT.

Figure 5. OS by number of prior treatment lines

Abbreviation: OS = overall survival

Figure 6. PFS-IRC by number of prior treatment lines

Abbreviation: PFS-IRC = progression-free survival assessed by independent review committee.

Additional results from the Duell 2021 poster presented at ASCO are summarised below in Table 9.[18]

Table 9. Key efficacy outcomes for TAFA+LEN by number of prior treatment lines (Duell 2021)[18]

Outcome	1 prior treatment line (N=40)	2 or more prior treatment lines (N=40)	Overall L-MIND population (N=80)
Best Objective Response, n (%)			
CR	19 (47.5)	13 (32.5)	32 (40.0)
PR	8 (20.0)	6 (15.0)	14 (17.5)
SD	7 (17.5)	6 (15.0)	13 (16.3)
PD	5 (12.5)	8 (20.0)	13 (16.3)
NE*	1 (2.5)	7 (17.5)	8 (10.0)
ORR (CR + PR), n (%) [95% CI]†	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]	46 (57.5) [45.9–68.5]
Median DoR, months (95% CI)‡	43.9 (9.1–NR)	NR (15.0–NR)	43.9 (26.1–NR)

Clarification questions

Outcome	1 prior treatment line (N=40)	2 or more prior treatment lines (N=40)	Overall L-MIND population (N=80)
Median PFS, months (95% CI)‡	23.5 (7.4–NR)	7.6 (2.7–NR)	11.6 (6.3–45.7)
Median OS, months (95% CI)‡	45.7 (24.6–NR)	15.5 (8.6–NR)	33.5 (18.3–NR)

*No valid post-baseline response assessments. †Two-sided 95% Clopper-Pearson exact method based on a binomial distribution. ‡Kaplan-Meier estimate. Data cut-off: October 30, 2020.

Abbreviations: CR = complete response; DoR = duration of response; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

B12. HRQoL is listed in the NICE Final Scope as a relevant outcome. Please provide results from the SLR of HRQoL in terms of the underpinning HRQoL scores that informed the utility values presented in Table 28 of the CS (Summary of utility values for cost-effectiveness analysis).

Response: As noted in Section 3.4.3 of the CS, further information on the SLR of HRQoL is provided in Appendix G and Appendix H of the CS.

Indirect comparisons

B13. Priority question: The company states that due to the absence of head-to-head clinical studies of tafasitamab + lenalidomide versus comparators, one of the types of analysis employed was nearest neighbour (NN) matching, using two retrospective cohorts: 'An Observational Retrospective Cohort Study of Lenalidomide Monotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma to Generate a Historical Control for Clinical Trial MOR208C203' (RE-MIND); and 'An Observational Retrospective Cohort Study of Systemic Therapies for Relapsed or Refractory Diffuse Large B-Cell Lymphoma to Compare Outcomes to those from Tafasitamab + Lenalidomide in the L-MIND Study' (RE-MIND2).

a. **Given that this analysis appears to have included comparator individual patient data (IPD), please refer to Technical Support Document (TSD) 17 to explain the choice of methodology.**

Response: We thank the ERG for this question.

Relative-efficacy estimates of TAFA+LEN against comparators were derived using non-randomised evidence from the L-MIND study and the observational retrospective cohorts from the RE-MIND and RE-MIND2 studies.

To allow controlling for bias in the relative efficacy estimates arising from imbalances in key prognostic factors or treatment-effect modifiers, 1:1 nearest neighbour matching analyses were conducted to construct comparator cohorts similar to the L-MIND population. Residual differences in the L-MIND and comparator matched populations were evaluated through the use of standardised mean differences.

In a sensitivity analyses, average treatment effect (ATE) was also derived through the use of propensity score weighting in the RE-MIND2 primary analyses. Results obtained through these means were aligned with the results reported in the base case. In the RE-MIND2 post-hoc analyses, average treatment effect on the treated (ATT) was evaluated using inverse probability of treatment weighting to extract as much information by a limited dataset and ensure specific results were not driven by a specific methodological choice. Comparative analyses of TAFA+LEN v. BR and R-GemOx using propensity score weighting and of TAFA+LEN v. POLA+BR using inverse probability of treatment weighting were aligned with the base case analyses (1:1 matching). Some volatility was observed in the ATT weights, with some patients becoming highly influential of the results and thus results from this approach should be interpreted with caution.

Regression analyses were not considered because of the observed differences in the L-MIND and observational cohorts that could have led to quasi separation of the data in the estimation of the models, particularly in the analyses against POLA+BR, and concerns over the possibility of finding good models to fit the outcomes of interest (PFS and OS).

Additional information provided on 20th January 2022

In addition, regression adjustment was not considered as the sensitivity of the results to method selection was already investigated through the use of both propensity score matching and weighting methods. It can also be noted that post-hoc estimation of regression models, either through regression adjustment or regression analysis, is expected to be difficult or unfeasible given the small sample size and number of

observed events in some of the observational cohorts, as well as the number of covariates to include in the adjustment.

b. Please follow Figure 3 in TSD 17 in considering selection of methods for controlling for confounding and perform sensitivity analyses where one method is not unequivocally better.

Response: Weighting methods including overlap weighting and inverse probability of treatment weighting were used in sensitivity analyses and provided results aligned with the base case results. It can be noted that some concerns were raised due to the overdispersion of the weights in the analyses of TAFA+LEN vs. POLA+BR.

As noted above, because of the difference observed between the L-MIND population and some of the observational cohorts which could have led to separation of the data and the difficulty to find good predictive models for the outcomes of interest, regression analyses were not conducted. Therefore, 1:1 nearest neighbour matching was considered in the base case.

Additional information provided on 20th January 2022

As detailed above, regression adjustment was not considered as the sensitivity of the results to method selection was already investigated through the use of both propensity score matching and weighting methods. Conduction of regression adjustment or regression analysis is expected to be difficult or impossible owing to the sample size, number of events in some of the observational populations and number of variables to include in the adjustment.

c. Please provide all of the results of the analysis of RE-MIND 2 for the comparisons with pola-BR and pixantrone, as reported for BR and R-GemOx in the CS.

Response: We thank the ERG for this question.

RE-MIND2 comparison versus pixantrone

Because of the small accrual of patients treated with pixantrone in the RE-MIND2 study (n=17), no comparative efficacy analyses of TAFA+LEN versus pixantrone could be conducted.

RE-MIND2 comparison versus POLA+BR

In RE-MIND2, TAFA+LEN (in L-MIND) was compared with POLA+BR in a post-hoc analysis. Due to the recent availability of POLA+BR at the time of RE-MIND2 data collection, the sample size was small and 1:1 nearest neighbour matching on 9 covariates could not be performed with the available data.

The RE-MIND2 post-hoc results of TAFA+LEN versus POLA+BR are provided below. The data are from analyses in the matched analysis set (MAS) with 1:1 nearest neighbour matching performed using 9 covariates and multiple imputation to address missing data (MASMI_9cov analysis set). Similar results were seen with TAFA+LEN vs POLA+BR in other matched sensitivity analyses of the RE-MIND2 data, including 1:1 matching with 6 covariates [redacted] ([redacted] and MAS_6cov analysis sets respectively). Data in the MAS-6cov analysis set are available from an oral presentation at ASH 2021 (Nowakowski et al. 2021; provided with this response).[19]

Overall survival

The TAFA+LEN cohort had a longer overall survival (OS) time than the POLA+BR cohort. [redacted]. The hazard ratio was 0.42 (95% CI: 0.23, 0.78; [redacted]). A KM plot of OS is shown in Figure 7.

Figure 7. KM plot of OS for the MASMI_9cov analysis set

Progression-free survival

[redacted].

Figure 8. KM plot of PFS for the MASMI_9cov analysis set

Duration of response

[redacted].

Figure 9. KM plot of DoR for the MASMI_9cov analysis set

Event-free survival

[redacted].

Figure 10. KM plot of event-free survival in the MASMI_9cov analysis set

Clarification questions

Objective response rate and complete response rate

[redacted]

Figure 11. Forest plot of difference of ORR in the different analysis sets

d. Please provide evidence that no IPD were available for any of the other comparators or, if they are available, then use them to perform analyses of tafasitamab + lenalidomide versus all comparators for all relevant outcomes including overall survival (OS), progression-free survival (PFS), duration of response (DoR) and objective response rate (ORR).

Response: As noted in response to clarification question B1, only POLA+BR, BR and R-GemOx were considered to be relevant comparators for TAFA+LEN based on UK clinical expert feedback. Detailed results from RE-MIND2 are provided in B.2.9 and Appendix D of the CS, with additional results from the post-hoc analysis for POLA+BR provided above in response to part (c).

e. **Please conduct quality assessments of these two observational studies and any others used for either IPD or matching adjusted indirect comparison (MAIC) analyses and provide details concerning the appraisal tool and approach taken.**

Response: We thank the ERG for this question.

RE-MIND / RE-MIND2

A quality assessment of the RE-MIND and RE-MIND2 studies using the QuEENS checklist is provided in the Appendix.

MAIC

To our knowledge, no accepted quality assessment tools exist to evaluate an MAIC.

f. **Although allogeneic stem cell transplant was an exclusion criterion for patients on the RE-MIND 2 study, please clarify if autologous stem cell transplantation was permitted for patients in this cohort.**

Response: Prior autologous stem cell transplant (SCT) was not an exclusion criterion for RE-MIND2.[20] Patients included in the RE-MIND2 observational cohort study were selected to closely resemble characteristics of the patients treated in the L-MIND study.[20] In L-MIND, 9 (11%) patients had received a prior autologous SCT.[12] Prior autologous SCT (Yes vs. No) was one of the nine baseline covariates used for 1:1 matching in RE-MIND2 to ensure balance between the L-MIND population and each comparator cohort; in the RE-MIND2 comparison of TAFA+LEN vs POLA+BR (FAS matching with 9 covariates and multiple imputations), 9 (11.8%) patients in the TAFA+LEN arm and 4 (11.1%) of patients in the POLA+BR arm had received prior autologous SCT.[21]

g. **The population of the RE-MIND cohort were patients with DLBCL who were not eligible for high-dose chemotherapy following autologous stem cell transplantation (ASCT). Please explain the limitations of using this patient population in lieu of that in the decision problem ("….not eligible for ASCT").**

Response: We thank the ERG for this question. Part G refers to wording in Appendix D.1.1.7 (RE-MIND methodology overview). This should read 'high-dose

chemotherapy *followed by* autologous stem cell transplant (ASCT)' and not *'following* ASCT'. The RE-MIND population is aligned with the population specified by the decision problem. High-dose chemotherapy is given as salvage therapy prior to ASCT; patients who are not fit to receive this intensive therapy are therefore ineligible for ASCT.

h. Please discuss how the population of these two cohorts are generalisable to the UK population of adults with relapsed or refractory DLBCL and who are not eligible for ASCT. Please provide supporting evidence.

Response: Patients in the RE-MIND and RE-MIND2 studies were matched 1:1 with patients in the L-MIND study. Please refer to our response to question B9b in this document for discussion regarding the generalisability of L-MIND to the UK population with R/R DLBCL who are ineligible for transplant.

RE-MIND2 was conducted to assess comparability of TAFA+LEN in L-MIND with treatments used in routine clinical practice, including the R-GemOx, BR and POLA+BR cohorts. POLA+BR, R-GemOx and BR were noted as key comparators for the UK population and representative of UK clinical practice by UK clinical experts at 1:1 interviews (reference 50 in the CS, provided 06 December 2021).[8] The UK clinical experts noted that the outcomes for R-GemOx and BR in RE-MIND2 were aligned with their experience and expectations in routine clinical practice.[8] This indicates that these RE-MIND2 cohorts are reflective of the population with R/R DLBCL treated in UK clinical practice.

Regarding the POLA+BR cohort, as discussed in the CS and the answer to question B13c in this document, the RE-MIND2 data were highlighted as pessimistic by UK experts. This may reflect the recent introduction of POLA+BR into the market and a lack of clinical experience with this treatment at the time of the RE-MIND2 data collection. Therefore, the POLA+BR arm of RE-MIND2 was not included in the base case economic analyses of the CS.

Regarding generalisability of the RE-MIND population to the UK population, lenalidomide monotherapy is not a key comparator for UK clinical practice, according to clinical expert feedback.[8] However, the lenalidomide monotherapy cohort of RE-

MIND was matched with 1:1 nearest neighbour matching to the L-MIND population, which is largely reflective of the population in UK clinical practice (please see answer to B9b).

B14. Priority question: The company states that due to the absence of head-to-head clinical studies of tafasitamab + lenalidomide vs. comparators, several MAICs were conducted.

a. **Please provide a list of the eligibility criteria for selecting comparator studies.**

Response: We thank the ERG for this question. Details of the selection criteria for inclusion of SLR-identified studies in the MAIC are presented in Appendix D.1.1.34 of the CS and are outlined below. Comparator study designs were thoroughly assessed against the L-MIND study, which enrolled only patients who were ineligible for SCT and who had received at least one but no more than three prior lines of therapy, including an anti-CD20 agent, to ensure that meaningful comparisons could be conducted.[22]

Eligibility criteria were selected according to clinical expert advice to ensure a meaningful population-adjusted comparison between L-MIND and comparator studies. Key initial study exclusion criteria were as follows:[22]

- Studies reporting large proportions of patients with non-DLBCL non-Hodgkin's lymphoma (NHL)
- Studies that enrolled a large proportion of patients with double- or triple-hit lymphoma
- Studies that enrolled patients eligible for SCT
- Studies that enrolled a majority of patients treated in the fourth-line setting or beyond
- Studies reporting retrospective evidence

Following this initial selection process, inclusion/exclusion criteria of each of the studies were applied to the L-MIND population to estimate the retained sample size of the L-MIND population upon which further population adjustment would be attempted. A final decision on the inclusion of the evidence in the MAIC was made

after assessing this sample size against the extent of the remaining imbalances in population characteristics between the L-MIND and comparator studies.[22]

b. Please elaborate on the clinical expert interviews used to generate the MAIC study eligibility criteria. Please provide supporting evidence in the form of reference #50 from the CS (this is missing from the submitted reference pack) or other documentation. Reference #50 was requested by the ERG in an email to NICE on 3rd December 2021.

Response: Minutes of three interviews conducted with UK clinical experts (reference 50) were provided to NICE on 06 December 2021. These minutes include advice from the UK experts on topics including patient population, relevant comparators in the UK and extrapolation of survival curves for use in cost-effectiveness modelling.

Eligibility criteria for the MAIC were generated in two separate interviews with clinical experts from France and Spain, conducted in October 2020. The minutes of these interviews are provided with this response document *['ID3795_Minutes of Clinical Expert Interview to inform MAIC analysis, October 2020 - France'* and '*ID3795 Minutes of Clinical Expert Interview to inform MAIC analysis, October 2020 - Spain.*].[23,24] In particular, the following points were discussed regarding the study selection criteria for the MAIC.

- It was advised not to include studies enrolling a mixed population of patients with NHL. Although DLBCL studies often include a heterogeneous population of patients with NHL, with results often expanded to refer to DLBCL specifically, the prognosis of patients with other NHL subtypes (such as untransformed follicular lymphoma or mantle-cell lymphoma) differs from the prognosis of patients with de novo DLBCL or transformed indolent lymphoma. Therefore, studies reporting large proportions of patients with untransformed follicular lymphoma or mantle-cell lymphoma were excluded from the MAIC.[23,24]
- Although a history of double- or triple-hit lymphoma (high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements) was stated as an exclusion criterion for the L-MIND study, it was noted that double- or triple-hit status does not appear to have been proactively verified for patients at inclusion and that these data may not always be available for many patients due to a lack of testing equipment.[23,24]

  - However, as patients with double- or triple-hit lymphoma have worse prognosis at baseline than other patients with DLBCL, studies that enrolled a large proportion of patients with double- or triple-hit lymphoma were considered not comparable to L-MIND and excluded from the MAIC

- The L-MIND study was explicitly conducted among patients not eligible for ASCT. As patients who are not eligible for SCT are typically frailer than those who are eligible for SCT (i.e., older patients, patients with comorbidities), studies that enrolled patients eligible for SCT were considered not comparable to L-MIND. While a proportion of patients ineligible for SCT initially may become eligible following chemotherapy,[23,24] interviews with UK clinical experts (minutes shared 06 December), indicated that this proportion of patients is expected to be small and unlikely to impact cost-effectiveness analyses.[8]
- The L-MIND study was conducted in patients who had received at least one but no more than three prior lines of anti-cancer therapy (i.e., 2L to 4L). It was noted that each disease relapse and subsequent line of therapy risks emergence of different mutation types, with disease becoming more difficult to treat at each therapy line. As such, studies that enrolled a majority of patients treated in the fourth-line setting or beyond were considered not comparable to the L-MIND study and excluded from the MAIC analysis.[23,24]

Specific patient characteristics that could act as prognostic factors or effect modifiers were also discussed with the experts during the interviews. For example, IPI score, ECOG PS, refractory disease status, lactate dehydrogenase (LDH) levels and disease characteristics such as cytogenetic factors. These factors were accounted for in the MAIC by applying eligibility criteria from the comparator studies to the L-MIND population during the MAIC process.[23,24]

c. Please provide a list of all 32 studies included from the SLR together with the eligibility criteria used to exclude each one from a comparison with tafasitamab + lenalidomide by any means, including MAIC or naïve comparison.

Response: The SLR conducted to inform the MAIC identified 36 unique studies reporting data on key treatments of interest for patients with R/R DLBCL, which are

presented in Table 20 of Appendix D (Section D.1.1.34) of the CS and below (Table 10):

Table 10. Summary of the inclusion of evidence in the MAIC

Treatment	Study	Inclusion in the MAIC analyses
Lenalidomide	DLC-001[25]	Yes
	NHL-002 (NCT00179660)[26]	No: 40.8% patients enrolled in this study had mantle cell lymphoma or follicular lymphoma.
	NHL-003 (NCT00413036)[27,28]	No: 35.1% of patients enrolled in this study had mantle cell lymphoma or follicular lymphoma.
	Lakshmaiah et al., 2015[29]	No: Only 60% of patients enrolled in this study had DLBCL.
	NCT00799513[30,31]	No: The setting of the intervention is different as LEN maintenance therapy is investigated in this study.
	Broccoli et al., 2019[32]	No: This study is a retrospective study.
	Rodgers et al., 2020[33]	No: The intervention investigated in this study is a mix of R-LEN and LEN monotherapy and results are not reported specifically by treatment.
	Zinzani et al., 2015[34]	No: This study is a retrospective study.
POLA+BR	**GO29365[35,36]**	Yes
	Dujmovic et al., (2020)[37]	No: This study is a retrospective study.
Tisagenlecleucel	NCT02030834[38]	No: In the NCT02030834 study, 22% of patients had a double-hit disease. In addition, there were some concerns about survivor bias. Out the 23 patients with DLBCL enrolled, 9 did not receive treatment as planned. Three of these patients discontinued the study because of rapid disease progression, and did not contribute to the efficacy analyses.
	JULIET[38,39]	No: In the JULIET study, 17% of patients had double- or triple-hit disease. Some concerns about survivor bias were also raised for the JULIET study: out of 165 patients enrolled and who underwent leukapheresis, 50 patients did not receive an injection, 16 of whom died before receiving an infusion, and did not contribute to the main efficacy analyses.
Axicabtagene ciloleucel	ZUMA-1[40]	No: The pre-filtering of the L-MIND population to match inclusion/exclusion criteria from ZUMA-1 excluding patients non-refractory to their previous therapy line, with histology other than DLBCL or who were ECOG PS 2 retained only 27 patients, with large differences still observed on prior treatment lines and patients' ages that would need to be adjusted for by the MAIC.
	Logue et al., 2020[41]	No: This study is a retrospective study.
	Perkins et al., 2020[42]	No: This study is a retrospective study.
	Nastoupil et al., 2020[43]	No: This study is a retrospective study.
	Faramand et al., 2020[44]	No: This study is a retrospective study.
Pixantrone	PIX301[45]	No: The pre-filtering of L-MIND population to match inclusion/exclusion criteria from the PIX301 trial excluding patients treated in the second-line setting or who had a history of primary refractoriness retained 30 patients, with large differences still observed on prior

Treatment	Study	Inclusion in the MAIC analyses
		treatment lines that would need to be adjusted for by the MAIC.
BR	**GO29365[35,36]**	Yes
	Ohmachi et al., 2013[46]	Yes
	Kiguchi et al., 2020[47]	No: Only a conference abstract was available for this study.
	Vacirca et al., 2014[48]	Yes
	Rigacci et al., 2012[49]	No: This study is a retrospective study.
	Walter et al., 2012[50]	No: This study is a retrospective study.
	Hong et al., 2018[51]	No: This study is a retrospective study.
	Arcari et al., 2016[52]	No: This study is a retrospective study.
	Mercchione et al., 2014[53]	No: This study is a retrospective study.
	Ionescu-Ittu et al., 2019[54]	No: This study is a retrospective study.
R-GemOx	Mounier et al., 2013[55]	Yes
	El Gnaoui et al., 2007[56]	No: 28% of patients enrolled in this study had mantle cell lymphoma or follicular lymphoma.
	Lopez et al., 2008[57]	No: 34% of patients included in this study were reported to have ECOG PS 3 or above at baseline. As no patients with ECOG >2 were enrolled in L-MIND, no adjustment would be possible on this factor. Conducting an analysis using this source of evidence would therefore produce results biased in favour of TAFA+LEN and this study was not considered further.
	Corazzelli et al., 2009[58]	No: Only 50% of patients enrolled in Corazzelli et al. 2009 had DLBCL. Note: in Appendix D.1.1.34, the wrong reason for exclusion was noted (this study was labelled as a retrospective study). We apologise for this error.
	Cazelles et al., 2019[59]	No: This study is a retrospective study.
	Ionesco-Ittu et al., 2019[54]	No: This study is a retrospective study.
R-LEN	Zinzani et al., 2011[60]	No: Pre-filtering of the L-MIND population to match inclusion/exclusion criteria from Zinzani et al.,2011 led to a population of 27 patients, with large differences still observed on prior treatment line and LDH levels at baseline.
	Wang et al., 2013[61]	No: 60% of responders to this study were treated with subsequent ASCT which raised concerns about the comparability of the setting of this study with L-MIND.
	Rodgers et al., 2019[33]	No: The intervention investigated in this study is a mix of R-LEN and LEN monotherapy and results were not reported specifically by treatment.
	Conde-Royo et al., 2020[62]	No: This study is a retrospective study.

Abbreviations: ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LEN = lenalidomide; MAIC = matching adjusted indirect comparison; R-LEN = rituximab and lenalidomide; TAFA+LEN = tafasitamab and lenalidomide.

d. If any study was excluded because of having a retrospective design then please include that study in a comparison with tafasitamab + lenalidomide by any means, including MAIC or naïve comparison.

Clarification questions

Response: We thank the ERG for this question.

We present below a detailed overview of the feasibility assessment to conduct MAICs of TAFA+LEN against comparators investigated in the retrospective studies identified by the SLR. In summary, all of the retrospective studies were not considered appropriate for a MAIC analysis. It is also important to note that the use of real-world data was considered through the RE-MIND2 study, where individual level patient data was available and matched 1:1 with patient level data from the L-MIND study, whereas, aside from other potential feasibility concerns identified, more limited summary level outcome and patient characteristics data would be available from published observational studies for conducting a MAIC.

TAFA+LEN v. BR

6 retrospective studies of BR were identified by the SLR: Rigacci et al. 2012, Walter et al. 2012, Arcari et al. 2016, Ionesco-Ittu et al. 2019, Mercchione et al. 2014 and Hong et al. 2018.

Rigacci et al. 2012, Walter et al. 2012, Arcari et al. 2016 and Ionesco-Ittu et al. 2019 showed important differences in inclusion / exclusion criteria compared to the L-MIND study:

- Rigacci et al. 2012 was a multicentre retrospective study conducted in 24 centres in Italy that included 175 patients with non-Hodgkin lymphoma. As it focused on the outcomes of patients with non-Hodgkin Lymphoma a minority of patients included in the analyses had DLBCL (34 patients out of 175, corresponding to 19%). Because of this large difference in patients' histology, an MAIC of TAFA+LEN against BR using this source of evidence is not feasible as the L-MIND study was primarily conducted among patients with R/R DLBCL.
- Walter et al. 2012 was a single centre retrospective analysis of 23 patients with DLBCL. Most patients enrolled in this study had newly diagnosed disease (15 patients out of 23, corresponding to 65%) and thus are not comparable to patients enrolled in L-MIND, a study that focused on R/R DLBCL. Only 8 patients had relapsed or refractory disease and appeared to be generally more heavily pre-treated than the L-MIND population (median number of prior lines of therapy of 3 vs. 1.5 in L-MIND). In addition, no KM curve was reported for the relapsed or

refractory DLBCL population. Due to the reduced size of the R/R DLBCL population included in Walter et al. 2012 (8 patients), differences observed in number of prior lines of therapy and lack of accurate data for time-to-event outcomes, conducting an MAIC of TAFA+LEN v. BR using Walter et al. 2012 as a source of evidence is not feasible.

- Arcari et al. 2016 was a retrospective study that included 55 patients in 15 centres in Italy. Specifically, only patients that completed at least two cycles of BR were included in this study. As a result, a selection bias in the patient population is expected as patients with early death or progression (i.e. within the first 2 cycles of administration of BR) were not included in this study. In particular, it appears that no events were recorded in the first two months on therapy as a result of this selection criteria. As a result, conducting an MAIC of TAFA+LEN v. BR using Arcari et al. 2016 as a source of evidence is not feasible.
- Ionesco-Ittu et al. 2019 was a retrospective study conducted out of electronic medical records from the US Veterans health data base. It is unclear from the study material whether the patient population was selected so as to only include patients ineligible to stem cell transplantation. In addition, important prognostic factors or treatment-effect modifiers were not reported in this study such as ECOG at baseline, IPI or treatment with prior ASCT. Due to the nature of the data collected in this study some other factors might not be comparable to factors recorded in L-MIND, such as refractory DLBCL which was defined as patients having <180 days between their first line and second line start in the Ionescu-Ittu et al. study, while in L-MIND it was defined as a progression on or within 6-months of the initiation of the first line of therapy. As a result, conducting an MAIC of TAFA+LEN v. BR using Ionesco-Ittu et al. 2019 as a source of evidence is not feasible.

Mercchione et al. 2014 was a retrospective study that included 28 patients with R/R DLBCL. Despite generally similar inclusion criteria compared to the L-MIND study large differences were observed in baseline population characteristics: 57.2% of patients included in Mercchione et al. 2014 had ECOG ≥ 2, while 8.6% of L-MIND patients had ECOG 2, with no patients with ECOG > 2. Other large differences were observed in Revised IPI status and number of prior lines of therapy with 43.8% of

L-MIND patients had a good R-IPI status and 50% treated in the second line setting versus 60.7 of patients included in Mercchione et al. with a good R-IPI status, and 28.6% treated in the second line setting. As a result of these differences a large decrease in the ESS is expected and an MAIC of TAFA+LEN vs. BR using Mercchione et al. 2014 as a source of evidence is not feasible.

Hong et al. 2018 was a retrospective study that included 58 patients with R/R DLBCL in 11 centres in Korea. Some differences were noted between the L-MIND study population and the Hong study populations, in particular, it can be noted that patients with ECOG PS up to 4 were enrolled in Hong et al 2018, although the proportion of patients that would have had ECOG 3 or 4 cannot be quantified in Hong et al. 2018. Due to potential concerns about the generalisability of a Korean patient population to the L-MIND study or a UK patient population, this study was excluded from consideration.

TAFA+LEN vs R-GemOx

2 retrospective studies of R-GemOx were identified by the SLR: Ionesco-Ittu et al. 2019, discussed previously, and Cazelles et al. 2019.

As discussed previously important differences were found in the designs and inclusion / exclusion criteria of the L-MIND and Ionesco-Ittu et al. 2019 studies and thus an MAIC of TAFA+LEN vs. R-GemOx using this source of evidence is not feasible.

Cazelles et al. was a retrospective study of patients with R/R DLBCL conducted in 2 centres in France. Evidence for this study is scarce and at the moment only an abstract seems available without KM curves available and a limited number of baseline characteristics reported. In particular, ECOG of patients at baseline was not reported for this study. Due to the scarcity of the data available for Cazelles et al. an MAIC of TAFA+LEN vs. R-GemOx using this source of evidence is not feasible.

TAFA+LEN v. POLA+BR

The Dujmovic et al. 2020 study[37,63] was the only retrospective study of POLA+BR in patients with R/R DLBCL identified by the SLR. This study included 23 patients with

R/R DLBCL from 9 centres in Croatia. Some differences were found in the baseline characteristics of patients included in Dujmovic et al. and the L-MIND study:

- The median number of prior lines received by patients in Dujmovic et al. 2020 was three, versus 1.5 in the L-MIND study, with only 7.5% of patients in the L-MIND study having received three lines or more of prior therapy.
- 31% of patients had an ECOG score of 3 or 4 in the Dujmovic et al. study, while no patients with an ECOG score of >2 were enrolled in L-MIND, hence no adjustment would be possible on this important confounder.

Because of the differences observed in important prognostic factors of DLBCL an MAIC of TAFA+LEN vs. POLA+BR using this source of evidence is not feasible.

B15. In Appendix D.1.1.6 of the CS, the company discusses likely residual error due to unobserved prognostic factors and effect modifiers in the MAIC. As unanchored indirect comparisons are susceptible to large amounts of residual error, please estimate the likely systematic error, or provide justification as to why it could not be quantified.

Response: We thank the ERG for this question.

Residual bias due to imbalances in unobserved characteristics is an important limitation of MAIC analyses. In addition to potential unobserved differences in baseline characteristics between the L-MIND and comparator populations at baseline, population adjustment for observed factors might further imbalances the distribution of these unobserved characteristics yielding to an increase in the bias. Such bias is difficult to quantify on a comparison per comparison basis as the proportion of patients with a given characteristic in the comparator populations is not available.

Table 11 and Table 12 illustrate the prognostic ability of key factors included in the MAIC through univariate HR estimates alongside 95% CI on OS and PFS assessed by independent review committee (PFS-IRC).

To provide a quantification the unobserved residual bias the expected HR between the L-MIND unweighted data and a fictive population based on the L-MIND study in which a given characteristic would be 10% more frequent (respectively 10% less frequent) all other things being equal are also presented below. It should be noted

that the actual proportions of patients in the comparator data with these characteristics are unknown and might be different than this 10% variation that is provided here for illustration purposes.

The HR between the fictive population and the L-MIND unweighted population is obtained by taking the exponential of the difference between the proportions multiplied it by the appropriate coefficient.

Estimates for all factors of interest from the L-MIND study according to clinical experts are presented for completion, despite some of these factors being available for most or all comparisons (e.g., age).

It can be observed that difference in the histology of patients at baseline, or in the proportion of patients with elevated LDH levels appear to have an important impact on the OS and PFS-IRC outcomes, while not always being possible to include in the population adjustment:

- No population adjustment could be conducted on DLBCL histology in the comparison of TAFA+LEN vs. BR using Vacirca et al. 2014 or Ohmachi et al. 2013 as sources of evidence or in the comparison of TAFA+LEN vs. R-GemOx due to the absence of centrally confirmed histology data reported.
- Despite being reported in the Ohmachi et al. 2013 and in Mounier et al. 2013 no adjustment was made on LDH levels as other factors were prioritised in the population adjustment as per clinical experts' opinion. It can be noted that a sensitivity MAIC model where a population adjustment was carried out on the proportion of patients with elevated LDH levels was conducted using evidence from Ohmachi et al. 2013 and yielded results similar to the base case model.

Table 11 Prognostic ability of key factors included in the MAIC on OS in the L-MIND study

Factor	Levels	Observed data from L-MIND				Scenario – HR between a fictive population that would have a more frequent (resp. less frequent) given characteristic and the L-MIND population all other things being equals			
		Proportion	Coefficient (SE)	HR (95%CI)	Pr(>|z|)	Proportion 10% less frequent	HR 10% less frequent v. L-MIND (95%CI)	Proportion 10% more frequent	HR 10% more frequent v. L-MIND (95%CI)
Age (ref. <65)	>= 65	0.713	0.29 (0.36)	1.34 (0.67,2.69)	0.407	0.641	0.98 (0.49, 1.96)	0.784	1.02 (0.51, 2.05)
Sex (ref. Female)	Male	0.538	0.06 (0.31)	1.06 (0.58,1.95)	0.84	0.484	1.00 (0.54, 1.82)	0.591	1.00 (0.55, 1.84)
ECOG (ref. 0)	1	0.563	0.90 (0.35)	2.45 (1.23, 4.89)	0.011	0.506	0.95 (0.48, 1.90)	0.619	1.05 (0.53, 2.10)
	2	0.075	1.32 (0.60)	3.75 (1.17,12.06)	0.026	0.068	0.99 (0.31, 3.18)	0.083	1.01 (0.31, 3.25)
IPI (ref. Low risk)	Low-Intermediate Risk	0.300	0.91 (0.67)	2.50 (0.67, 9.34)	0.174	0.270	0.97 (0.26, 3.64)	0.330	1.03 (0.27, 3.84)
	Intermediate-High Risk	0.300	1.76 (0.67)	5.79 (1.56,21.55)	0.009	0.270	0.95 (0.25, 3.53)	0.330	1.05 (0.28, 3.92)
	High Risk	0.200	1.83 (0.72)	6.26 (1.54,25.54)	0.011	0.180	0.96 (0.24, 3.93)	0.220	1.04 (0.25, 4.23)
Ann Arbor stage (ref. I-II)	III and IV	0.750	0.44 (0.38)	1.56 (0.73,3.31)	0.249	0.675	0.97 (0.46, 2.06)	0.825	1.03 (0.49, 2.20)
Histology (ref. non-DLBCL patients)	DLBCL patients	0.886	1.08 (0.73)	2.94 (0.70,12.28)	0.14	0.797	0.91 (0.22, 3.80)	0.975	1.10 (0.26, 4.60)
	Unknown	0.013	-15.08 (1.23)	0.00 (0.00, 0.00)	<0.001	0.011	1.02 (0.09, 11.36)	0.014	0.98 (0.09, 10.94)
History of transformed indolent lymphoma (ref. No)	Yes	0.100	-0.19 (0.44)	0.83 (0.35,1.97)	0.673	0.090	1.00 (0.42, 2.37)	0.110	1.00 (0.42, 2.36)
Bulky disease (ref. Absent)	Present	0.177	0.53 (0.43)	1.70 (0.74,3.90)	0.214	0.159	0.99 (0.43, 2.28)	0.195	1.01 (0.44, 2.32)
High LDH levels (ref. No)	Yes	0.550	0.88 (0.33)	2.41 (1.27,4.57)	0.007	0.495	0.95 (0.50, 1.81)	0.605	1.05 (0.55, 1.99)
Cell of origin of the disease by immunohistochemistry	GCB Phenotype	0.633	0.40 (0.36)	1.50 (0.74,3.03)	0.26	0.570	0.97 (0.48, 1.97)	0.697	1.03 (0.51, 2.07)

(ref. Non-GCB Phenotype)									
Cell of origin of the disease by genetic profiling (ref. ABC Phenotype)	GCB Phenotype	0.211	-0.44 (0.57)	0.65 (0.21,1.97)	0.443	0.189	1.01 (0.33, 3.08)	0.232	0.99 (0.32, 3.02)
	Not Evaluable	0.132	0.42 (0.55)	1.52 (0.52,4.45)	0.440	0.118	0.99 (0.34, 2.90)	0.145	1.01 (0.34, 2.93)
	Unclassified Phenotype	0.132	-1.07 (0.92)	0.34 (0.06,2.08)	0.245	0.118	1.01 (0.17, 6.17)	0.145	0.99 (0.16, 6.00)
Number of prior lines of therapy (ref. 1)	>= 2	0.500	0.68 (0.31)	1.98 (1.08,3.62)	0.027	0.450	0.97 (0.53, 1.77)	0.550	1.03 (0.57, 1.89)
Duration of response to last therapy (ref. >12 months)	<=12 months	0.625	0.39 (0.31)	1.47 (0.80,2.70)	0.212	0.563	0.98 (0.53, 1.79)	0.688	1.02 (0.56, 1.88)
	Unknown	0.013	-13.78 (1.07)	0.00 (0.00,0.00)	<0.001	0.011	1.02 (0.13, 8.28)	0.014	0.98 (0.12, 8.00)
Refractoriness to last therapy (ref. No)	Yes	0.438	0.28 (0.32)	1.32 (0.71,2.45)	0.376	0.394	0.99 (0.53, 1.83)	0.481	1.01 (0.55, 1.88)
Primary refractoriness (ref. No)	Yes	0.188	0.43 (0.43)	1.54 (0.67,3.57)	0.309	0.169	0.99 (0.43, 2.29)	0.206	1.01 (0.44, 2.33)
Prior ASCT (ref. No)	Yes	0.113	-0.27 (0.46)	0.77 (0.31,1.88)	0.559	0.101	1.00 (0.41, 2.46)	0.124	1.00 (0.41, 2.44)

Abbreviations: ABC = activated B cell; ASCT = autologous stem cell transplantation; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ECOG = eastern cooperative oncology group; GCB = germinal centre B-cell; HR = hazard ratio; IPI = international prognostic index; LDH = lactate dehydrogenase; SE = standard error.

Table 12 Prognostic ability of key factors included in the MAIC on PFS-IRC in the L-MIND study

Factor	Levels	Observed data from L-MIND				Scenario – HR between a fictive population that would have a more frequent (resp. less frequent) given characteristic and the L-MIND population all other things being equals			
		Proportion	Coefficient (SE)	HR (95%CI)	Pr(>|z|)	Proportion 10% less frequent	HR 10% less frequent v. L-MIND (95%CI)	Proportion 10% more frequent	HR 10% more frequent v. L-MIND (95%CI)
Age (ref. <65)	>= 65	0.713	0.16 (0.35)	1.17 (0.59,2.32)	0.656	0.641	0.99 (0.50, 1.96)	0.784	1.01 (0.51, 2.00)
Sex (ref. Female)	Male	0.538	0.16 (0.31)	1.17 (0.64,2.16)	0.606	0.484	0.99 (0.54, 1.82)	0.591	1.01 (0.55, 1.86)
ECOG (ref. 0)	1	0.563	0.44 (0.32)	1.55 (0.83,2.87)	0.167	0.506	0.98 (0.53, 1.81)	0.619	1.02 (0.55, 1.90)
	2	0.075	0.55 (0.59)	1.74 (0.55,5.52)	0.347	0.068	1.00 (0.31, 3.16)	0.083	1.00 (0.32, 3.18)
IPI (ref. Low risk)	Low-Intermediate Risk	0.300	0.36 (0.57)	1.43 (0.47, 4.33)	0.53	0.270	0.99 (0.33, 3.00)	0.330	1.01 (0.33, 3.07)
	Intermediate-High Risk	0.300	1.15 (0.54)	3.17 (1.11, 9.06)	0.032	0.270	0.97 (0.34, 2.76)	0.330	1.04 (0.36, 2.96)
	High Risk	0.200	1.37 (0.56)	3.93 (1.31,11.81)	0.015	0.180	0.97 (0.32, 2.92)	0.220	1.03 (0.34, 3.09)
Ann Arbor stage (ref. I-II)	III and IV	0.750	0.47 (0.42)	1.61 (0.71,3.64)	0.256	0.675	0.97 (0.43, 2.19)	0.825	1.04 (0.46, 2.35)
Histology (ref. non-DLBCL patients)	DLBCL patients	0.886	1.03 (0.74)	2.80 (0.66,11.84)	0.161	0.797	0.91 (0.22, 3.86)	0.975	1.10 (0.26, 4.63)
	Unknown	0.013	-15.11 (1.23)	0.00 (0.00, 0.00)	<0.001	0.011	1.02 (0.09, 11.27)	0.014	0.98 (0.09, 10.85)
History of transformed indolent lymphoma (ref. No)	Yes	0.100	-0.22 (0.42)	0.80 (0.35,1.84)	0.599	0.090	1.00 (0.44, 2.30)	0.110	1.00 (0.43, 2.29)
Bulky disease (ref. Absent)	Present	0.177	0.45 (0.42)	1.57 (0.69,3.55)	0.279	0.159	0.99 (0.44, 2.25)	0.195	1.01 (0.45, 2.28)
High LDH levels (ref. No)	Yes	0.550	0.79 (0.32)	2.20 (1.17,4.12)	0.014	0.495	0.96 (0.51, 1.80)	0.605	1.04 (0.56, 1.96)
Cell of origin of the disease by immunohistochemistry (ref. Non-GCB Phenotype)	GCB Phenotype	0.633	0.49 (0.37)	1.63 (0.80,3.34)	0.179	0.570	0.97 (0.47, 1.98)	0.697	1.03 (0.50, 2.11)

Cell of origin of the disease by genetic profiling (ref. ABC Phenotype)	GCB Phenotype	0.211	-0.08 (0.53)	0.92 (0.32,2.63)	0.882	0.189	1.00 (0.35, 2.85)	0.232	1.00 (0.35, 2.84)
	Not Evaluable	0.132	0.38 (0.54)	1.46 (0.51,4.19)	0.479	0.118	1.00 (0.35, 2.85)	0.145	1.01 (0.35, 2.88)
	Unclassified Phenotype	0.132	-0.50 (0.64)	0.61 (0.17,2.12)	0.437	0.118	1.01 (0.29, 3.51)	0.145	0.99 (0.29, 3.46)
Number of prior lines of therapy (ref. 1)	>= 2	0.500	0.45 (0.30)	1.58 (0.87,2.85)	0.133	0.450	0.98 (0.54, 1.77)	0.550	1.02 (0.57, 1.85)
Duration of response to last therapy (ref. >12 months)	<=12 months	0.625	0.19 (0.30)	1.21 (0.67,2.20)	0.522	0.563	0.99 (0.55, 1.79)	0.688	1.01 (0.56, 1.83)
	Unknown	0.013	-14.90 (1.04)	0.00 (0.00,0.00)	<0.001	0.011	1.02 (0.13, 7.86)	0.014	0.98 (0.13, 7.58)
Refractoriness to last therapy (ref. No)	Yes	0.438	0.28 (0.30)	1.32 (0.73,2.40)	0.355	0.394	0.99 (0.54, 1.79)	0.481	1.01 (0.56, 1.84)
Primary refractoriness (ref. No)	Yes	0.188	0.39 (0.43)	1.48 (0.64,3.41)	0.364	0.169	0.99 (0.43, 2.30)	0.206	1.01 (0.44, 2.33)
Prior ASCT (ref. No)	Yes	0.113	-0.28 (0.52)	0.75 (0.27,2.10)	0.589	0.101	1.00 (0.36, 2.79)	0.124	1.00 (0.36, 2.77)

Abbreviations: ABC = activated B cell; ASCT = autologous stem cell transplantation; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ECOG = eastern cooperative oncology group; GCB = germinal centre B-cell; Hr = hazard ratio; IPI = international prognostic index; LDH = lactate dehydrogenase; SE = standard error.

Because the L-MIND study is a single-arm study, effect modification could not be quantified in this study.

Section C: Clarification on cost-effectiveness data

Effectiveness Inputs

C1. Priority question: Please provide the exact definitions of OS and PFS as defined in the L-MIND trial. If there was more than one definition, e.g., investigator-assessed (INV-assessed) or independent review committee-assessed (IRC-assessed), please provide all of them. Please also indicate which one was used to model OS/PFS in the economic model. If IRC-assessed OS/PFS outcomes were not used in the model, please amend the model to include this option.

Response: We thank the ERG for this question.

OS is a hard outcome that does not need review by an investigator or a committee to be assessed. As such, OS was defined as the time from the date of the first administration of any study drug until death from any cause (documented by the date of death). Patients who were alive or who dropped out early for any reason were censored at date of last contact. If for a patient's death month and year were provided but the day was missing, the day was set to the first day of the month, unless other qualifying study data support survival until a later date during the same month. If day and month or year was missing, no imputation was made, and the date of death was censored at the date of last contact.

PFS was defined as the time (in months) from the date of the first administration of any study drug to the date of tumour progression or death from any cause. The date of progression corresponds to the first date for which PD was assessed as the objective response. The tumour assessments were derived according to the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007),[14] by an Independent Radiology/Clinical Review Committee (IRC). If a patient was alive and progression-free at the date of the analysis the patient was censored, and the reason for censoring was provided. The date of last adequate tumour assessment was the date of the last tumour assessment with overall lesion response of CR, PR or SD

before an event or a censoring reason occurred. In this case the last tumour evaluation date at that assessment was used. If no post-baseline assessments were available (before an event or a censoring reason occurred) the date of start date of treatment was used.

In a sensitivity analysis investigator response assessment was used to inform PFS using otherwise the same definition and censoring rules.

Parametric survival extrapolations of the L-MIND study were performed by considering PFS-IRC as IRC-assessed surrogate endpoint were the primary endpoints of the L-MIND study. L-MIND PFS data and associated parametric survival extrapolations for TAFA+LEN included in the economic model were based on PFS-IRC.

PFS as assessed by the independent review committee and PFS as assessed by the investigators were used as appropriate to generate relative efficacy estimates of TAFA+LEN against POLA+BR, BR and R-GemOx in the MAIC analyses. Specifically, PFS-INV was used in the comparison against R-GemOx as investigated in Mounier et al. 2013, and PFS-IRC were used for all other comparisons.

Relative efficacy estimates of TAFA+LEN v. BR, R-GemOx and BR obtained from the RE-MIND2 study were derived by considering PFS-INV for the L-MIND study data and observational data for the comparator cohorts.

C2. Priority question: Please provide an alternative model, where the OS and PFS distributions *for all comparators* can be informed by parametric extrapolation curves based on RE-MIND2. Please provide updated cost effectiveness results assuming that OS and PFS *for all comparators* are based on RE-MIND2.

Response: The option to select the relevant dataset for each treatment option (MAIC, RE-MIND2) is included in the submitted economic model as a drop-down option on the “Context” sheet of the economic model in cells I37 to I41. A scenario analysis using the RE-MIND2 dataset for all comparator treatments was included in Table 61 (Section B.3.7.3.) of the CS as scenario 9.

C3. Priority question: Please provide an alternative model, where the OS and PFS distributions *for all comparators* can be informed by the MAIC results. Please provide updated cost effectiveness results assuming that OS and PFS *for all comparators* are based on the MAIC results.

Response: The option to select the relevant dataset for each treatment option (MAIC, RE-MIND2) is included in the submitted economic model as a drop-down option on the "Context" sheet of the economic model in cells I37 to I41. A scenario analysis using the MAIC data for all comparator treatments was included in Table 61 (Section B.3.7.3.) of the CS as scenario 13.

C4. Priority question: Please provide updated version of Figures 8 and 9 of the CS including confidence intervals for the Kaplan-Meier (K-M) curves. In these curves, please indicate exactly the number of censored observations and explain the reasons why they were censored.

Response: Updated figures are provided below in Figure 12 and Figure 13. A tabulation of the reasons for censoring is provided in Table 13.

Figure 12 Kaplan-Meier estimator of OS in the L-MIND study using the October 2020 data cut

OS = overall survival

Figure 13 Kaplan-Meier estimator of PFS-IRC in the L-MIND study using the October 2020 data cut

Table 13. Reason for censoring of patients in the analyses of OS and PFS-IRC

Outcomes	Reason for censoring	Number of patients
OS		
PFS-IRC		

Abbreviations: ICF = informed consent form; OS = overall survival; PFS-IRC = progression-free survival as assessed by an independent review committee.

C5. Parametric models were fitted to the tafasitamab time to discontinuation (TTD) data to extrapolate the curve beyond the L-MIND trial follow-up.

[redacted].

a. Please clarify how uncertainty associated to lenalidomide TTD was incorporated in the economic model.

Response: Uncertainty for all K-M curves used in the model was incorporated using a “z-score” approach. This method applies a perfectly correlated adjustment to the whole KM curve taking into account the specific SE for each point of the curve, whereby a normally distributed random number is drawn for the whole curve (z-score), and each survival probability on the curve is then adjusted by their own estimated variance times the common z-score.

b. Please provide an alternative model where TTD for lenalidomide is also derived from extrapolating survival curves.

Response: Survival models for lenalidomide TTD were included in the submitted economic model, with the parametric model parameters for lenalidomide TTD shown on the “Tx Disc Details” sheet and option to switch between application of the KM curve and the parametric fits available via a drop-down in cell H76 of the “Efficacy” sheet.

C6. Please provide more details regarding the modelling of mortality within PFS, e.g., why this was assumed to be equal to 10% for all treatments and why the standard error (SE) was 1%.

Response: Mortality within PFS was calculated using patient level data from L-MIND. Since no such data was available for comparator regimens, it was assumed that the same proportion holds for all treatments in the model.

From subsequent review of the figures, we noticed a miscalculation regarding the proportion of mortality within PFS. In the submitted model, this proportion was calculated as the number of deaths divided by the total number of patients in L-MIND, while in fact this should be calculated as number of deaths divided by the number of progression events. We have fixed this proportion in the revised model, considering a ratio of 8/42 = 19%.

C7. Please explain the difference between the two approaches used to derive effectiveness data for the comparators in the economic model (RE-MIND2 and MAIC). Please also clarify the following points:

a. On page 15 in Appendix M, it is mentioned that "*In the absence of clinical studies providing direct head-to-head comparisons of TAFA+LEN vs. the comparators, efficacy data for comparators was generated from two key sources: the RE-MIND2 study, where statistical matching of patients from L-MIND vs. retrospective real-world patients on comparator therapies was performed, and a MAIC against available clinical trial data (Appendix D)*". Please explain the difference between "statistical matching" and MAIC.

Response: We thank the ERG for the opportunity to clarify.

In this paragraph provided in Appendix M, the term "statistical matching" was meant to refer to the 1:1 nearest neighbour matching approach used to match individual patient level data for patients receiving tafasitamab and lenalidomide from the L-MIND study with individual patient level data for comparator treatments from the RE-MIND2 study, rather than the MAIC, which refers to the matching adjusted indirect comparison used to match the individual patient level data for patients receiving tafasitamab and lenalidomide from the L-MIND study with available summary level data from published clinical trials for comparator treatments. We apologise for any confusion caused.

b. Please explain the differences between RE-MIND2 primary and post-hoc analyses (see page 26 in Appendix M).

Response: The RE-MIND2 primary analyses aimed to determine relative efficacy estimates of TAFA+LEN vs. POLA+BR, BR, R-GemOx and other comparator treatments.

The main analyses consisted of 1:1 nearest neighbour matching based on the estimated propensity score between patients enrolled in the L-MIND study and patients from the control cohorts. In a sensitivity analysis ATE was estimated using overlap weights based on the estimated propensity score. Due to the low accrual of patients in the POLA+BR cohort for the primary analyses (n=36 complete cases profile), 1:1 matching could not be implemented as fewer control patients than L-

MIND patients were available. Similarly, the weighting based on the propensity score were also not conducted due to the small number of patients treated with POLA+BR included in RE-MIND2.

To generate relative efficacy estimates of TAFA+LEN v. POLA+BR, post-hoc analyses of the RE-MIND2 study were conducted. They consisted of a 1:1 nearest neighbour matching using the observational cohort as the basis to obtain a matched population of L-MIND patients, as discussed above in response to question B13.

C8. Please explain the criteria used to decide that "*the mechanism of action and schedule of administration of tafasitamab was considered sufficiently different from rituximab and chemotherapy combination regimens to justify the use of an alternative parametric model*" or that "*As polatuzumab has a different mechanism of action to both tafasitamab and rituximab plus chemotherapy regimens, it was considered reasonable to apply a different type of parametric model for POLA+BR OS*".

Response: NICE DSU TSD14[64] recommends that the same type of parametric model be selected for each treatment arm given that most standard parametric models (excluding exponential) allow for a multi-dimensional treatment effect across each model parameter, unless the use of different types of parametric model can be justified based on biological plausibility, statistical analysis and clinical expert judgement.

For TAFA+LEN, only the generalised gamma distribution produced a reasonable statistical fit and visual fit to the observed PFS data, while lognormal models appeared to provide the best overall fits for both BR and R-GemOx for PFS. As tafasitamab has a different treatment stopping rule compared to BR and R-GemOx (treat until progression versus fixed maximum treatment duration), a different mechanism of action compared to rituximab (targeting the CD19 antigen instead of CD20) and chemotherapy treatments, and an apparent plateau in the PFS curve was observed (which was not observed for BR and R-GemOx in RE-MIND2 or published clinical trial data), it was therefore considered biologically plausible to apply a different type of parametric model for tafasitamab and lenalidomide from those selected for BR and R-GemOx.

For the POLA+BR OS and PFS parametric fits for RE-MIND2, all parametric models (both adjusted and unadjusted) appeared to provide overly pessimistic long-term survival predictions in relation to clinical expert expectations and BR parametric fits. As such, the parametric models with the most optimistic long-term predictions (generalised gamma for OS, exponential for PFS) were selected for the RE-MIND2 scenario analysis. However, this resulted in the use of different types of parametric models for POLA+BR compared to tafasitamab and lenalidomide (lognormal for OS, generalised gamma for PFS) as well as BR and R-GemOx (lognormal for both OS and PFS). A potential rationale for this in terms of biological plausibility was provided based on differences in mechanism of action between polatuzumab and other modelled therapies, with polatuzumab an antibody drug conjugate targeting the CD79b antigen compared to CD19 and CD20 for tafasitamab and rituximab, respectively.

In addition, while both polatuzumab and rituximab are given in combination with chemotherapy agents (e.g., bendamustine, oxaliplatin or gemcitabine), tafasitamab is given in combination with an immunomodulatory agent (lenalidomide). In pre-clinical studies, lenalidomide was shown to cause both direct cell death and to enhance the action of tafasitamab.[65] Therefore, the chemotherapy free combination of tafasitamab (given until disease progression) and lenalidomide is considered to be biologically different to polatuzumab or rituximab combined with chemotherapy (given for fixed treatment durations).

Adverse events

C9. Priority question: Please answer the following questions regarding the modelling of adverse events (AEs):

a. **There is a substantial mismatch between the adverse events shown in e.g., Table 29 of the CS and those included in the economic model. Please clarify this issue and amend either Table 29 or the economic model so that they align with each other.**

Response: The economic model includes the option to include a range of AE, including those for potential comparators that were later excluded based on clinical expert feedback. However, given the comparator treatments included in the

economic analysis (POLA+BR, BR and R-GemOx) and inclusion criteria adopted for the economic model (grade 3 or above AEs occurring in ≥5% of patients for each treatment arm), only the adverse events stated in Table 55 of the CS were incorporated into the analysis.

b. Please explain how the probabilities shown in Table 55 of the CS were derived.

Response: Please see the response to part (a).

c. On page 136 of the CS, it is mentioned that AEs affect both costs and utilities of patients receiving treatment and are assumed to occur only in the first year of treatment. Therefore, patients who remain 'on treatment' for subsequent years do not incur further AE-related costs. Please explain the rationale of this assumption and why these AE-related costs and utilities are not applied to each treatment as long as patients are still on treatment (if it's possible to be on treatment for more than one year), e.g., by providing supporting evidence.

Response: Regarding the application of adverse events in the model over time, we would like to further clarify that the statement around AE costs and disutility occurring in the first year of treatment reflects the approach used to apply costs and disutility rather than the duration of time reflected by the adverse event probabilities themselves. As all comparator regimens were fixed maximum duration therapies (with maximum treatment durations <1 year), adverse events for these treatments were expected to occur within the first year of the model, and costs and disutility associated with AEs were applied in the first cycle. For TAFA+LEN, adverse event probabilities used in the model were reflective of the AEs occurring across the full duration of the L-MIND study (not only the first year of treatment) with costs and disutility applied within the first cycle of the model as a simplifying assumption and for consistency with the approach adopted for other treatments.

While patients may continue to receive treatment with tafasitamab beyond the duration of the L-MIND study, the adverse event profile of tafasitamab beyond the duration of L-MIND is currently unknown. In addition, it was expected that the risk of AEs would be lower in the long-term following discontinuation of lenalidomide, as indicated in Duell et al. 2021 where the number of any grade treatment-emergent

AEs per year of exposure was shown to be substantially lower for patients on extended tafasitamab monotherapy compared to patients on combination treatment with TAFA+LEN (6.64 vs 25.77, respectively).[66] In addition, as shown in Salles et al. 2020, grade 3-4 adverse events were also shown to be lower for patients on extended tafasitamab monotherapy compared to patients those on combination treatment with TAFA+LEN.[67] This indicates a reduced AE burden in the long term during the TAFA monotherapy phase of therapy compared, with the initial TAFA+LEN combination therapy phase of treatment.[66] Furthermore, given the relatively low costs and QALY losses associated with serious AEs in the model, subsequent costs and disutility associated with serious AEs for tafasitamab occurring beyond the duration of the trial were not anticipated to have a substantial impact on the economic model results.

d. Please compare the AEs included in the model with those considered in TA649 and explain the differences between the two approaches, if any.

Response: In the company submission for NICE TA649, the approach to AE inclusion in the model was described as follows: “For Pola+BR and BR, treatment-related AEs of CTCAE Grade 3 or greater from GO29365 that were deemed to be serious were included in the model (data cut-off, April 2018). Serious AEs were defined as those that would require NHS resources to treat them. The type and frequency of AEs experienced with R-GemOx treatment were derived from grade 3–5 AEs affecting >5% of patients in a Phase II study on the treatment of R/R DLBCL patients with R-GemOx.”

Adverse event incidence applied in TA649 is shown in Table 14.

Table 14: AE probabilities from TA649

AE	Incidence (GO29365 trial[4] and Mounier 2013[55])		
	POLA+BR	BR	R-GemOx
Acute kidney injury	2.6%	0%	0%
Artial fibrillation	2.6%	0%	0%
Atrial flutter	2.6%	0%	0%
Aanemia	0%	0%	33%
Diarrhoea	0%	2.6%	0%
Febrile neutropenia	2.6%	2.6%	4%
Leukopenia	2.6%	0%	0%

AE	Incidence (GO29365 trial[4] and Mounier 2013[55])		
	POLA+BR	BR	R-GemOx
Neutropenia	2.6%	0%	73%
Pneumonia	0%	2.6%	0%
Lower respiratory tract infection	5.1%	0%	0%
Pyrexia	0%	2.6%	0%
Septic shock	2.6%	0%	0%
Thrombocytopenia	0%	2.6%	23%
Vomiting	0%	2.6%	0%
Cytomegalovirus infection	2.6%	0%	0%
Decreased appetite	0%	2.6%	0%
Supraventricular tachycardia	2.6%	0%	0%
Herpes virus infection	0%	2.6%	0%
Meningoencephalitis herpetic	0%	2.6%	0%
Myelodysplastic syndrome	0%	2.6%	0%
Neutropenic sepsis	2.6%	0%	0%
Oedema peripheral	2.6%	0%	0%
Leukoencephalopathy	2.6%	0%	0%
Pulmonary oedema	0%	2.6%	0%

Abbreviations: AE = adverse event; BR = bendamustine and rituximab; POLA+BR = polatuzumab, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaliplatin.

In the CS, any grade ≥3 AEs occurring in ≥5% of study subjects in the L-MIND population or comparator trials are used in the model.

Adverse event probabilities described in Table 55 of the CS are reproduced below in Table 15.

Table 15: AE probabilities from the CS

AE	TAFA+LEN	POLA+BR	BR	R-GemOx
Anaemia	7.4%	28.20%	17.90%	33.00%
Febrile neutropenia	12.3%	10.30%	12.80%	
Hypokalaemia	6.2%			
Leukopenia	11.1%			
Neutropenia	49.4%	46.20%	33.30%	73.00%
Pneumonia	9.9%			
Thrombocytopenia	17.3%	41.00%	23.10%	23.00%
Lymphopenia		12.80%		

Source	L-MIND CSR[68]	GO29365 (Sehn 2020)[35]	GO29365 (Sehn 2020)[35]	NICE TA649,[4] Mounier 2013[55]

Abbreviations: AE = adverse event; BR = bendamustine and rituximab; POLA+BR = polatuzumab, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaliplatin; TAFA+LEN = tafasitamab and lenalidomide.

Excluding neutropenia (4%), which was lower than the 5% threshold considered in the CS for inclusion in the model, other adverse event incidence figures for R-GemOx used by the submitting company in NICE TA649[4] are consistent with those described in the CS. However, for POLA+BR and BR, AE incidence estimates in the CS were based on the published clinical trial data for the GO29365 trial (Sehn et al 2020),[35] which reports substantially higher incidence of grade 3-4 AEs than the grade 3-5 AEs used by the submitting company in NICE TA649 (for example, 46.2% of POLA+BR patients in the GO29365 trial publication had grade 3-4 neutropenia events, compared to the 2.6% estimate applied in NICE TA649). Based on the description of the AE inclusion criteria provided by the submitting company in NICE TA649, the reasons for the discrepancies between the figures used by the submitting company in NICE TA649 and those in the clinical trial publication are likely to be associated with differences in the types of adverse event included in the model for POLA+BR and BR (e.g. treatment-related vs treatment-emergent) or possible differences in duration of follow-up over which the adverse event data were collected.

Utility/HRQoL

C10. Priority question: Please provide information on:

a. **How many patients provided data for the calculation of progression free and progressed utility (separately for each health state utility value) from the 'Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants with Refractory Aggressive Non-Hodgkin Lymphoma' (ZUMA-1)?**

Response: Utility values from the ZUMA-1 trial were sourced from prior appraisals (NICE TA649, NICE TA559).[4,7] In Section B.3.4. of the company submission for NICE TA559,[7] it is stated that the EQ-5D data were collected from the safety management cohort of the ZUMA-1 trial which included 34 patients providing 87 observations for the EQ-5D-3L utility values.

However, information on the number of patients informing the utility values by health state is redacted in Table 10 of the company submission in the NICE TA559 committee papers.

b. The characteristics of patients who provided utility data in ZUMA-1 (and how these compare to the characteristics of patients in L-MIND).

Response: Patient characteristics of the safety management cohort, provided in response to clarification question B6 from the ERG (Table 21) by the submitting company, are also redacted in the NICE TA559 committee papers. As such, a direct comparison of the patients from L-MIND with those from the safety management cohort of the ZUMA-1 trial used to produce the utility data could not be conducted.

In the absence of patient characteristics data for the safety management cohort from the ZUMA-1 trial, a comparison of the patient characteristics of patients in the L-MIND study with the total DLBCL patient cohort treated with axicabtagene ciloleucel from the ZUMA-1 trial is provided below in Table 16.

Table 16. Comparison of patient characteristics of the L-MIND and ZUMA-1 trials

Variable		**L-MIND total population[68]**	**ZUMA-1 patients with DLBCL treated with axicabtagene ciloleucel[40]**
Population at baseline		N=81	N=77
Age, Years	Median	72	58
	Range	(41 to 86)	(25 to 76)
	≥ 65	58 (71.6)	17 (22)
Sex, n (%)	Male	44 (54.3)	50 (65)
	Female	37 (45.7)	27 (35)*
ECOG status, n (%)	0	29 (35.8)	28 (36)
	1	45 (55.6)	49 (64)
	2	7 (8.6)	0 (0)
Ann Arbor Disease Staging, n (%)	I or II	20 (24.7)	10 (13)
	III or IV	61 (75.3)	67 (87)
IPI Category, n (%)	0-2	40 (49.4)	40 (52)
	3-5	41 (50.6)	37 (48)**
Lines of previous systemic treatment (DLBCL medications), n (%)	1	40 (49.4)	2 (3)
	2	35 (43.2)	26 (34)
	3	5 (6.2)	22 (29)
	4	1 (1.2)	20 (26)
	≥ 3	6 (7.4)	49 (64)

Variable		L-MIND total population[68]	ZUMA-1 patients with DLBCL treated with axicabtagene ciloleucel[40]
	≥ 4	1 (1.2)	27 (35)
	Range	(1 to 4)	(1 to > 5)
Primary refractoriness, n (%)	Yes	15 (18.5)	23 (30)
	No	66 (81.5)	54 (70)*

Prior autologous SCT, n (%)	Yes	9 (11.1)	16 (21)
	No	72 (88.9)	61 (79)*
CD-19 status — no./total no. (%)	Negative	NA	7/63 (11)
	Positive	NA	56/63 (89)

Abbreviations: DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = international prognostic index; NA = not available; SCT = stem cell transplant.

Note: * Value computed directly from publication reporting; ** No patients in the ZUMA-1 trial had an IPI score of 5; *** Derived as patients refractory to their last therapy line.

As described in Section B.3.4.5. of the CS, differences in age and sex between the L-MIND and ZUMA-1 trial populations were adjusted for when calculating health state utilities in the economic model. While other differences were also observed between populations, such as differences in terms of ECOG status, number of prior treatment lines and proportion of patients with primary refractoriness, utilities from the ZUMA-1 trial were applied in the base case analysis due to the absence of available utility data specific to a R/R DLBCL population ineligible for ASCT, limitations of alternative studies identified in the SLR or prior R/R DLBCL technology appraisals (with other values identified mapped from SF-36 data or based on older general non-Hodgkin lymphoma utility values) and in line with the NICE appraisal for POLA+BR (TA649).

C11. Priority question: On page 107 of the CS, starting on line 14, it is quoted: "*A total of 30 studies were identified in the review of HRQoL evidence. Of these, only three studies with health state utility estimates for relevant model comparators included in the final scope (Betts 2019 and Betts 2020(101), Patel 2020(102)) were identified.*" Please provide details of which "*relevant model comparators*" were used to identity these studies.

Response: The "relevant model comparators" description stated in the CS refers to the treatment regimens identified by UK clinical experts as being the most relevant comparators for the economic model (POLA+BR, BR and R-GemOx).

C12. Priority question: In the scenario analysis, all patients with DLBCL who are event-free at two years are expected to have a similar pre-progression state utilities and mortality to the general population; please clarify whether the utilities used in the model were age and sex matched. If not, then please provide an option in the model to generate age and sex matched utilities.

Response: In the scenario analyses where cure assumptions are applied, age and sex matched general population utility is assumed for scenarios where “cured” patients are assumed to have equal health-related quality of life to the general population.

For scenarios where general population utility is not assumed for “cured” patients, utility for these patients is set equal to the base case pre-progression utility data. As stated in Section B.3.4.5. of the CS, all health state utilities and disutilities in the economic model were adjusted for age and sex using general population utility as a baseline to account for differences in age and sex characteristics of the modelled population compared to the reference populations associated with the original utility values, as well as model potential changes in quality of life over time in relation to increasing age (and prevent quality of life for pre-progression and post-progression patients from exceeding the general population). The option to apply age and sex adjustment of utilities (as well as switch between additive and multiplicative methods) is provided as a drop-down option in cell H9 of the “Utility” sheet of the economic model.

C13. Priority question: Please answer the following questions regarding the following disutilities included in the model:

a. **Table 28 in the CS includes a disutility associated to chimeric antigen receptor T-cell (CAR-T) treatment. Please explain how this disutility was implemented in the model (e.g., to which treatment arms and in what proportions).**

Response: The one-off disutility for CAR-T treatment was included for all patients who receive CAR-T as a subsequent therapy for any treatment arm. In the base case analysis, CAR-T disutility was therefore applied to 0.0%, 5.1%, 4.0% and 4.1% of patients receiving TAFA+LEN, POLA+BR, BR and R-GemOx respectively, as per the subsequent treatment figures described in Table 38 of the CS.

b. **In the model “Utility” sheet a disutility for allogenic stem cell transplant (SCT) and autologous SCT are defined. These seem to be included in the analyses (“Parameters” sheet column N = TRUE). Please clarify whether this was indeed the case and justify this assumption**

given that the patient population in this submission explicitly states that patients are not eligible for ASCT.

Response: Although the patient population considered in the submission is based on a population not eligible for ASCT, it is possible that some patients may subsequently become eligible for SCT (autologous or allogeneic) following discontinuation of treatment with TAFA+LEN or other comparators included in the economic analysis. Therefore, the option to apply disutility for patients receiving subsequent SCT (autologous or allogeneic) was included in the model. However, as 0% of patients in the matched RE-MIND2 patient populations received subsequent SCT, and UK clinical experts indicated that the proportion of patients receiving SCT as a subsequent treatment would be small and unlikely to impact the results of the CEM, it was assumed for the base case analysis that no patients would receive SCT as a subsequent treatment. As such, disutilities for allogeneic or autologous SCT, while included in the economic model, do not impact the base case model results.

Resource use/costs

C14. Priority question: please provide updated cost effectiveness results assuming:

a. **Patient Access Scheme (PAS) price for tafasitamab and list price for lenalidomide.**

Response: Base-case results based on the revised economic model are provided below in Table 17.

Table 17. Base-case results based on the proposed PAS price for tafasitamab and list price for lenalidomide

Intervention	Total costs (£)	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	[redacted]	5.08	[redacted]	-	-	-	-
POLA+BR	[redacted]	2.20	1.45	[redacted]	2.88	[redacted]	[redacted]
BR	[redacted]	1.76	1.13	[redacted]	3.32	[redacted]	[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]	3.26	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab and lenalidomide.

Incremental analysis results are shown below in Table 18. [redacted].

Table 18: Base case results – full incremental analysis based on the proposed PAS price for tafasitamab and list price for lenalidomide

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs previous non-dominated alternative
BR	[redacted]	1.13	[redacted]	[redacted]	-
R-GemOx	[redacted]	1.16	[redacted]	[redacted]	[redacted]
POLA+BR	[redacted]	1.45	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; POLA+BR = polatuzumab vedotin, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab and lenalidomide.

b. List price for tafasitamab and list price for lenalidomide.

Response: Base case results based on the revised economic model are provided below in Table 19.

Table 19. Base-case results based on the list price for tafasitamab and list price for lenalidomide

Intervention	Total costs (£)	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	[redacted]	5.08	[redacted]	-	-	-	-
POLA+BR	[redacted]	2.20	1.45	[redacted]	2.88	[redacted]	[redacted]
BR	[redacted]	1.76	1.13	[redacted]	3.32	[redacted]	[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]	3.26	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab and lenalidomide.

Incremental analysis results are shown below in Table 20. [redacted].

Table 20: Base case results – full incremental analysis based on the list price for tafasitamab and list price for lenalidomide

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs previous non-dominated alternative
BR	[redacted]	1.13	[redacted]	[redacted]	-
R-GemOx	[redacted]	1.16	[redacted]	[redacted]	[redacted]

POLA+BR	[redacted]	1.45	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; POLA+BR = polatuzumab vedotin, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab and lenalidomide.

C15. Priority question: please provide the currency codes, descriptions, and settings for all unit costs that were sourced from the National Health Service (NHS) Reference costs.

Response: Further details on the currency codes, descriptions and settings for all unit costs sourced from NHS reference costs or Personal Social Services Research Unit 2020 cost inputs are described in Table 21, Table 22, Table 23 and Table 24, respectively.

Table 21. Administration Costs

Mode of Administration	Unit Cost	References	Code/Description
IV/SC admin: first attendance (SB13Z)	£302.53	NHS reference costs 2019/20[69]	CHEMOTHERAPY (SB13Z; description: Outpatient)
IV/SC admin: subsequent (SB15Z)	£253.77		CHEMOTHERAPY (SB15Z; description: Outpatient)
Radiotherapy (SC25Z)	£367.32		RADIOTHERAPY (SC25Z; description: Outpatient)

Abbreviations: IV = intravenous; NHS = National Health Service; SC = subcutaneous

Table 22. Unit Costs for Monitoring Tests

Monitoring Test	Unit Cost	References	Code/Description
Anti-MOR00208 antibodies	£7.40	NHS reference costs 2019/20.[69] PSSRU Unit Costs of Health and Social Care 2020.[70]	DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS06; description: Immunology)
B-, T- and NK cell flow cytometry (blood)	£7.40		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS06; description: Immunology)
Blood sampling	£2.53		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS05; description: Haematology)
Bone marrow biopsy	£36.58		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS02; description: Histopathology and histology)
Calcium phosphate	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Calcium)

Monitoring Test	Unit Cost	References	Code/Description
Chemistry panel (including liver function test)	£8.40		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Hepatic function panel, must include the following 7 Tests: Albumin; Bilirubin, total; Bilirubin, direct; Phosphatase, alkaline; Protein, total; Transferase, alanine amino (ALT) (SGPT); Transferase, aspartate amino (AST) (SGOT))
Coagulation panel	£2.53		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS05; description: Haematology)
CT scan	£185.15		DIAGNOSTIC IMAGING (HRG: RD22Z; description: Computerised Tomography Scan of One Area, with Pre- and Post-Contrast)
ECG: electrocardiogram	£85.13		DIRECTLY ACCESSED DIAGNOSTIC SERVICES (HRG: EC22Z; description: Electrocardiogram Monitoring or Stress Testing, for Congenital Heart Disease)
Full blood counts	£2.53		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS05; description: Haematology - FBC)
Haematology panel	£2.53		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS05; description: Haematology - FBC)
Immunoglobulin	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)
Lactate dehydrogenase	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)
Liver function test	£8.40		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Hepatic function panel, must include the following 7 Tests: Albumin; Bilirubin, total; Bilirubin, direct; Phosphatase, alkaline; Protein, total; Transferase, alanine amino

Monitoring Test	Unit Cost	References	Code/Description
			(ALT) (SGPT); Transferase, aspartate amino (AST) (SGOT))
MRI	£306.54		DIAGNOSTIC IMAGING (HRG: RD03Z; description: Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast)
PET/CT	£958.49		NUCLEAR MEDICINE (HRG: RN01A; description: Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over)
Pregnancy test (serum and urine)	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)
Renal function	£12.00		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Renal function panel must include the following 10 tests: Albumin; Calcium, total; Carbon dioxide (bicarbonate); Chloride; Creatinine; Glucose; Phosphorus inorganic (phosphate); Potassium; Sodium; Urea nitrogen (BUN))
Serology parameters (Hepatitis B: HbsAg, anti-HBc; anti-HBs; HBV-DNA)	£7.40		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS06; description: Immunology - each test)
Urinalysis	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)
Comprehensive metabolic panel	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)
Uric acid	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)

Monitoring Test	Unit Cost	References	Code/Description
Serum lactate dehydrogenase	£1.20		DIRECTLY ACCESSED PATHOLOGY SERVICES (HRG: DAPS04; description: Clinical Biochemistry - Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each)

Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; HBc = hepatitis B core; HBs = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NHS = National Health Service; PET = positron emission tomography; PSSRU = Personal and Social Services Research Unit; UK = United Kingdom.

Table 23. Disease Management Resource Unit Cost

Disease Management Resource	Unit Cost	References	Code/Description/Setting
Consultant visit	£200.20	NHS reference costs 2019/20. [69 67 6769] PSSRU Unit Costs of Health and Social Care 2020.[70]	CONSULTANT LED (370; Medical Oncology - Follow-up)
Day care	£65.41		PSSRU (1.4; Local authority own-provision day care for older people (age 65+))
District nurse (visit)	£43.46		COMMUNITY HEALTH SERVICES (N02AF; District Nurse, Adult, Face to face)
GP (visit)	£39.23		PSSRU (10.3b; General practitioner — unit costs: Per patient contact lasting 9.22 minutes)
Haematologist (visit)[1]	£171.18		CONSULTANT LED (303; Clinical Haematology - First Visit)
Home care (day)	£24.00		PSSRU (11.5; Home care worker: Per weekday hour)
Hospice (day)	£161.65		SPECIALIST PALLIATIVE CARE (SD02S; Inpatient Specialist Palliative Care, Same Day, 19 years and over – Daycase)
Hospitalisation	£1,158.18		ELECTIVE INPATIENT (SA31A-SA31F; Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 15+)
ICU stay (day)	£1,689.08		CRITICAL CARE (XC01Z-XC07Z; Adult Critical Care, 6 or more Organs Supported)
Inpatient (day)	£1,158.18		ELECTIVE INPATIENT (SA31A-SA31F; Malignant Lymphoma, including Hodgkin's and Non-

Disease Management Resource	Unit Cost	References	Code/Description/Setting
			Hodgkin's, with CC Score 15+)
Nurse (visit)	£42.00		PSSRU (10.2; Nurse (GP practice) - per hour)
Oncologist (visit)[1]	£200.20		CONSULTANT LED (370; Medical Oncology - Follow-up)
Palliative care team[1]	£356.73		CONSULTANT LED (315; Palliative Medicine - Multiprofessional, Follow-up)
Radiologist (visit) [1+]	£153.41		CONSULTANT LED (811; Interventional Radiology - Follow-up)
Residential care (day)	£109.00		PSSRU (1.2; Residential care for older people (age 65+): Establishment cost plus personal living expenses and external services per permanent resident day)
Specialist nurse (visit)	£99.30		COMMUNITY HEALTH SERVICES (N10AF; Specialist Nursing, Cancer Related, Adult, Face to face)
Terminal care cost[2]	£2,712.38	NICE TA567[6]	

Abbreviations: GP = general practitioner; ICU = intensive care unit; NHS = National Health Service; PSSRU = Personal and Social Services Research Unit; UK = United Kingdom.

[1] Assumed follow-up cost

[2] In the Tisagenlecleucel NICE submission (ID1166), terminal care cost of £2,653.73 was applied for the last three months of life, therefore this value is applied as a one-off cost.

Table 24. Cost of Managing AEs per Event

AE	Cost per Event	Reference	Code/Description/Setting
Anaemia	£1,238.06	NHS reference costs 2019-20[69]	NON-ELECTIVE ADMISSIONS (HRG: SA09; description: Other Red Blood Cell Disorders)
Febrile neutropenia	£1,785.62		NON-ELECTIVE ADMISSIONS (HRG: SA35; description: Agranulocytosis)
Hypokalaemia	£1,456.44		NON-ELECTIVE ADMISSIONS (HRG: KC05; description: Fluid or Electrolyte Disorders)
Leukopenia	£1,533.37		NON-ELECTIVE ADMISSIONS (HRG: SA08; description: Other Haematological or Splenic Disorders)
Neutropenia	£1,785.62		NON-ELECTIVE ADMISSIONS (HRG: SA35; description: Agranulocytosis)

Pneumonia	£1,908.15		NON-ELECTIVE ADMISSIONS (HRG: DZ11; description: Lobar, Atypical or Viral Pneumonia)
Thrombocytopenia	£1,915.08		NON-ELECTIVE ADMISSIONS (HRG: SA12; description: Thrombocytopenia)
Lymphopenia	£1,533.37		NON-ELECTIVE ADMISSIONS (HRG: SA08; description: Other Haematological or Splenic Disorders)

Abbreviations: AE = adverse event; NHS = National Health Service.

C16. Priority question: please provide details, including any assumptions made, for all unit costs that were sourced from the Personal Social Services Research Unit 2020.

Response: Additional details on PSSRU input data are provided above in response to clarification question C15.

C17. Priority question: subsequent treatments after progression are based on RE-MIND2, indicating substantial differences in the proportions of patients in each arm receiving specific treatments

a. **Please justify that the subsequent treatments that patients receive in each arm are reflective of clinical practice in the UK, including the differences in the proportions of patients receiving them.**

Response: All subsequent treatments used in the model are licensed and used in the UK in the 3L+ setting. As discussed in the CS (Section B.1.3.5) and in the answer to question B.1 in this document, there is a lack of a standard-of-care treatment for patients with R/R DLBCL who are ineligible for transplant, including limited guidance from NICE in guideline NG52 and the NICE clinical pathway for DLBCL.[2,3,71,72] Consequently, the range of regimens used in clinical practice is varied. This reflects guidance from ESMO and the US NCCN, which recommend rituximab-based chemotherapy, encompassing a range of possible chemoimmunotherapy regimens.[2,72] POLA+BR, rituximab monotherapy and, in some cases, pixantrone monotherapy, are additional guideline-recommended therapies in this setting.[4,5,72]

As there is a lack of data regarding specific treatment patterns for this population in the UK, subsequent treatments, and the proportion of patients receiving each

treatment, were determined based on the RE-MIND2 FAS data, as outlined in CS Section B.3.5.5. The relevance of the RE-MIND2 study to the UK population is discussed in response to Question B13 part (h) of this document. The RE-MIND2 FAS was the best available data source to determine subsequent treatment proportions, in the absence of alternative data to inform subsequent treatment proportions for TAFA+LEN.

Additionally, a summary of the relevance of each treatment regimen to UK clinical practice is provided below.

R-GemOx, POLA+BR and BR are used in the UK in the 2L+ setting and are relevant as subsequent treatments as well as comparators to TAFA+LEN per UK expert feedback. Pixantrone monotherapy is reimbursed by NICE in the 3L and 4L settings only and, although not widely used in UK clinical practice according to clinical expert feedback, is received by a proportion of patients.[5,13]

CAR-T cell therapies are reimbursed by NICE in the 3L+ setting for R/R DLBCL; however, the proportion of patients receiving these therapies is relatively low due to the intensity of the treatment process. Clinical expert feedback indicated that a small proportion of patients would receive subsequent CAR-T cell therapy but this would be unlikely to impact results of economic analyses.

Some additional subsequent treatments are listed in a real-world, retrospective multicentre cohort study assessing efficacy of pixantrone monotherapy in the UK (Eyre 2016).[13] These include lenalidomide & rituximab, lenalidomide monotherapy, and rituximab with dexamethasone, high-dose cytarabine and cisplatin (R-DHAP),[13] consistent with findings in RE-MIND2. The Eyre 2016 study also listed cyclophosphamide, etoposide & prednisone, which is a subsequent treatment in the current model with the addition of procarbazine.

The carboplatin, etoposide, ifosfamide & rituximab (RICE) regimen is also listed as a potential subsequent treatment in the model. Use of this regimen is well established in the UK.[73]

Cyclophosphamide, fludarabine phosphate & other antineoplastic agents is another subsequent treatment combination used in the model based on data from RE-MIND

2. An example of such regimen commonly used in the UK is Fludarabine, cyclophosphamide and rituximab (FCR).[74]

Methotrexate, another subsequent treatment listed in the model, is the most common drug used as prophylaxis for patients with DLBCL at high risk of central nervous system (CNS) relapse.[75] CNS prophylaxis is recommended in NICE NG52 guideline for DLBCL patients who have factors associated with increased risk of CNS relapse.[3]

Radiotherapy is also among the subsequent treatments listed in the model. Use of radiotherapy is mentioned in the UK guidelines for the management of DLBCL.[76]

Use of the RE-MIND 2 subsequent treatments included in the model were also investigated using the latest IPSOS data for DLBCL in the UK.[77] The Q3 2021 regimens used in the 3L+ patients in the UK included R-GemOx, pixantrone, POLA+BR, BR, RICE, CAR-T therapies, and GemOx, which are all listed as subsequent treatments in the current model.

R-DHAX and rituximab monotherapy were subsequent treatments used in ≥2% of patients in RE-MIND2. R-DHAX is a variation of R-based chemotherapy used in 3L+ DLBCL management in alignment with NICE/ESMO guidance and Figure 1.[2,72] Rituximab monotherapy is recommended as an option in this population by the NCCN, which is the most recently updated set of international guidelines.[72]

b. Please provide the option in the model to assume the same proportions of patients receiving each subsequent treatment for each treatment arm in the model, based on the 'systemic therapies pooled cohort' in RE-MIND2. In case this would lead to patients in a specific arm receiving treatments that are contradictory with UK clinical guidelines, then please adjust for this.

Response: The option to apply subsequent treatment proportions for all treatments based on the matched pooled systemic therapies cohort from the RE-MIND2 study has been added to the revised economic model.

c. Please justify the plausibility of 0% of patients receiving CAR-T after progression in the tafasitamab + lenalidomide arm in UK clinical

practice, in contrast to 4 to 5.1% of patients in other treatment arms receiving CAR-T.

Response: During interviews conducted in September of 2021, one of the clinical experts interviewed stated that for the population and comparators considered in the economic model, a limited number of patients may become eligible for subsequent CAR-T therapy. This was in line with matched population data collected from RE-MIND2, where some patients on POLA+BR, BR and R-GemOx went on to receive CAR-T as a subsequent therapy. However, regarding TAFA+LEN, it is important to note that both tafasitamab and CAR-T are CD19 targeting therapies. While some early data exists in relation to sequencing of CD19 targeting therapies, this has not been studied in a clinical trial, and as such the lack of patients observed receiving CAR-T as a subsequent treatment following discontinuation of TAFA+LEN in the matched RE-MIND2 population data was considered clinically plausible.

C18. Priority question: in Table 39 of the CS, the maximum number of treatment cycles is specified for each (component of) subsequent treatments.

a. **Please explain whether it is assumed that all subsequent treatments were given for the maximum number of cycles and justify the plausibility of that assumption.**

Response: Subsequent treatment durations have been updated in the revised economic model to reflect the median treatment durations for subsequent treatments from available studies. A summary of the updated estimates is provided below in Table 25.

Table 25. Median treatment durations for subsequent treatments

Subsequent treatments used in the model (cut-off: 2%)	Median treatment duration (number of treatment cycles)	Source/Notes
R-GemOx	7.50	Mounier 2013[55]
R2	4.00	Zinzani 2011[60] Fewer than 50% of patients (10/23) received maintenance therapy with lenalidomide, therefore median lenalidomide treatment duration assumed to be 4 x 28-day treatment cycles in line with the duration of the induction period of the study For rituximab, median treatment duration also assumed to be 4 x 28-day treatment cycles in line with length of induction period of the study

Subsequent treatments used in the model (cut-off: 2%)	Median treatment duration (number of treatment cycles)	Source/Notes
Pixantrone	2.00	Eyre 2016[13]
Lenalidomide	4.25	RE-MIND[78] Based on median duration of exposure to treatment in the lenalidomide monotherapy arm of the RE-MIND study (3.91 months)
POLA+BR	4.64	NICE TA649[4] Converted from 3.20 months into 3-week treatment cycles
BR	2.03	NICE TA649[4] Converted from 1.39 months into 3-week treatment cycles
Rituximab	2.00	Coiffier 1998[79] As >50% of patients completed 8-week treatment course (36/54 patients), median treatment duration therefore assumed to be 2 x 28-day treatment cycles
Carboplatin, Etoposide, Ifosfamide & Rituximab	3.00	Gisselbrecht 2010[80] Study reports that 11 pts only had one treatment cycle, 17 had two treatment cycles, and the remaining 169 completed all three treatment cycles, median treatment duration of 3 treatment cycles therefore assumed
Cyclophosphamide, Etoposide, Prednisolone & Procarbazine	3.00	Chao 1990[81]
Cyclophosphamide, Doxorubicin hydrochloride & Rituximab	3.00	Assumed equal to 3 treatment cycles as per cyclophosphamide, etoposide, prednisolone & procarbazine
R-DHAP	3.00	Lignon 2010[82]
CAR-T	1.00	1 administration of CAR-T therapy assumed
Cyclophosphamide & Fludarabine phosphate	3.00	Assumed equal to 3 treatment cycles as per cyclophosphamide, etoposide, prednisolone & procarbazine
Methotrexate	1.00	Methotrexate SmPC[83] All patients assumed to receive 5 days of treatment as per recommendations for Burkitt's lymphoma
GemOx	5.00	Corazzelli 2009[58]
Radiotherapy	1.00	1 course of radiotherapy assumed

Abbreviations: BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell; GemOx = gemcitabine and oxaliplatin; IV = intravenous; POLA+BR = polatuzumab + bendamustine + rituximab; R2 = lenalidomide and rituximab; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-GemOx = rituximab, gemcitabine and oxaliplatin; SmPC = summary of product characteristics.

b. **Please check, and amend where needed, for all subsequent treatments that assumptions for the maximum number of cycles are in line with UK clinical practice. For example, a maximum number of 7 cycles is assumed for R-GemOx whereas UK guidelines recommend a maximum of 6 cycles.**

Response: Please see the response to part (a).

C19. Priority question: to calculate the health state unit costs in the model, resource use related to monitoring (i.e., Tables 42 to 44 of the CS) and disease management (i.e., Tables 48 to 49 and Tables 52 to 54 in the CS) was informed using different sources for the different treatment arms in the model:

- **for tafasitamab + lenalidomide these were sourced from L-MIND for PFS and from TA649 for progressed disease (PD);**
- **for Pola-BR and BR these were sourced from TA649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma), which in turn were sourced from TA306 (Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma), where it was based on clinical expert opinion;**
- **for R-GemOx these were sourced from TA567, which in turn were sourced from Appendix A in NICE NG52 which in turn were based on McNamara et al. 2011 (British Journal of Haematology. 156: 446-467) and assumptions for PFS from Muszbek et al. 2016 (Clin Ther 38:503-15) where it was based on clinical expert opinion for PD.**

a. **Please justify the consistency of the assumptions on health care resource use across the different treatment arms in the model.**

Response: Resource use data for POLA+BR, BR and R-GemOx were sourced from available resource use data for these therapies from previous NICE technology appraisals for R/R DLBCL.

For TAFA+LEN, pre-progression resource use was based on the L-MIND study schedule of assessments in the absence of available data for this treatment, and given that TAFA+LEN pre-progression resource use was not necessarily anticipated to be the same as POLA+BR and BR due to differences in treatment stopping rules and toxicity profiles for example, especially where tafasitamab monotherapy was well tolerated in patients until disease progression (as discussed in response to question

C9 part (c)). Post-progression resource use for TAFA+LEN was assumed equal to POLA+BR and BR.

b. Please indicate which items of resource use are specifically associated with the monitoring requirements of each treatment.

Response: Monitoring tests costs are the resources associated with monitoring of the treatment (Tables 42-46 in CS Document B). Some monitoring tests continue up to progression, while others are short-term resources consumed only for a limited number of cycles. The short-term monitoring resource use is captured as a one-off cost applied in the first cycle of the model (Table 43 of the CS).

c. Please justify that the health care resource use assumptions reflect current UK clinical practice for the relevant patient population.

Response: As noted in response to part (a), resource use data for POLA+BR, BR and R-GemOx were sourced from available resource use data for these therapies from previous NICE technology appraisals for R/R DLBCL, in the absence of other alternative published estimates, with limited published data available to inform resource use for UK patients with R/R DLBCL.

In the absence of available data for TAFA+LEN, post-progression resource use was assumed to be equal to POLA+BR and BR, with pre-progression resource use based on available information from the L-MIND study.

d. Please provide the options in the model to assume the same health care resource use (except in relation to specific monitoring requirements for each treatment) for all treatment arms, based on all of the included sources (i.e., L-MIND, TA649 and TA567).

Response: As noted in response to part (a), we don't believe that assuming equal resource use for TAFA+LEN for pre-progression is necessarily appropriate given the lack of available data for TAFA+LEN, and differences in treatment stopping rules and toxicity profile compared to other comparators included in the model.

C20. For all treatments for which dosage is based on body weight or body surface area (BSA) a normal distribution was assumed to distribute the proportions of

patients requiring different numbers of vials, to calculate a weighted average cost per dose.

a. Please justify the preference for using this approach over a more standard approach that uses the mean weight and BSA for the deterministic analyses, and variations in body weight and BSA based on the SEs for the probabilistic analyses.

Response: For modelling weight and BSA, a normal distribution was used to distribute the proportions of patients requiring different numbers of vials to more accurately estimate a weighted average cost per dose for the deterministic base case analysis accounting for vial wastage and produce better consistency with results generated by the probabilistic sensitivity analysis. While the mean weight and BSA could be used to calculate treatment costs, this may bias the deterministic results if the precise number of vials required for the mean weight or BSA does not accurately reflect the potential vial wastage. For example, if the precise number of vials required for the mean weight or BSA is slightly less than a whole number of vials, then this would likely underestimate the wastage costs with only a small amount of the last vial being wasted. Conversely, if the precise number of vials required for the mean weight or BSA is slightly more than a whole number of vials, then this would likely overestimate the wastage costs as only a small proportion of the last vial is used with the remainder potentially wasted.

b. Please include the option in the model to use the mean weight and BSA for the deterministic analyses, and variations in body weight and BSA based on the SEs for the probabilistic analyses.

Response: Functionality has been added to the updated model to allow for the use of the mean weight and BSA to model treatment costs.

c. Please justify that the assumed normal distributions represent plausible ranges (e.g., including the non-zero proportions of patients with body weights lower than 30 kg) or amend the model to ensure plausible ranges.

Response: While the use of normal distributions can technically result in patients with weights below 30kg, the proportion of patients below this threshold in the model

for the vial optimisation calculations is very small (<0.5%) and as such was expected to be unlikely to substantially impact the resulting cost calculations.

C21. Dose intensities for R-GemOx were assumed to be 100% in absence of available data, as stated on p. 114 of the CS. Please amend the model to include the dose intensities as reported on p. 1728 in Mounier et al. 2013 (Haematologica 98: 1726-1731) for R-GemOx.

Response: The model has been updated with the relevant dose intensity figures from Mounier et al. 2013 (91.6% for rituximab, 93.3% for gemcitabine and 92.5% for oxaliplatin).[55]

Validation

C22: Priority question: Please provide all details of the validation efforts mentioned in section B.3.9 of the CS. Please explain whether the validation efforts included all steps (e.g., conceptual model validation, input data validation, model verification, validation of the model outcome) as explained for example in the 'Assessment of the Validation Status of Health Economic decision models' (AdvisHE) tool (https://advishe.wordpress.com/). If this was not the case, please include these steps as well.

Response: The validation steps taken for the economic model are described below, in the order suggested by the AdViSHE questionnaire.

Part A: Validation of the conceptual model

The conceptual model was validated by UK clinical experts, as well as review of previous relevant HTA submissions and published economic models.

Part B: Input data validation

The model inputs were extracted from different literature sources as well as the L-MIND and Re-MIND 2 studies. One analyst extracted the inputs at different stages of the model development, with a senior project member checking the extracted inputs. The inputs were double checked in a few stages of model development, through the development of the early model up to the global mode and then the UK model specific inputs.

For the efficacy data and assumptions, the selections were made based on the following steps:

- Investigation of proportional hazards using visual assessment and the Schoenfeld residuals method
- Comparing model fit parameters (Akaike information criterion (AIC), Bayesian information criterion (BIC))
- Visual fit of the survival models to the observed data
- Feedback from UK clinical experts on the plausibility of long-term extrapolations and hazard profiles
- External validation of model predictions based on available external data

Other key model inputs and assumptions were also validated with UK clinical experts during 1:1 interviews. Where experts were not convinced about certain input values, alternative assumptions and inputs were considered.

Part C: Validation of the computerised model

The validity of the economic model was tested by experts outside the model development team. The validation was conducted in different rounds. This included:

- Validation of the global model by a team of validators within Evidera (not involved in the model development team)
- Validation of the global model by an external research service provider
- Validation of the modifications made to the global model in order to derive the UK model by a modelling expert not involved in the model development team
- Whole validation of the UK model by an external expert

Prior to each round of the validation, an extreme value testing (EVT) was conducted by the project team and any errors captured were corrected.

Throughout each round of the validation process, a comprehensive and rigorous quality check was fulfilled, which included validating the logical structure of the model, mathematical formulas, sequences of calculations, and values of the numbers supplied as model inputs. Unexpected model behaviour/implementation and typing errors were identified through this review.

Part D: Operational validation

The extrapolated predictions of survival models for OS and PFS for L-MIND and RE-MIND2 for comparators were validated with UK clinical experts and compared against the published literature and existing clinical trials in order to help validate outcomes for the model (which are largely derived from the OS and PFS curves).

Alternative input values and assumptions were tested in scenario analyses. The results of the scenario analyses were carefully investigated and interpreted, and if the results did not have the expected direction, the root of the problem was investigated and corrected.

C23: Priority question: Please provide a comparison of the cost effectiveness results in this submission and those in TA659. Results for the comparators pola+BR and BR are expected to be similar in this submission and in TA659 given that the population and indication are the same but this does not seem to be the case, especially for pola+BR. In particular:

a. Please compare the populations in L-MIND and GO29365.

Response: A comparison of patient characteristics from the L-MIND and GO29365 trials is summarised below in Table 26.

Table 26. Comparison of patient characteristics of the L-MIND and GO29365 trials

Variable		L-MIND total population[68]	GO29365 trial – POLA+BR[35]	GO29365 trial – BR[35]
Population at baseline		N=81	N=40	N=40
Age, Years	Median	72	67	71
	Range	(41 to 86)	(33 to 86)	(30 to 84)
	≥ 65, n (%)	58 (71.6)	23 (57.5*)	26 (65.0*)
Sex, n (%)	Male	44 (54.3)	28 (70.0)	25 (62.5)
	Female	37 (45.7)	12 (30.0*)	15 (37.5*)
Race, n (%)	White	72 (88.9)	26 (65.0)	31 (77.5*)

Variable		L-MIND total population[68]	GO29365 trial – POLA+BR[35]	GO29365 trial – BR[35]
	Black or African American	NR	3 (7.5)	0
	Asian	2 (2.5)	6 (15.0)	4 (10.0*)
	American Indian or Alaska Native	NR	0	1 (2.5*)
	Other	1 (1.2)	NR	NR
	Not reported/ unknown/missing	6 (7.4)	5 (12.5)	4 (10.0*)
ECOG status, n (%)	0	29 (35.8)	NR	NR
	1	45 (55.6)	NR	NR
	0-1	74 (91.4)	33 (82.5)	31 (77.5)
	2	7 (8.6)	6 (15.0)	8 (20.0)
Ann Arbor Disease Staging, n (%)	I or II	20 (24.7)	6 (15.0*)	4 (10.0*)
	III or IV	61 (75.3)	34 (85.0)	36 (90.0)
IPI score, n (%)	0	5 (6.2)	0	0
	1	11 (13.6)	9 (22.5)	3 (7.5)
	2	24 (29.6)	9 (22.5)	8 (20.0)
	3	24 (29.6)	13 (32.5)	12 (30.0)
	4	14 (17.3)	8 (20.0)	12 (30.0)
	5	3 (3.7)	1 (2.5)	5 (12.5)
	≥3	41 (50.6)	22 (55.0*)	29 (72.5*)
Lines of previous systemic treatment (DLBCL medications), n (%)	1	40 (49.4)	11 (27.5)	12 (30.0)
	2	35 (43.2)	11 (27.5)	9 (22.5)
	3	5 (6.2)	NR	NR
	4	1 (1.2)	NR	NR
	≥ 3	6 (7.4)	18 (45.0)	19 (47.5)
	Median	2	2	2
	Range	(1 to 4)	(1-4)*	(1-4)*
DoR or duration of remission of last treatment, n (%)	≤ 12 months	33 (40.7)	32 (80.0)	33 (82.5)
	> 12 months	29 (35.8)	8 (20.0)*	7 (17.5)*
	Unknown	19 (23.5)	0	0
Cell of origin based on gene expression profiling, n (%)	GCB	7 (8.6)	15 (37.5)	17 (42.5)
	ABC	19 (23.5)	19 (47.5)	19 (47.5)
	Unclassified	6 (7.4)	NR	NR
	Not evaluable	5 (6.2)	NR	NR
	Missing	44 (54.3)	6 (15.0)*	4 (10.0)*
NHL Subtype, central pathology, n (%)	Composite lymphoma with DLBCL component	9 (11.1)	NR	NR
	DLBCL	54 (66.7)	NR	NR
	DLBCL (double-hit lymphoma)	1 (1.2)	NR	NR

Variable		L-MIND total population[68]	GO29365 trial – POLA+BR[35]	GO29365 trial – BR[35]
	DLBCL (triple-hit lymphoma)	1 (1.2)	NR	NR
	EBV-positive DLBCL	2 (2.5)	NR	NR
	Follicular lymphoma (grade 2+3A)	1 (1.2)	NR	NR
	Follicular lymphoma (grade 2)	2 (2.5)	NR	NR
	Mantle cell lymphoma, classic type	1 (1.2)	NR	NR
	Marginal zone lymphoma	5 (6.2)	NR	NR
	T-cell/histiocyte rich large B-cell lymphoma	2 (2.5)	NR	NR
	Unknown	2 (2.5)	NR	NR
	Missing	1 (1.2)	NR	NR
	DLBCL, NOS	NR	38 (95.0)	40 (100.0)
	Burkitt lymphoma	0	1 (2.5)	0
	Follicular lymphoma	3 (3.7)	1 (2.5)	0
Bulky Disease ≥ 7.5 cm, n (%)	Yes	15 (18.5)	10 (25.0)	15 (37.5)
Refractoriness to last prior therapy, n (%)	Yes	36 (44.4)	30 (75.0)	34 (85.0)
	No	45 (55.6)	10 (25.0)	6 (15.0)
Prior Autologous SCT, n (%)	Yes	9 (11.1)	10 (25.0)	6 (15.0)
	No	72 (88.9)	30 (75.0)	34 (85.0)
Primary reason for transplantation ineligibility**, n (%)	Age	37 (46.3)	13 (32.5)	19 (47.5)
	Comorbidities	11 (13.8)	1 (2.5)	1 (2.5)
	Performance Status	NA	0	2 (5.0)
	Insufficient response to salvage therapy	NA	12 (30.0)	9 (22.5)
	Chemo-refractory patients	18 (22.5)	NR	NR
	Failed prior transplantation	NR	10 (25.0)	6 (15.0)
	Patient refused	13 (16.3)	2 (5.0)	2 (5.0)
	Other	1 (1.3)	2 (5.0)	1 (2.5)

Abbreviations: DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; IPI = international prognostic index; NA = not available; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; NR = not reported; SCT = stem cell transplantation.
Note: * Value computed directly from publication reporting; **N=80 for L-MIND.

Some differences in populations were observed, with patients enrolled in the L-MIND study appeared to have been less heavily pre-treated, less likely to have been refractory to their prior therapy line, to be ECOG 2, or to have Ann Arbor Stage III or

IV DLBCL at baseline than patients in the POLA+BR or BR cohorts of the GO29365 study.

b. Please compare the approach to modelling HRQoL in this appraisal and in TA659 and highlight any potential difference.

Response: Health state utility values for pre-progression (0.72) and post-progression (0.65) applied in the CS are the same as those applied in NICE TA649. Where AEs were common, AE disutilities applied in the submitted economic model were also consistent with those used in NICE TA649.

However, as noted above in response to clarification question C9, discrepancies were observed between the adverse event probabilities used in the submitted economic model for POLA+BR and BR with those in TA649, which likely contribute to differences in adverse event disutility for these treatments. Furthermore, different adverse event inclusion criteria appear to have been applied, given the inclusion of values in TA649 below the 5% threshold considered for the CS.

In addition, treatment-related disutility was included in the submitted model for patients receiving subsequent treatment with CAR-T, which was not considered in TA649.

Regarding age and sex adjustment of utilities, as described in Section B.3.4.5 of the CS and above in response to clarification question C13, all utilities and disutilities in the economic model were adjusted for age and sex in relation to general population utility and, for relevant “cure” scenarios, age and sex matched utility for the general population was applied for “cured” patients.

While age- and sex- matched general population utility values were applied to patients considered to be in long-term remission in NICE TA649, from the description provided in the TA649 committee papers, it does not appear that the underlying health state utility values or disutilities applied in the model were adjusted over time relative to general population utility to account for differences in age and sex in compared to the reference population characteristics for the ZUMA-1 trial population or account for expected changes in quality of life over time for the model health states with increasing age. In addition, due to differences in baseline ages applied in the economic models, age and sex matched general population utilities applied in

cure scenarios differences. Furthermore, a difference source of general population utility data was applied in the CS (Chang-Douglass 2020)[84] compared to that applied in TA649 (Ara and Brazier 2010),[85] although both studies were based on Health Survey for England (HSE) data, with the Chang-Douglass 2020 study used in the CS including more recent HSE datasets.

c. Please compare the approach to modelling costs and resource use in this appraisal and in TA659 and highlight any potential difference. The differences in total costs between the current submission and TA649 is quite substantial, please explain what might cause these differences.

Response: From comparing the costs between the CS, the most substantial difference in costs identified for the submitted model and TA649 was driven by the pre-progression resource use. After double checking the unit costs and resource use data applied in the CS, we concluded that the disease management costs for POLA+BR and BR were overestimated in our model. This was due to the fact that while different resource use frequencies for the on and off treatment period were applied in TA649, in the model used for the CS, only the on-treatment frequencies were applied for POLA+BR and BR in the PFS health state regardless of treatment status. To address this issue, a new table has been added to the "Disease Mgmt Details" sheet of the model to allow the user to specify resource use frequency inputs for patients that are off treatment while within the PFS health state for any model comparator, with the model engine calculations modified accordingly to apply relevant disease management costs for patients in the PFS health state depending on whether they are on or off treatment. For TAFA+LEN and R-GemOx, off treatment resource use frequencies were assumed to be the same as the on-treatment resource use frequencies. An overview of the updated resource use frequencies applied in the model is summarise below in Table 27 and Table 28. Please note that the resource use frequencies shown reflect the total healthcare resource use for each category and include the "treatment follow-up" resource use for haematologist, oncologist, nurse, radiologist and GP visits for POLA+BR and BR from Table 55 of the company submission for TA649.

Table 27. Disease Management: Frequency of Use per Model Cycle - PFS without prolonged PFS – on treatment

Disease Management Resource	TAFA+LEN	POLA+BR	BR	R-GemOx
Consultant visit	0.42			0.40
Day care		1.12	1.12	
District nurse (visit)		1.50	1.50	
GP (visit)		2.01	2.01	
Haematologist (visit)		1.02	1.02	
Home care (day)		4.67	4.67	
Hospice (day)		0.05	0.05	
Inpatient (day)		0.25	0.25	
Nurse (visit)		4.38	4.38	
Oncologist (visit)		1.72	1.72	
Radiologist (visit)		1.67	1.67	
Residential care (day)		2.99	2.99	
Specialist nurse (visit)	2.29	0.67	0.67	
Source:	L-MIND CSR	NICE TA649	NICE TA649	NICE TA567

Abbreviations: BR = bendamustine and rituximab; CSR = clinical study report; GP = general practitioner; PFS = progression-free survival; POLA+BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

Table 28. Disease Management: Frequency of Use per Model Cycle - PFS without prolonged PFS – off treatment

Disease Management Resource	TAFA+LEN	POLA+BR	BR	R-GemOx
Consultant visit	0.42			0.40
Day care		0.28	0.28	
District nurse (visit)		0.38	0.38	
GP (visit)		0.51	0.51	
Haematologist (visit)		0.43	0.43	
Home care (day)		1.70	1.70	
Hospice (day)		0.02	0.02	
Inpatient (day)		0.25	0.25	
Nurse (visit)		1.37	1.37	
Oncologist (visit)		0.47	0.47	
Radiologist (visit)		0.33	0.33	
Residential care (day)		0.75	0.75	
Specialist nurse (visit)	2.29	0.17	0.17	
Source:	L-MIND CSR	NICE TA649	NICE TA649	NICE TA567

Abbreviations: BR = bendamustine and rituximab; CSR = clinical study report; GP = general practitioner; PFS = progression-free survival; POLA+BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

However, while the correction described above produced per cycle medical resource use costs closer to those from TA649, some differences still remain in total pre-progression resource use costs (so called supportive care costs in TA649). One key difference between the CS and the base case analysis from TA649 is the use of cure assumptions, with the base case model submitted in TA649 assuming no subsequent resource use costs for PFS patients after 2 years which would generate lower total resource use costs compared to the CS (where cure assumptions were explored via scenario analysis and not applied in the base case). Based on the total pre-progression life years observed in the model for POLA+BR (1.84) and BR (0.94), and the fixed maximum treatment durations of 18 weeks for both therapies, total pre-progression resource use costs (£22,188 for POLA+BR, £13,295 for BR) appear accurate compared to the per cycle (4-weekly) disease management costs applied for both treatments (£1,973.21 for PFS on treatment, £754.40 for PFS off treatment), with the modelled values towards the lower bound of potential disease management costs for progression-free patients generated by the total progression-free life years multiplied by the annualised per cycle off-treatment and on treatment PFS costs (£18,107 to £47,361 for POLA+BR, £9,250 to £24,195 for BR).

Differences in subsequent treatment costs are also expected given the use of different sources of subsequent treatment probabilities (RE-MIND2 for the CS and GO29365 trial data in TA649), with RE-MIND2 used for the CS given the availability of subsequent treatment data specific to TAFA+LEN. While subsequent treatments listed in TA649 are mostly standard of care chemotherapies, the RE-MIND2 data includes a larger variety of subsequent treatment options, which may contribute to differences in overall subsequent treatment costs. Importantly, the CS includes the cost of subsequent CAR-T therapy, which was not included in the TA649 base case submitted by the company.

Furthermore, as noted in response to clarification question C9, some differences were also observed in the adverse event probabilities applied for POLA+BR and BR in the CS compared to TA649 (with higher adverse event probabilities in the CS), which in turn is likely to generate higher adverse events costs in the submitted model for the CS for POLA+BR and BR.

d. ***Most importantly*: life years gained (and, therefore, quality adjusted life years [QALYs]) for pola+BR and BR in this appraisal are expected to be comparable to those in TA659. However, substantial differences are observed, especially in pola+BR. It seems that the current model predicts longer life years for BR and shorter for pola+BR, the latter to a large extent, compared to the results in TA659. In particular, please note that the TA659 committee papers reported that the "*ERG base-case showed a total 2.08 life years gain between two interventions*", thus between pola+BR and BR. Given this result, the ERG is concerned that the current model might be (substantially) underestimating life years and QALYs in the pola+BR arm. Please explain what might be causing the difference in life years/QALYs between the two studies and whether this difference affects the validity of the outcomes (especially for Pola-BR) presented in this submission.**

Response: Differences in total life years and QALYs are likely to be related to differences in survival modelling approaches applied for these treatments compared to NICE TA649.

For BR, OS, PFS and TTD for the base case analysis were based on real-world data from RE-MIND2 that was 1:1 matched with patients from the L-MIND study. Given that the data for BR applied in the base case analysis was derived from the RE-MIND2 study and not the GO29365 trial data, this is likely to cause differences in life year and QALY results compared to NICE TA649. UK clinical experts indicated that the RE-MIND2 data and associated parametric extrapolations of OS and PFS for BR were plausible representations of UK clinical practice, and as a larger sample size of patients were available as well as improved capability for statistical matching of patients was possible with the patient level data from RE-MNIND2 compared to the summary level data available for the GO29365 trial data used for the MAIC, the RE-MIND2 data was applied in the base case analysis.

For POLA+BR, the data applied in the economic model was derived through a MAIC conducted between the L-MIND study and the GO29365 trial data. However, it is important to note that TAFA+LEN was used as the reference arm when applying the MAIC results in the economic model rather than the POLA+BR data from the

GO29365 trial, and therefore extrapolations are more representative of an “L-MIND”-like population which, given slight differences observed between model populations (as noted above and in response to part (a)), may contribute to differences in long-term survival. Furthermore, the fewer life years and QALYs observed in the CS may also be related to the use of time-varying HRs for POLA+BR. As described in Section 1.1.5 of Appendix M of the CS, visual inspection of the log-cumulative hazard plot for both OS and PFS indicated a violation of the proportional hazard’s assumption, with hazard plots appearing to show convergence from approximately 4 months before subsequently crossing. Use of different HRs before and after 4 months was also considered biologically plausible based on differences in treatment stopping rules, as the 4-month time point broadly corresponded to the maximum treatment duration for the POLA+BR regimen (18 weeks), while TAFA+LEN patients received treatment up to 48 weeks before continuing tafasitamab monotherapy until disease progression. Examination of alternative time points for the application of time-varying HRs (3, 9 and 11 months) also suggested consistency in terms of directionality of the HRs.

In addition, as noted in response to part (b), differences in approaches to age- and sex-adjustment of utility values may also contribute to differences in overall QALY results between the CS and those presented in TA649.

Additional information provided on 20th January 2022

Furthermore, differences observed in life years and QALYs between the CS and TA649 for POLA+BR may also be related to the use of cure-mixture models for POLA+BR for PFS and OS in TA649. These types of parametric models were not explored in the CS following UK clinical expert feedback on the uncertainty of cure assumptions for patients with relapse/refractory DLBCL, with hybrid cure assumptions explored through scenario analysis instead. When comparing the base case OS curve for POLA+BR from the CS against the predicted OS for POLA+BR using the (dependent fit) standard parametric models shown in Figure 19 of the company submission in TA649, the base-case extrapolation used in the CS appears reasonable. For example, 5-year OS from the base case model OS curve for POLA+BR in the CS (11.7%) falls within the range of 5-year OS predictions from the dependent fit standard parametric models in TA649 (~7-16%).

Sensitivity/scenario/subgroup analyses

C24. Priority question: please clarify the following points regarding the probabilistic sensitivity analysis (PSA):

a. **Please provide the selection criteria for the parameters to be included in the PSA. Appendix L reports 76 parameters while in the economic model "Parameters" sheet, a total of 318 inputs have a "TRUE" value on column N.**

Response: Parameters included in Appendix L of the CS reflect those that are used in the base case economic analysis, and therefore those that were varied as part of the DSA and PSA. While other inputs are listed on the "Parameters" sheet with "TRUE" values stated in column N, this is to ensure that these parameters are included correctly should the user populate the relevant cells with non-zero values or select certain options within the model.

b. **The parameters BSA, height and weight take the same value for males and females (except for some SEs). Please clarify the rationale for discriminating per gender if values are the same, and whether this is expected to have any impact on the model results.**

Response: The model includes the option to specify gender-specific BSA, height and weight characteristics. However, the overall patient population characteristics were applied as the use of gender-specific values, of which a weighted average would be taken for the purposes of the model based on the L-MIND trial population characteristics (which would then match the overall population average), was not anticipated to have a significant impact on the model results.

c. **As, explained in question C13, it is unclear why some disutilities were included in the model. Please clarify whether this is an error.**

Response: As noted in the response to clarification question C13, the inclusion of SCT disutility in the model is intentional to allow for users to apply disutility in case of the use of SCT as a subsequent treatment. However, the proportion of patients receiving subsequent SCT was set to 0% for all treatments in the base case model according to the subsequent treatment figures for the matched population data from RE-MIND2 and UK clinical expert feedback.

d. Please confirm that parameters modelled with normal distributions do not result in e.g., undesired negative values.

Response: Parameters assigned normal distributions for the PSA include baseline age, BSA, weight, height, reference age values for health state utility estimates and overall disutility for each model comparator associated with AEs as well as CAR-T disutility associated with subsequent treatment. Normal distributions are commonly assigned to population variables like age, BSA, weight and height, and were applied in line with recommendations from Briggs et al 2006.[86] Although the use of normal distributions for these variables can potentially result in values that may be implausible for an adult population, the likelihood of this occurring is expected to be low given the average values and associated uncertainty data. For example, as indicated in the response to clarification question C20, the probability of generating a low weight value below 30kg was expected to be very low (<0.5%) and was therefore not expected substantially impact the overall PSA results.

Assigned distributions for the overall treatment disutility associated with AEs, as well as other disutilities, have been changed to gamma distributions in the updated economic model in line with recommendations from Briggs et al 2006.[86]

e. Please check the consistency between the deterministic and probabilistic results, amend the model where needed, and explain any remaining inconsistencies

Response: For the revised economic model results, mean PSA total costs and QALYs were similar for TAFA+LEN and R-GemOx to the base-case results, and were all within 0.5% of the base-case values. For POLA+BR and BR, mean PSA total costs were 5.1% and 3.7% higher than the base-case estimates. Mean PSA total QALYs were also increased for POLA+BR and BR by 5.5% for both comparators. Differences in the mean values for POLA+BR and BR are likely driven by variations in underlying survival-related parameters (such as the HRs used to model relative efficacy for OS compared to TAFA+LEN).

Please see the updated results provided in the Appendix for more details.

f. **Please provide a new corrected model with PSA, where all (and only) relevant parameters are included, with the description of the selection criteria for relevant parameters.**

Response: Please see responses to parts (a) through (e). Results from the revised economic model are presented in the Appendix.

Section D: Textual clarification and additional points

D1. Priority question: Three clinical study report documents were included with the company submission, however all three appear to be incomplete. For example, all of these documents include a section "Tables, Figures and Graphs referred to but not included in the text", i.e., there is a clear indication of information that has not been included. Please provide the complete documentation. This was requested by the ERG in an email to NICE on 1st December 2021.

Response: The complete CSRs were provided to NICE on 06 December 2021 and are available for review.

D2. Appendix I appears to be missing from the CS. Please provide this. This was requested by the ERG in an email to NICE on 1st December 2021.

Response: As the HRQoL and Economic SLRs were conducted together, Appendix I is redundant for this submission. Please refer to the document shared on 06 December 2021 entitled "SLR content locations" for an overview of the locations of relevant SLR content.

Appendix

Updated results from revised economic model

Base-case results

The base-case cost-effectiveness results for TAFA+LEN and each model comparator (POLA+BR, BR and R-GemOx) are presented in Table 29 based on the updated economic model. While TAFA+LEN generated increased total costs against each model comparator, it also produced substantial increases in discounted total life years (2.88-3.32) and QALYs ([redacted]). Undiscounted life year gains for TAFA+LEN were 3.97, 4.46 and 4.41 vs POLA+BR, BR and R-GemOx, respectively.

The ICERs for TAFA+LEN against POLA+BR, BR and R-GemOx were [redacted], [redacted] and [redacted] per QALY, respectively.

Table 29. Base-case results (revised model)

Intervention	Total costs (£)	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	[redacted]	5.08	[redacted]	-	-	-	-
POLA+BR	[redacted]	2.20	1.45	[redacted]	2.88	[redacted]	[redacted]
BR	[redacted]	1.76	1.13	[redacted]	3.32	[redacted]	[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]	3.26	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

Incremental analysis results are shown below in Table 30. [redacted].

Table 30: Base case results – full incremental analysis (revised model)

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs previous non-dominated alternative
BR	[redacted]	1.13	[redacted]	[redacted]	-
R-GemOx	[redacted]	1.16	[redacted]	[redacted]	[redacted]
POLA+BR	[redacted]	1.45	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Tafa+Len, tafasitamab + lenalidomide; POLA+BR, polatuzumab + bendamustine + rituximab; BR, bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaplatin; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

Sensitivity Analyses

Probabilistic Sensitivity Analysis

The mean probabilistic results are presented in Table 31**Error! Reference source not found.** for the revised model are alongside the deterministic base-case results. Mean PSA total costs and QALYs were similar for TAFA+LEN and R-GemOx to the base-case results, and were all within 0.5% of the base-case values. For POLA+BR and BR, mean PSA total costs were 5.1% and 3.7% higher than the base-case estimates. Mean PSA total QALYs were also increased for POLA+BR and BR by 5.5% for both comparators.

Table 31. Mean PSA results (revised model)

Intervention	Deterministic results		Mean PSA results	
	Total costs	Total QALYs	Total costs (95% CI)	Total QALYs (95% CI)
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]
POLA+BR	[redacted]	1.45	[redacted]	[redacted]
BR	[redacted]	1.13	[redacted]	[redacted]
R-GemOx	[redacted]	1.16	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomideThe distribution of incremental costs and QALYs for TAFA+LEN vs. POLA+BR, BR and R-GemOx is shown in Figure 14, Figure 15, Figure 16, respectively.

Figure 14. PSA cost-effectiveness plane for TAFA+LEN vs. POLA+BR (revised model)

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 15. PSA cost-effectiveness plane for TAFA+LEN vs. BR (revised model)

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 16. PSA cost-effectiveness plane for TAFA+LEN vs. R-GemOx (revised model)

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The cost-effectiveness acceptability curve (CEAC) for TAFA+LEN vs. POLA+BR, BR and R-GemOx is shown in Figure 17 for willingness to pay (WTP) thresholds between £0 and £200,000 per QALY, in increments of £4,000 per QALY. The CEAC indicates that .

Figure 17. CEAC (revised model)

Deterministic Sensitivity Analysis

Tornado diagrams illustrating the key drivers of ICER values in the comparison are shown in Figure 18, Figure 19 and Figure 20. Xxxxxxxxxxxxxxxxxxxxxxxxx, xxxxxxxx

[redacted]

Figure 18. Tornado diagram of ICER results for TAFA+LEN vs. POLA+BR (revised model)

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 19. Tornado diagram of ICER results for TAFA+LEN vs. BR (revised model)

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 20. Tornado diagram of ICER results for TAFA+LEN vs. R-GemOx (revised model)

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Scenario Analysis

Scenarios exploring alternative long-term extrapolations and data source of survival parameters, cure assumptions, utilities and vial sharing, along with shorter model time horizons and lower discount rates, are summarised in Table 32.

Scenarios with the largest increases in the ICER were shorter time horizons (to and to for five and 10-year time horizons, respectively), use of the Weibull model for TAFA+LEN OS (to for each comparator), use of the log-normal model for TAFA+LEN PFS (to), use of MAIC constant HRs for POLA+BR (increase in ICER vs. POLA+BR) and applying MAIC HRs and median TTD data for R-GemOx (increase in ICER vs. R-GemOx).

Scenarios generating the largest decreases in the ICER were the cure assumption scenarios with scenarios 16 and 17 generating the largest ICER decreases of between to across comparators, as well as use of RE-MIND2 data for POLA+BR (), health state utilities from NICE TA567 (to) and assuming vial-sharing for all IV therapies (to).

Table 32. Scenario analysis results (revised model)

Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
-	**Base-Case**			
1	5-year time horizon			
2	10-year time horizon			

Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
3	1.5% discount rate for costs and outcomes	[redacted]	[redacted]	[redacted]
4	TAFA+LEN OS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
5	TAFA+LEN OS parametric model: Weibull	[redacted]	[redacted]	[redacted]
6	TAFA+LEN PFS parametric model: log-normal	[redacted]	[redacted]	[redacted]
7	POLA+BR: apply MAIC HRs with 11-month split for OS and PFS	[redacted]	[redacted]	[redacted]
8	POLA+BR: apply constant MAIC HRs for OS and PFS	[redacted]	[redacted]	[redacted]
9	POLA+BR: apply RE-MIND2 survival data (generalised gamma for OS, exponential for PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
10	BR PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
11	R-GemOx OS parametric model: Gompertz	[redacted]	[redacted]	[redacted]
12	R-GemOx PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
13	Applying MAIC HR estimates for OS/PFS and median TTD durations for BR and R-GemOx	[redacted]	[redacted]	[redacted]
14	Fixed 2-year cure point with 78.6% of PFS patients at 2 year achieving cure: general population mortality only	[redacted]	[redacted]	[redacted]
15	Scenario 14 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
16	Scenario 15 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
17	Scenario 16 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
18	Cure point at crossing of OS and PFS curves: general population mortality only	[redacted]	[redacted]	[redacted]
19	Scenario 18 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
20	Scenario 19 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
21	Scenario 20 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]

Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
22	Utility of 0.83 for PFS and 0.71 for PD based on NICE TA567	[redacted]	[redacted]	[redacted]
23	Vial sharing for all IV administered treatments	[redacted]	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PFS = progression-free survival; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R=GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = Tafasitamab + lenalidomide; TTD = time to treatment discontinuation

QuEENS checklist assessment of RE-MIND

<table>
<tr><th>Question</th><th>Comments</th></tr>
<tr><td>Q1: Have different methods been compared within the study?</td><td>1:1 nearest neighbour matching was explored in the base case analyses of the RE-MIND study.
Population balancing using overlap weights were also used in the sensitivity analyses of the RE-MIND study.
Results obtained from the 1:1 matching and using overlap weights were consistent as presented in the table below.
Table 33. RE-MIND results using 1:1 matching and overlap weights
<table>
<tr><td rowspan="2"></td><td colspan="2">TAFA+LEN v. LEN: HR (95%CI)</td></tr>
<tr><td>OS</td><td>PFS</td></tr>
<tr><td>Base case: 1:1 matching</td><td>0.499 (0.317, 0.785)</td><td>0.463 (0.307, 0.698)</td></tr>
<tr><td>Sensitivity: overlap weights</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: CI = confidence interval; HR = hazard ratio; LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; TAFA = tafasitamab.</td></tr>
<tr><td>Q2: Have the results of the study been compared to others in the literature?</td><td>The estimates derived in the RE-MIND are aligned with the results of MAIC analyses of TAFA+LEN v. LEN conducted using prospective evidence from the DLC-001 trial. Results of these analyses haven’t been published yet but were provided as part of the evidence to this submission dossier.
No estimates of relative efficacy of TAFA+LEN versus LEN either from head-to-head comparison or indirect comparisons could be found in the literature to allow a comparison with the RE-MIND analyses.</td></tr>
<tr><td>Q3: Is there a discussion of what treatment effect is identified and of the assumptions needed?</td><td>In the RE-MIND primary analyses both average treatment effect on the treated (through 1:1 nearest neighbour matching based on estimated propensity score) and average treatment effect (through overlap weighting) were investigated.
Both methods rely on the ignorability assumption which states that conditionally on the set of variables included in the population adjustment, the treatment outcomes and treatment allocation group are independent. To give more plausibility to the ignorability assumption the following steps were taken:
Similar eligibility and non-eligibility criteria were used in the L-MIND and for the observational cohort patient selection. A complete description of the population filtering is available in the CSR of the RE-MIND study.
A rich set of factors was included in the population adjustment including patients’ age, Ann Arbor staging, refractoriness to last therapy line, number of prior lines of therapy, primary refractoriness, treatment with prior ASCT, LDH levels, neutropenia, and anaemia status.
The overlap assumption was evaluated through a comparison of the baseline characteristics of the L-MIND and LEN cohorts after population adjustment (i.e., 1:1 matching or weighting) and computation and standardised mean differences.
Clinical expert mentioned the possibility treatment-effect modifications caused by age of patients, sex of patients, creatinine clearance, primary refractoriness, and refractoriness to last line of therapy, IPI score, LDH levels, cell of origin of the disease and cytogenetic factors.</td></tr>
<tr><td>Q4: Is the model chosen consistent with the outcome variable if using a parametric method?</td><td>Time-to-event outcomes events were investigated trough semi-parametric models (i.e., Cox regression models).</td></tr>
</table>

<table>
<tr><td>Q5: Were any checks conducted on the model specification?</td><td>Assessment of proportional hazards were conducted to assess the validity of the use of time-constants HR obtained from the Cox regression models.</td></tr>
<tr><td>Q6: On selection: Is the assumption of selection on observables assessed?</td><td>Clinical expert opinion was sought to identify the variable included in the population adjustment. The following 9 variables were included in the population adjustments (either 1:1 matching or weighting):
Age
Ann Arbor staging
Refractoriness to last therapy line
Number of prior lines of therapy
Primary refractoriness
Treatment with prior ASCT
LDH levels
Neutropenia
Anaemia status
Because of data missingness or unavailability in the observational cohort, no adjustment was carried out on IPI, ECOG or early relapse despite being highlighted as important factors by clinical experts in the primary RE-MIND analyses. A sensitivity analysis was conducted adding ECOG to the list of factors included in the population adjustment and provided similar results to the base case as presented in the table below.
Table 34. RE-MIND results using 1:1 matching with 9 and 10 covariates<table><tr><td></td><td colspan="2">TAFA+LEN v. LEN: HR (95%CI)</td></tr><tr><td></td><td>OS</td><td>PFS</td></tr><tr><td>Base case: 1:1 matching using 9 covariates†</td><td>0.499 (0.317, 0.785)</td><td>0.463 (0.307, 0.698)</td></tr><tr><td>Sensitivity: 1:1 matching using 10 covariates ‡</td><td>0.374 (0.227, 0.613)</td><td>0.387 (0.241, 0.620)</td></tr></table>Abbreviations: CI = confidence interval; HR = hazard ratio, LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; TAFA = tafasitamab.
† Age, Ann Arbor staging, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, LDH levels, Neutropenia, Anaemia status. ‡ Age, Ann Arbor staging, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, LDH levels, Neutropenia, Anaemia status, ECOG
Although no adjustment was possible on IPI, adjustments were made on 3 of its 5 individual components in the base case (age, Ann Arbor staging, LDH levels). In addition, the sensitivity model that included an adjustment on ECOG provided results similar to the base case. Hence it is expected that the bias accrued by potential unobserved difference on IPI would be limited.</td></tr>
<tr><td>Q7: What checks were conducted to assess overlap?</td><td>The overlap assumption was assessed through the computation of standardised mean differences in key factors included in the population adjustment prior to the population balancing.
Overlap of the propensity score was evaluated by side-by-side boxplots overlapping line graphs of the estimated propensity score.</td></tr>
<tr><td>Q8: Has balancing of the covariates been checked after matching and propensity score methods?</td><td>Balancing of the cohort was checked following the population adjustment through the monitoring of SMD.
Only one variable included in the population adjustment was imbalanced after the matching using a threshold of 0.25 on the SMD to assess differences as suggested by the NICE TSD DSU 17 following the population-matching in the RE-MIND analyses (number of prior lines of therapy). A doubly robust estimation of the treatment effect was therefore implemented consisting in a covariate adjustment for</td></tr>
</table>

	variables with SMD after matching >0.2 (i.e., Ann Arbor staging, number of prior lines of therapy). In addition, the use of a caliper in the matching also permitted to resolve this imbalance. Results obtained from the base case model, the doubly robust model and the model that used a caliper are aligned with base case results as presented below. Table 35. RE-MIND results using 1:1 matching in the base case, with doubly robust estimation and using a caliper

	TAFA+LEN v. LEN: HR (95%CI)	
	OS	PFS
Base case: 1:1 matching using 9 covariates†	0.499 (0.317, 0.785)	0.463 (0.307, 0.698)
Base case: 1:1 matching using 9 covariates with doubly robust estimation‡	[redacted]	[redacted]
Sensitivity: 1:1 matching using 9 covariates and a caliper	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio, LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; TAFA = tafasitamab.

† Age, Ann Arbor staging, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, LDH levels, Neutropenia, Anaemia status. ‡ Ann Arbor staging and number of prior lines of therapy were inserted as covariates from the Cox regression models.

Q9: Is the propensity score function sufficiently flexible?	Propensity score was model using logistic regression model excluding interactions or squared terms in the base case as good balancing of the populations was achieved with a model including only main effects.
Q10: Are potential IVs excluded from the set of conditioning variables?	No concerns were raised on the inclusion of potential instrumental variable in the conditioning sets. All variables included in the conditional sets were observed prior to treatment initiation.
Q11: Are there data quality issues	Some limitations of the RE-MIND2 analyses arise from the difference in the nature of the source of evidence: while the L-MIND study was an interventional prospective study, the RE-MIND2 study was a retrospective observational study. Therefore, it is possible that some bias could be introduced in the comparisons due to differences in designs with some potential differences in treatment adherence or monitoring of the patients. In addition, although outcomes were defined similarly across sources of evidence, differences in patients monitoring may have affected the comparisons of surrogate endpoints such as PFS. The direction of the expected bias is unclear but might be conservative as treatment from the observational cohorts could be favoured, as patients from the L-MIND study were thoroughly followed using a defined assessment schedule. These two limitations are shared by any comparative efficacy analysis employing prospective and retrospective data. It's important to note that investigator-assessed efficacy endpoints from the L-MIND study were used in the comparison against efficacy endpoints investigated in the LEN cohort from RE-MIND. As discussed earlier, data missingness prevented from using IPI in the population adjustment in the RE-MIND analyses. However, it should be noted that most of the individual components from the IPI score were included in the population adjustment (age, Ann Arbor stage, LDH levels, ECOG) either in base case or through sensitivity analyses.

Question 12: For Nearest Neighbour matching: Has bias adjustment been conducted if more than one variable was included?	To our knowledge, the correction from Abadie and Imbens is appropriate for matching on more than one continuous covariate. This was not the case in these analyses where the only continuous covariate was age.
Q13: Is the choice of replacement (with/without) reasonable?	Matching without replacement was performed in RE-MIND study.
Q14: Is the choice of the number of matches/caliper matching/radius matching reasonable?	Only 1:1 matching was attempted as part of the RE-MIND study analysis. A caliper was used for matching in a sensitivity analysis. The width of the caliper was not set a priori. The biggest caliper using an SMD ≤0.20 for all covariates included in the 1:1 matching was chosen based on the following steps: • A caliper constant of 0.99 and a sorting order provided by the seed "2019" was used on the L-MIND and observational cohort to perform 1:1 matching. The caliper width was computed as $Caliper\ width = caliper\ contant\ \times SD_{logit\ ePS}$ • SMD were calculated on the 9 covariates used in the population adjustment. • If SMD ≤0.2 for all covariates the process stops, and the caliper is retained. If SMD >0.2 for any covariate, 9 new seed are drawn using "2019 + i" with i=1,…,9 and the propensity score models are re-estimated, and matching are re-performed one at a time using the seeds in an ascending order. • If SMD >0.2 for any covariates persists after using the set of new seeds, a smaller caliper is used. The caliper constant was chosen from the set of (0.98, 0.97,…,0.01) one at a time in a descending order and the previous steps are repeated. For more than one choice of caliper and seed for which SMD ≤ 0.2 for all 9 covariates is achieved, the largest caliper and the smallest seed will be chosen.

Abbreviations: ASCT = autologous stem cell transplant; DSU = Decision Support Unity; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LEN = lenalidomide; NICE = National Institute for Health and Care Excellence; SMD = standardised mean difference; TAFA+LEN = tafasitamab and lenalidomide; TSD = Technical Support Document.

QuEENS checklist assessment of RE-MIND2

Question	Comments
Q1: Have different methods been compared within the study?	1:1 nearest neighbour matching was explored in the base case analyses of the primary and post-hoc analyses from RE-MIND2. In the primary RE-MIND2 analyses patients from the observational cohorts were matched to TAFA+LEN treated patients from L-MIND, while in the post-hoc analyses patients from L-MIND were matched to patients enrolled in the L-MIND study. Weighting methods were used in both primary and post-hoc analyses of RE-MIND2 in sensitivity analyses. Results obtained from the 1:1 matching and using overlap weights were consistent in the primary analyses of RE-MIND2 as presented in the table below. Table 36. Primary RE-MIND2 results using 1:1 matching and overlap weights

	TAFA+LEN v. BR: HR (95%CI)	TAFA+LEN v. R-GemOx: HR (95%CI)

	OS	PFS	OS	PFS
Base case: 1:1 matching	0.418 (0.272, 0.644)	0.527 (0.344, 0.809)	0.467 (0.305, 0.714)	0.433 (0.288, 0.653)
Sensitivity: use of overlap weights	0.433 (0.256, 0.732)	Not conducted	0.494 (0.289, 0.843)	Not conducted

Abbreviations: BR = bendamustine + rituximab; CI = confidence interval; HR = hazard ratio, LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab.

Results obtained from the 1:1 matching and using IPTW were consistent in the post-hoc analyses of RE-MIND2 as presented in the table below. It can be noted that overdispersion of the IPT weights was observed and thus results of the IPTW analyses should be interpreted with caution.

Table 37. Post-hoc RE-MIND2 results using 1:1 matching and IPTW

	TAFA+LEN v. POLA+BR: HR (95%CI)	
	OS	PFS
Base case: 1:1 matching with multiple imputation	0.420 (0.226, 0.781)	0.505 (0.271, 0.941)
Sensitivity: IPTW	0.282 (0.178, 0.446)	0.348 (0.220, 0.551)

Abbreviations: BR = bendamustine + rituximab; CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; POLA = polatuzumab; TAFA = tafasitamab.

Q2: Have the results of the study been compared to others in the literature?

The estimates derived in the RE-MIND2 analyses primary and post-hoc analyses are aligned with the results of the MAIC analyses conducted on prospective evidence. Results of these analyses were presented at ISPOR 2021[22] and were provided as part of the evidence to this submission dossier.

No estimates of relative efficacy of TAFA+LEN versus comparators either from head-to-head comparison or indirect comparisons could be found in the literature to allow a comparison with the RE-MIND2 analyses.

Q3: Is there a discussion of what treatment effect is identified and of the assumptions needed?

In the RE-MIND2 primary analyses both average treatment effect on the treated (through 1:1 nearest neighbour matching based on estimated propensity score) and average treatment effect (through a sensitivity analysis based on overlap weighting) were investigated. In the RE-MIND2 post-hoc analyses average treatment effect on the treated was investigated through both 1:1 nearest neighbour matching based on estimated propensity score and inverse probability of treatment weighting were investigated.

Both methods rely on the ignorability assumption which states that conditionally on the set of variables included in the population adjustment the treatment outcomes and treatment allocation group are independent. To give more plausibility to the ignorability assumption the following steps were taken:

Similar eligibility and non-eligibility criteria were used in the L-MIND and for the observational cohort patient selection. A complete description of the population filtering is available in the CSR of the RE-MIND2 study.

A rich set of factors was included in the population adjustment from RE-MIND2 primary and post-hoc analysis, including patients' age, Ann Arbor staging, refractoriness to last therapy line, number of prior lines of therapy, primary refractoriness, treatment with prior ASCT, LDH levels, neutropenia, and anaemia status.

It cannot be ruled out that POLA+BR patients treated in the real-world setting may have been patients more difficult to treat than others from the observational cohort, in dimensions potentially difficult to capture in a population adjustment, with POLA+BR only being recently introduced onto the market at the time of RE-MIND2 data collection. Hence there is a possibility for selection on unobservable in the post-hoc analyses of RE-MIND2.

The overlap assumption was evaluated in both RE-MIND2 primary and post-hoc analysis through a comparison of the baseline characteristics of the L-MIND and observational cohorts after population adjustment (i.e., 1:1 matching or weighting) and computation and standardised mean differences. No concerns were raised in

<table>
<tr><td></td><td>the matching of observational patients to L-MIND patients in the comparison of TAFA+LEN v. BR and R-GemOx. In the post-hoc analysis of the RE-MIND2 study no concerns were raised in the matching of L-MIND patients to POLA+BR treated patients.
Clinical expert mentioned the possibility treatment-effect modifications caused by age of patients, sex of patients, creatinine clearance, primary refractoriness, and refractoriness to last line of therapy, IPI score, LDH levels, cell of origin of the disease and cytogenetic factors.</td></tr>
<tr><td>Q4: Is the model chosen consistent with the outcome variable if using a parametric method?</td><td>In both the RE-MIND2 primary and post-hoc analyses time-to-event outcomes events were investigated trough semi-parametric models (i.e., Cox regression models).</td></tr>
<tr><td>Q5: Were any checks conducted on the model specification?</td><td>Assessment of proportional hazards were conducted to assess the validity of the use of time-constants HR obtained from the Cox regression models.</td></tr>
<tr><td>Q6: On selection: Is the assumption of selection on observables assessed?</td><td>Clinical expert opinion was sought to identify the variable included in the population adjustment. 9 variables were considered in the adjustment on both the primary and post-hoc analyses of the RE-MIND2 study (either 1:1 matching or weighting):
Age
Ann Arbor staging
Refractoriness to last therapy line
Number of prior lines of therapy
Primary refractoriness
Treatment with prior ASCT
LDH levels
Neutropenia
Anaemia status
Because of data missingness or unavailability in the observational cohort, no adjustment was carried out on IPI, ECOG or early relapse despite being highlighted as important factors by clinical experts in the primary RE-MIND2 analyses. A sensitivity analysis was conducted adding ECOG and early relapse to the list of factors included in the population adjustment and provided similar results to the base case as presented in the table below:
Table 38. Primary RE-MIND2 results using 1:1 matching using 9 and 11 covariates
<table>
<tr><td></td><td colspan="2">TAFA+LEN v. BR: HR (95%CI)</td><td colspan="2">TAFA+LEN v. R-GemOx: HR (95%CI)</td></tr>
<tr><td></td><td>OS</td><td>PFS</td><td>OS</td><td>PFS</td></tr>
<tr><td>Base case: 1:1 matching using 9 covariates†</td><td>0.418 (0.272, 0.644)</td><td>0.527 (0.344, 0.809)</td><td>0.467 (0.305, 0.714)</td><td>0.433 (0.288, 0.653)</td></tr>
<tr><td>Sensitivity: 1:1 matching using 11 covariates‡</td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
</table>
Abbreviations: BR = bendamustine + rituximab; CI = confidence interval; HR = hazard ratio, LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab.
† Age, Ann Arbor staging, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, LDH levels, Neutropenia, Anaemia status. ‡ Age, Ann Arbor staging, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, LDH levels, Neutropenia, Anaemia status, ECOG, Early relapse.</td></tr>
</table>

	In the post-hoc analysis a sensitivity model that included an adjustment on a reduced set of factors (Number of prior lines of therapy, Refractoriness to last therapy line, primary refractoriness, prior ASCT and age) added an adjustment on ECOG status and provided results similar to the base case results as presented in the table below. Table 39. Post-hoc RE-MIND2 results using 1:1 matching using 9 and 6 covariates

	TAFA+LEN v. POLA+BR: HR (95%CI)	
	OS	PFS
Base case: 1:1 matching using 9 covariates with multiple imputation †	[redacted]	[redacted]
Sensitivity: 1:1 matching using 6 covariates without multiple imputation ‡	0.441 (0.203, 0.956)	0.482 (0.217, 1.073)

Abbreviations: CI = confidence interval; HR = hazard ratio, LEN = lenalidomide; OS = overall survival; PFS = progression-free survival; POLA+BR = polatuzumab + bendamustine + rituximab; TAFA = tafasitamab.

† Age, Ann Arbor staging, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, LDH levels, Neutropenia, Anaemia status. ‡ Age, Refractoriness to last therapy line, Number of prior lines of therapy, Primary refractoriness, Treatment with prior ASCT, ECOG, Early relapse.

	Although no adjustment was possible on IPI in either the primary or the post-hoc analyses base case, adjustments were made on 3 of its 5 individual components (age, Ann Arbor staging, LDH levels). Hence it is expected that the bias accrued by potential unobserved difference on IPI would be limited. Of note, in the post-hoc analyses of RE-MIND2 multiple imputation technique were used to infer missing values on some of the factors included in the population adjustment.
Q7: What checks were conducted to assess overlap?	The overlap assumption was assessed through the computation of standardised mean differences in key factors included in the population adjustment prior to the population balancing. In the primary analyses of RE-MIND2 no concerns were raised on population overlap for the analyses versus BR and R-GemOx, as numerous patients were enrolled in these observational cohorts. Unfortunately, this was not the case in the observational cohort treated with POLA+BR with patients observed to be worse off compared to L-MIND enrolled patients. As a result, due to this lack of overlap in the populations the post-hoc analyses were conducted by matching L-MIND patients to POLA+BR treated patients as no overlap concerns were raised in the reverse matching. It should be noted however that the reverse matching led to a departure from the L-MIND original population.
Q8: Has balancing of the covariates been checked after matching and propensity score methods?	Balancing of the cohort was checked following the population adjustment through the monitoring of SMD. None of the variables included in the population adjustment were imbalanced after the matching using a threshold of 0.25 on the SMD to assess differences as suggested by the NICE TSD DSU 17 following the population-matching in the RE-MIND2 primary analyses. In the post-hoc analyses the use of multiple imputation did not allow to assess in the SMD in the base case model. However, sensitivity models that use 6 covariates in the 1:1 matching showed good balance in populations and had results similar to the base case model.
Q9: Is the propensity score function sufficiently flexible?	Propensity score was model using logistic regression model excluding interactions or squared terms as good balancing of the populations was achieved with a model including only main effects.

Q10: Are potential IVs excluded from the set of conditioning variables?	No concerns were raised on the inclusion of potential instrumental variable in the conditioning sets. All variables included in the conditional sets were observed prior to treatment initiation.
Q11: Are there data quality issues	Some limitations of the RE-MIND2 analyses arise from the difference in the nature of the source of evidence: while the L-MIND study was an interventional prospective study, the RE-MIND2 study was a retrospective observational study. Therefore, it is possible that some bias could be introduced in the comparisons due to differences in designs with some potential differences in treatment adherence or monitoring of the patients. In addition, although outcomes were defined similarly across sources of evidence, differences in patients monitoring may have affected the comparisons of surrogate endpoints such as PFS. The direction of the expected bias is unclear but might be conservative as treatment from the observational cohorts could be favoured, as patients from the L-MIND study were thoroughly followed using a defined assessment schedule. These two limitations are shared by any comparative efficacy analysis employing prospective and retrospective data. It's important to note that investigator-assessed efficacy endpoints from the L-MIND study were used in the comparison against efficacy endpoints investigated in the observational cohorts from RE-MIND2. Differences in follow-up times were observed for patients treated with TAFA+LEN (median 31.8 months) and patients from the observational cohort treated with POLA+BR (median 14.6 months) which might confound the results of the OS comparisons. As discussed earlier, data missingness prevented from using IPI in the population adjustment in either the RE-MIND2 primary analyses or post-hoc analyses. However, it should be noted that most of the individual components from the IPI score were included in the population adjustment (age, Ann Arbor stage, LDH levels). In addition, due to missingness on other factors multiple imputation was used on the propensity score in the for the 1:1 matching in the RE-MIND2 post-hoc analyses. Finally, it can be noted that due to the low accrual of the RE-MIND2 study in patients treated with POLA+BR, not all patients from the L-MIND study could be matched with a control patient. As a result, the relative efficacy analyses were conducted in a population that differed from the original L-MIND population. However, the CEM included additional adjustments to tackle this difference.
Question 12: For Nearest Neighbour matching: Has bias adjustment been conducted if more than one variable was included?	To our knowledge, the correction from Abadie and Imbens is appropriate for matching on more than one continuous covariate. This was not the case in these analyses where the only continuous covariate was age.
Q13: Is the choice of replacement (with/without) reasonable?	Matching without replacement was performed in the primary and post-hoc RE-MIND2 analyses.
Q14: Is the choice of the number of matches/caliper matching/radius matching reasonable?	The choice of the number of matches in the primary analyses of the RE-MIND2 study was driven by the extent of the population of control patients included in the observational cohorts and on the magnitude of the SMD after each step of the matching: 1:1 matching was attempted at first. If following the 1:1 matching SMD for all covariates included was ≤0.2 and the size of the observational cohorts was more than double the size of the L-MIND population 1:2 matching was attempted. If SMD for covariates included was <0.2 after 1:2 matching, and the size of the observational cohorts was more than tripe the size of the L-MIND population 1:3

	matching was attempted. If this was not the case patients included in the 1:1 matching were selected for the analysis set. Similar steps were repeated while attempting 1:3 and 1:4 matching. In the case were SMD > 0.2 for any of the covariates following 1:1 matching, 1:1 matching was re-attempted using up to 9 different seeds. If none of these seeds allowed to reach SMD≤0.2 for all covariates, the biggest caliper ensuring SMD ≤0.2 was used following Austin 2011. The caliper constant was chosen between values ranging from 2.5 to 0.01 using 0.01 decrements and the caliper width was calculated as: $$Caliper\ width = caliper\ contant\ \times SD_{logit\ ePS}$$ Following achievement of SMD≤0.2 for all covariates after the use of a caliper in 1:1 matching, 1:2, 1:3 and 1:4 matching were attempted as described above.

Abbreviations: ASCT = autologous stem cell transplant; BR = bendamustine and rituximab; CEM = cost-effectiveness model; CSR = clinical study report; DSU = Decision Support Unit; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPI = International Prognostic Index; IPT = inverse probability of treatment; IPTW = inverse probability of treatment weighting; LDH = lactate dehydrogenase; NICE = National Institute for Health and Care Excellence; OS = pverall survival; PFS = progression-free survival; POLA+BR = polatuzumab, bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaliplatin; SMD = standardised mean difference; TAFA+LEN = tafasitamab and lenalidomide; TSD = Technical Support Document.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

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

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- 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	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 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.	Incyte Corporation: £20,000 (support for information and education activities) Celgene: £35,000 (support for information and education activities; coronavirus funding) Kyowa Kirin: £16,800 (support for information and education activities) Roche Products: £20,000 (support for information and education activities)

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 have used information from UK-respondents to the Lymphoma Coalition's 2020 Global Patient Survey, which seeks to understand patient experience in lymphomas as well as the impact of treatment and care. A total of 679 people from the UK responded to the patient survey, 8% of whom had DLBCL. An additional 64 people responded to the caregiver survey, 11% of whom cared for a person with DLBCL. We also sent a survey to our network of patients and carers asking about specifically about their experience of current treatment for relapsed and refractory DLBCL and their opinions on tafasitamab + lenalidomide, with particular emphasis on quality of life. We received four responses from patients with relapsed or refractory DLBCL who had had at least two previous treatments, whose experiences we have included in this submission. We have also included information based on our prior experience with patients with relapsed or refractory DLBCL.
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 an aggressive lymphoma. Most people with DLBCL first notice rapidly-enlarging lumps, often in the neck, armpit or groin but they can be in the chest or abdomen. Symptoms can vary depending on where the lymphoma is growing. Systemic symptoms are common, including fevers, night sweats, unexplained weight loss, fatigue, loss of appetite and severe itching. Symptoms of DLBCL usually develop rapidly and progress quickly. Patients can be extremely unwell for many months. One patient told us, "For me, progression was very fast and it was a traumatic experience for me and my family."

	DLBCL is treated with the aim of cure. However, up to 45% of patients are refractory to treatment or relapse after initial treatment. The prognosis for patients with relapsed or refractory DLBCL is poor, with median survival of around a year. During treatment, patients often spend many weeks in hospital, isolated from family and friends. Side effects of intensive chemotherapy, such as sickness, diarrhoea, hair loss and neutropenia can be extremely debilitating, affecting many aspects of life. Most patients are unable to carry on working during treatment. Spending many weeks in hospital can have a detrimental effect on the patient and the family as a whole. Even after successful treatment, the relief of getting back into some kind of normal life is marred by the anxiety of relapse. Late effects of treatment are also a psychological and physical challenge. One patient explained, “The biggest struggle is the recovery. I am extremely disabled by fatigue and bone/muscle pain right down into my hands and fingers. There are good days but I pay for over exerting my body for days afterwards. I have to be patient. I have after all had ‘an enormous amount of chemotherapy’.” Another told us, “In the worst times reading, concentration on anything at all has just gone out the window. I thought I had weathered it fairly well but looking back I have to accept that I became short tempered, easily agitated, and morose during any chemo treatment.” It can take months or even years after treatment to recover. Some side effects, especially fatigue and peripheral neuropathy, can last for many years and have a significant impact on quality of life. Younger patients may experience fertility issues or early menopause. Patients report feeling “tired all the time” and a constant lack of energy making everything seem an effort. Younger patients may experience fertility issues or early menopause. Others have told us of repeated infections requiring hospital admission. The psychological impact of the diagnosis is enormous. Patients report experiencing insomnia, anxiety and a ‘constant fear of dying’. One patient told us, “Second time round my anxiety was high during the early weeks; I struggled to sleep and felt very low.” People with DLBCL can be very ill and require a huge amount of support. Caring for someone with DLBCL is emotionally challenging and time-consuming. Some carers take significant amounts of time off work to transport their loved one to-and-from hospital, care for dependants, collect medications and visit hospital.

	Financially, it can be hard to cope. One patient told us, “I have had to give up work at present due to an increased risk of not coping with infection. I need to return to work eventually to honour previous financial commitments.” Another said, “Luckily this has all happened after my retirement so there has been no financial penalty to me. However it has caused me to question how those in work manage.” Yet another explained, “I wasn’t able to work because I had so many hospital appointments and felt so dreadful. I was off work for 12 months and went back on a phased return. I was lucky to have a supportive employer, however my sick pay was insufficient towards the end of that period, and we had to take a mortgage payment holiday. We were supported financially by family, and a grant from McMillan. I was able to return to work full time two years after my last treatment.” Support of loved ones is very important but comes with its own challenges. They often feel helpless, anxious and scared. Patients report that it is difficult for loved ones to understand what they are going through. One said, “It can be, and often was, very emotional for my wife but we deal with things as they occur.” Another told us that the effect on their family was “simply emotionally draining for months at a time.” Another said, “My family were very frightened, sometimes felt helpless, especially when I was poorly or emotional and they lived on good news.” Yet another explained, “It was a time of anguish and worry for my family, there were so many unknowns. A deep faith and trust in those caring for me coupled with the support of close family and friends was invaluable.” One patient described the impact of her diagnosis and treatment on her family: “My family were all very affected by the separation due to periods of treatment in hospital, and the anxiety and worry caused by the prospect of me not recovering… It had a long term effect on my children. It was very hard for them to see me going through treatment and have to visit me in hospital. My husband had to support the children, care for the dog, house and keep working, as well as visit me and care for me when I was home. His employers were not very supportive and this meant he was often exhausted.”

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most people with DLBCL are treated with chemo-immunotherapy, sometimes followed by radiotherapy. High-dose chemotherapy regimens might be used. For relapsed or refractory DLBCL, salvage chemotherapy followed by stem cell transplant is the most common treatment option. Treatment is very intense and some people are not able to tolerate it. People who are not able to have a stem cell transplant, might be offered polatuzumab vedotin with bendamustine and rituximab, a different chemo-immunotherapy regimen or a targeted drug as part of a clinical trial. People who experience a subsequent relapse might be eligible to have CAR T-cell therapy. These treatments are very intensive and can have a huge impact on patients. Many people are not able to tolerate them. Current treatment pathways are also associated with significant side effects and late effects that impact on patients' quality of life. One patient explained, “My first treatment (which was part of a trial) was very intensive. It involved inpatient treatment to receive high dose chemo. I was in hospital for about 10 weeks in total, with recovery time between cycles at home. I had significant side effects, including very bad sickness, and the time spent in hospital meant I lost muscle and was in very poor shape physically when I finished treatment. I couldn’t walk or stand for very long and needed to use a wheelchair at times… I really struggled to eat anything, particularly hospital food. This made me weaker and I needed the support of a dietician. Recovery from chemo took a lot longer than I expected, and I worked to rebuild my strength and fitness and recover from the trauma... The fatigue remained for several years. Other symptoms included brain fog and memory problems, and ongoing bowel issues. Another patient told us, “R/CHOP, BEAM (particularly) and pixantrone left me with no energy or enthusiasm for anything. No appetite, no enthusiasm for anything. Worst of all beyond description was the lack of control; over bodily functions which would come over quickly and leave just an overwhelming feeling debasement.” Another told us, “I continue to suffer with cytopenia which is being supported with growth factors three times a week… Due to the risk of infection I can not return to clinical dentistry as a specialist endodontist.” Another patient reported permanent side effects of loss of taste and smell after two courses of

	immunochemotherapy and radiotherapy.
8. Is there an unmet need for patients with this condition?	Patients feel there is an unmet need for more effective treatments for relapsed or refractory DLBCL, with a greater prospect of a durable response. Patients also express the need for less demanding treatments with fewer side effects.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients believe the main advantage of tafasitamab + lenalidomide is that it provides a lifeline for people who do not have any other options. As such, it provides hope and is potentially life-extending or even life-saving. It has the potential to allow patients more time with their family and friends. Patients said: • "I think it would provide huge advantage to those unable or unwilling to have SCT because it is likely to have a positive impact on their disease." • "If previous treatments have not been successful, then it could well be considered." • "If this treatment is a possible therapy where other avenues have been closed, patients will welcome this, despite the risk of the side effects." The outpatient administration was also viewed as an advantage. One patient explained, "Having treatment once a week, and/or taking tablets rather than having to spend time in hospital means families are less disrupted, and people with lymphoma can spend time with their families and friends. Being treated in this way would allow patients to continue to maintain more of a normal life, and keep well mentally and physically through access to exercise and the outdoors. Whilst I would always want to have the treatment that gave me the best chance of long term survival, any home-based treatment would have a significant, positive effect on the quality of life, for patients and their families."

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, patients are concerned about the potential side effects of tafasitamab + lenalidomide. However, they acknowledge that these need to be offset against the potential benefits. One said, "Living with neutropenia means you need to be careful with what you eat and with hygiene and cleanliness at home. The risk of neutropenic sepsis is a worry and can result in time spent in hospital for treatment. Having to take drugs daily or weekly for a long period of time can affect mental health. But on balance I don't think these are hugely significant, especially if the alternative is palliative care." Another patient commented, "The side effects… of pneumonia or other problems, would not be very welcome, especially when the patient's health is already at a low point."
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 feel this might particularly benefit older patients who are unable to tolerate the intensive chemotherapy required as part of a stem cell transplant.

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:

- Relapsed or refractory DLBCL has a significant impact on the quality of life of both patients and their families and carers. The psychological, social and economic impact of the disease is considerable.
- Patients with relapsed or refractory DLBCL have a poor prognosis with a median survival of around 1 year. Any new treatment offers a potential lifeline.

- Current treatments for relapsed or refractory DLBCL are very intensive, requiring long stays in hospital away from the support of family and friends and incurring serious side effects and late effects. Many patients are not able to tolerate the intensive regimens currently available, and these people have very limited treatment options.
- Tafasitamab + lenalidomide has the potential to improve outcomes in this challenging population.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ 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.)	Main aim: to delay progression. It may provide a durable response (so patients can be bridged to another form of consolidation) or potentially be curative in a cohort of patient The patient cohort 'for whom haematopoietic stem cell transplant is not suitable'. This encompasses 3 main groups of patients: 1. Patient who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant or CAR-T cell therapy 2. Patients who have already had a stem cell transplant or CAR-T cell therapy and have relapsed following it 3. Patients who are young and fit enough for a stem cell transplant and CAR-T cell therapy, but their disease is not in a good enough remission to proceed with this
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A clinically significant treatment response would be reduction in tumour size (CR/PR/ORR) Possible sustained resolution of the tumour so it's not detectable (Complete Response (CR)). Partial responses in DLBCL are rarely sustainable. Prolongation of survival (PFS/OS measured in months)

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there is clearly an unmet need for patients as presently palliative approaches are adopted, or regimens with poor outcome or unacceptable toxicities.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients who are not fit for transplant are offered low intensity chemotherapy regimens (sometimes with rituximab however there is no standard of care. The following comparators can be given with or without rituximab (depending on amount received by patient prior) • Rituximab Bendamustine and Polatuzumab (R-BP) • R-GemOx • R-Gem • R-P-MitCEBO • Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines) • (R-)DECC • PEP-C • R-COCKLE -

	For populations (2) and (3) above there is the option of CAR-T cells (recently introduced in UK in 2019). Benda+R+pola provides a bridging therapy to CAR T-cell therapy (presently only patients PS 0-1 are eligible for CAR-T therapy so this will be a small cohort) and this treatment modality may be used in a similar setting. The regimen may be used as part of a strategy to bridge to a potentially curative therapy such as allogeneic transplant – again this will be a small cohort
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH Guidelines 2013 (British Journal of Haematology): presently being revised. There are also ESMO guidelines and NCCN guidelines.
• 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.)	It has not well defined as this cohort of patients are hard to treat as there have been poor clinical options. It is being redefined as there are a number of newer clinical options (CAR-T therapy, Rituximab Bendamustine and Polatuzumab (R-BP) etc) Since the introduction of CAR-T therapy in UK (potentially for cohort 2 and 3) in 2019 the national CAR-T panel has been set up and this is being reviewed as it evolves.
• What impact would the technology have on the current pathway of care?	It could dramatically change patient care as it would offer another therapeutic option for a cohort of patients where the options are poor and limited and durable remissions are uncommon.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – in the same way. It involves immunotherapy and Lymphoma doctors and Haem-Onc departments have a wealth of experience in this field. Lenalidomide is an oral agent used widely in the UK for lymphoma patients (R/R Follicular lymphoma) The IV drug will be delivered in the chemotherapy day unit. Tafasitamab is a monoclonal antibody and would be a straightforward drug to administer as our units are used to delivering such therapies to our Lymphoma patients. The sustained period of administration of tafasitamab to patients until disease progression if less common with present regimens.
• How does healthcare resource use differ between the technology and current care?	The lymphoma treating community have amended their approach to this group of patients. The introduction of Rituximab-Bendamustine -Polatuzumab (R-BP) and CAR-T cell therapy in the last 3 years has transformed the approach to treating this patient group. The patient treatment pathway has been revised accordingly. Patients generally remain under consultant haematology / oncology care as well as receiving active palliative care (possible use of palliative radiotherapy for symptoms, possible use of steroids
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care as outlined above
• What investment is needed to introduce the technology? (For	Oral Lenalidamide is commonly prescribed across haematology units in the UK as it is a well-accepted treatment for a different lymphoma: follicular lymphoma.

example, for facilities, equipment, or training.)	Tafasitimab will be delivered in the chemotherapy day unit as are other monoclonal antibodies with monitoring of patients as is standard practice. In the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide for patients with relapsed or refractory diffuse large B-cell lymphoma patients received 28-day cycles of tafasitamab (12 mg/kg intravenously), once weekly during cycles 1-3, then every 2 weeks during cycles 4-12. Lenalidomide (25 mg orally) was administered on days 1-21 of cycles 1-12. After cycle 12, progression-free patients received tafasitamab every 2 weeks until disease progression. Although the prolonged nature of treatment duration for some patients would have an impact on our day units, the patient population is not common so we would expect the absolute impact to be modest.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, we would expect the technology to provide clinically meaningful benefits compared with current care. Antibody-drug conjugates have been applied successfully to high grade B-cell lymphomas. The data presented has shown impressive responses, durable in a group of patients. These 2 factors combined suggest this does have the potential to have a substantial impact on health-related benefits and is consistent with a step-change in the management of this condition. It is innovative in its potential in a population with a poor outcome and limited effective treatment options. Durable remissions are seen in a proportion of patients.
• Do you expect the technology to increase length of life more than current care?	Potentially it is another option to provide durable responses and provide prolonged PFS and OS in this subgroup of patients. The updated outcome published by Duell et al, in Haematologica in September 2021showed that after ≥35 months' follow-up:

	the objective response rate was 57.5% (n=46/80), including a complete response in 40.0% of patients (n=32/80) and a partial response in 17.5% of patients (n=14/80). The median duration of response was 43.9 months (95% confidence interval [95% CI]: 26.1-not reached) the median overall survival was 33.5 months (95% CI: 18.3-not reached) and the median progression-free survival was 11.6 months (95% CI: 6.3-45.7).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – by improving lymphoma-related symptoms. And an out-patient/day unit-delivered therapy
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Overall response and CR rates were consistent regardless of refractoriness in patient subgroups. Although subgroup analyses did show differences in PFS and OS, the nature of such analysis is hypothesis generating and firm conclusions as to whether some groups benefit are at present not possible to draw.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	No – the populations as defined above, `It has implications for patients (attending day unit as the tafasitamab is given intravenously continuously until progression whilst presently alternatives may be delivered orally or for shorter defined periods.

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.)	However, although the prolonged nature of treatment duration for some patients would have an impact on our day units, the patient population is not common so we would expect the absolute impact to be modest. Healthcare professionals will monitorside effects (cytopenias) and potential infective complications (but latter exists for oral therapies and other combinations). Lenalidamide/Tafasitamab has been associated with neutropenia and leukopenia and infectious complications so appropriate prophylaxis should be given (which is standard practice). Monitoring patients closely recommended when they have side effects
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stop treatment if progressive disease or unacceptable side effects
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	Yes – we expect this technology will result in health-related benefits and some may not be included in the quality-adjusted life year (QALY) calculation

quality-adjusted life year (QALY) calculation?	
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, we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and it will improve the way that current need is met. Patients have prolonged PFS and OS – especially if achieve CR or less prior treatments. A cohort of patients may be bridged to a curative line of therapy (CAR-T or allogeneic stem cell transplantation).
• Is the technology a 'step-change' in the management of the condition?	Yes, this is another part of 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 – the unmet need of patients who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant or CAR-T cell therapy where other options are palliative. Also bridging therapy to potentially curative therapies as outlined above.

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?	infectious complications so appropriate prophylaxis should be given. Review the need for thromboprophylaxis
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – as there is no standard comparator. The trial included patients with R/R DLBCL They had no more than 3 prior lines (although patients with R/R DLBCL rarely receive > 3 lines of therapy due to the aggressive nature of the disease)
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – outcomes important to patients involve reduction in tumour size (and associated reduction/resolution of associated symptoms). Prolongation of survival (PFS/OS measured in months).

	These were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• 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	No

appraisal guidance [TA306 and TA649]?	
21. How do data on real-world experience compare with the trial data?	
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.	N/A
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Improvement of tumour-associated symptoms
- Prolongation of progression-related survival
- prolongation of overall survival
- Well tolerated (low incidence of severe or persistent symptoms)
- A treatment approach for which there is no accepted standard of care

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Heath White contributed to the writing of this report.

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.

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Contributions of authors

Susan O'Meara and Robert Wolff acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Ayesha Sajjad, Pim Wetzelaer, Gimon de Graaf, Ingelin Kvamme, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance on the health economics part of the project. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACVBP	Doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisone
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AIC	Akaike information criterion
AiC	Academic in confidence
AICC	Corrected Akaike information criterion
ALT	Alanine transaminase
AP	Alkaline phosphatase
ASCT	Autologous stem cell transplant
ASHAP	Doxorubicin, solumedrol, cytarabine, and platinum
AST	Aspartate aminotransferase
ATE	Average treatment effect
ATT	Average treatment effect on the treated
AWMSG	All Wales Medicines Strategy Group
BC	Base-case
BCL	B-cell lymphoma
BEAM	Carmustine, etoposide, cytarabine, and melphalan
BENDA	Bendamustine
BIC	Bayesian information criterion
BL	Burkitt's lymphoma
BNF	British National Formulary
BR	Rituximab in combination with bendamustine
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor T-cell therapy
CASP	Critical Appraisal Skills Programme
CD	Cluster of differentiation;
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CEOP	Cyclophosphamide, etoposide, vincristine, prednisone
CEPP	Cyclophosphamide, etoposide, prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CiC	Commercial in confidence
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRR	Complete response rate
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DA EPOCH	Dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
DA EPOCH R	Dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab
DARE	Database of Abstracts of Reviews of Effects
DHAOx	Dexamethasone, cisplatin, oxaliplatin
DHAP	Dexamethasone, cisplatin, cytarabine

DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EBV	Epstein Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	EuroQoL-5 Dimensions, 3 levels
EQ-5D-5L	EuroQoL-5 Dimensions, 5 levels
ERG	Evidence Review Group
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
ESHPM	Erasmus School of Health Policy & Management
ESMO	European Society for Medical Oncology
EU	European Union
EUR	Erasmus University Rotterdam
FACT G	Functional Assessment of Cancer Therapy General
FACT Lym	Functional Assessment of Cancer Treatment Lymphoma;
FAS	Full analysis set
FAD	Final appraisal document
FDA	Food and Drug Administration
GDP	Gemcitabine, dexamethasone, cisplatin or carboplatin
GEP	Gastroenteropancreatic
GemOx	Gemcitabine, oxaliplatin
HAS	Haute Autorité de Santé
HDC	High-dose chemotherapy
HIV	Human immunodefficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HSE	Health Survey for England
HTA	Health technology assessment
HUI	Health utility index
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental cost effectiveness ratio
ICER	Institute for Clinical and Economic Review
IEV	Ifosfamide, etoposide, epirubicin
IGEV	Ifosfamide, gemcitabine, vinorelbine, prednisone
ImiD	Immunomodulatory drug
iMTA	Institute for Medical Technology Assessment
INAHTA	International Network of Agencies for Health Technology Assessment
INV	Investigator assessed
IPD	Individual participant data
IPI	International Prognostic Index
IPW	Inverse probability weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRC	Independent radiology/clinical review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat

IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LVEF	Left ventricular ejection fraction
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
MINE	Mesna, ifosfamide, mitoxantrone, etoposide
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NK	Natural killer
NL	The Netherlands
NN	Nearest-neighbour
NR	Not reached
NR	Not reported
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
p.o.	Taken orally
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PIM	Promising Innovative Medicines
pola-BR	Polatuzumab vedotin with bendamustine and rituximab
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PT	Preferred term
QALY	Quality-adjusted life year
R2	Rituximab and lenalidomide
R2 CHOP	Lenalidomide plus rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone
RA	Regression adjustment
R-BENDA	Rituximab + bendamustine
RCT	Randomised controlled trial
R-DECC	Rituximab, dexamethasone, etoposide, chlorambucil, lomustine
R-Gem	Rituximab in combination with gemcitabine
R-GemOx	Rituximab in combination with gemcitabine and oxaliplatin
R-P-MitCEBO	Rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine
R-pola	Rituximab and polatuzamab vedotin
R/R	Relapsed or refractory
SAE	Serious adverse event

SCT	Stem cell transplant
SE	Standard error
SF 6D	Short Form Six Dimension
SF12	12 Item Short Form Health Survey
SF36	36 Item Short Form Health Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean differences
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology assessment
TAFA	Tafasitamab
TEAE	Treatment emergent adverse events
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTP	Time to progression
Tx disc	Treatment discontinuation
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USA	United States of America
USD	United States dollar
WHO	World Health Organization

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness (CE). Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID3795	Summary of issue	Report Section
1	The company's selection of comparators is narrower than that shown in the NICE final scope, i.e. R-Gem, R-P-MitCEBO, (R-)DECC, Pixantrone and BSC were not included in the CS	2.3
2	The SLR of clinical effectiveness evidence was not conducted according to best recommended practice. Problems with the search and study selection might mean that potentially relevant studies might have been missed. Furthermore, there were issues regarding data extraction and quality assessment	3.1
3	Questionable validity of ITCs and a number of potentially relevant analyses have not been provided	3.3 and 3.4
4	OS/PFS parametric extrapolations lack clinical validity	4.2.6.9, 5.2 and 5.3
5	Cost effectiveness analyses should be based on lenalidomide list price	4.2.9.1
6	The supporting literature for the company's claim for end-of-life criteria had limited relevance to the population in the submission	7

BSC = best supportive care; CS = company submission; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; R-DECC = rituximab, dexamethasone, etoposide, chlorambucil, lomustine; R-Gem = rituximab in combination with gemcitabine; R-P-MitCEBO = rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine; SLR = systematic literature review

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the following:

- As detailed in Section 4.2.6.9, for ERG preferred different assumptions regarding modelling overall survival (OS; for two of the comparators) and progression-free survival (PFS; for the intervention and two of the comparators).

- Lenalidomide list price was assumed for the CE analyses (instead of a [redacted]).
- Excluding chimeric antigen receptor T-cell therapy (CAR-T) as subsequent treatment.
- As detailed in Section 4.2.9.4, different assumptions regarding the duration of subsequent treatments.
- As detailed in Section 4.2.9.5.2, different assumptions regarding disease management costs after disease progression.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (OS) 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, the new technology is modelled to affect QALYs by:

- Increasing the progression-free and reducing the post-progression health state occupancy.
- The decrease in utility due to adverse events associated to the new technology is minor.

Overall, the technology is modelled to affect costs by:

- Its higher unit price compared to current treatments.
- Increasing administration and monitoring costs.
- Decreasing costs associated to disease management and subsequent treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- Alternative overall and progression-free survival (PFS) assumptions.
- Alternative time-to-treatment-discontinuation assumptions.
- Alternative utility values.
- Including CAR-T as subsequent therapy.
- Assuming equal disease management costs for all treatments.

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, the selection of comparators in the CS is narrower than in the NICE final scope (Table 1.2).

Table 1.2: Key issue 1. Selection of comparators in CS narrower than NICE final scope

Report Section	**2.3**
Description of issue and why the ERG has identified it as important	The company's selection of comparators is narrower than that shown in the NICE final scope. The NICE final scope listed R-Gem, R-GemOx, BR, pola-BR, R-P-MitCEBO, (R-)DECC, Pixantrone and BSC as comparators whilst the company restricted their selection to R-GemOx, BR and Pola-BR. The alignment between the company's selection and drugs available in clinical practice in England and Wales was not clear to the ERG. By way of clarification, the company explained that their choices were informed by three interviews with UK clinical experts however the exact methods used for elicitation of advice are not clear.

Report Section	2.3
	The ERG remains unclear about whether the company's selection of comparators matches what would be encountered in clinical practice in England and Wales.
What alternative approach has the ERG suggested?	It would have been preferable to see an estimation based on all comparators mentioned in the NICE final scope. However, if some of these are not relevant to clinical practice in England and Wales, it would be useful to see a more transparent account of the interviews with the clinical experts so that the underlying advice about each excluded product is clearer.
What is the expected effect on the cost effectiveness estimates?	The impact of the narrow choice of comparators on clinical and cost effectiveness estimates remains uncertain.
What additional evidence or analyses might help to resolve this key issue?	Estimation based on more (or all) comparators would be helpful, however it may be that evidence is not available for the relevant population. If such evidence is not available, more detailed information about the advice underpinning the company's choices would be useful so that the selection can be more easily understood.
BR = rituximab in combination with bendamustine; BSC = best supportive care; CS = company submission; ERG = Evidence Review Group; NICE = National Institute of Health and Care Excellence; pola-BR = Polatuzumab vedotin with bendamustine and rituximab; R-DECC = rituximab, dexamethasone, etoposide, chlorambucil, lomustine; R-Gem = rituximab in combination with gemcitabine; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; R-P-MitCEBO = rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Regarding the clinical effectiveness evidence, the ERG identified two key issues, namely:

1. That the conduct of the systematic literature review (SLR) of clinical effectiveness evidence does not follow current best practice (see Table 1.3), and
2. The indirect treatment comparisons reported in the CS have questionable validity (see Table 1.4).

Table 1.3: Key issue 2. Conduct of the systematic literature review of clinical effectiveness evidence not according to best recommended practice

Report Section	3.1
Description of issue and why the ERG has identified it as important	The SLR of clinical effectiveness evidence was not conducted according to best recommended practice. Problems with the search (omission of some intervention and comparator terms plus the date restriction) and study selection (language and date restrictions) methods may mean that some relevant studies were missed. Data extraction was performed by one reviewer and checked by a second reviewer. Dual, independent data extraction is regarded as best practice, at least for outcome data. An inappropriate checklist was used to assess the methodological quality of the L-MIND (MOR208C203) and MOR208C201 studies. This necessitated the ERG carrying out further work, to assess the two studies using an appropriate tool.

Report Section	3.1
What alternative approach has the ERG suggested?	The search strategy should include all relevant terms for interventions and comparators and the date restriction should be broadened or lifted altogether unless a firm rationale can be provided for restriction. Study selection should allow for inclusion of reports in all languages. The date restriction needs to be clarified. If it is correct, a rationale is required. The L-MIND (MOR208C203) and MOR208C201 studies should have been assessed using a methodological quality checklist more suited to single-arm trials. The ERG has now done this.
What is the expected effect on the cost effectiveness estimates?	This is difficult to quantify but the possibility of the impact from missing evidence or inaccurate data cannot be discounted.
What additional evidence or analyses might help to resolve this key issue?	A search strategy that includes all relevant intervention and comparator terms; inclusion of studies reported in all languages; no date restriction imposed to the search or study selection or a clear and meaningful rationale for any restriction imposed; assessment of L-MIND (MOR208C203) and MOR208C201 with a suitable methodological quality checklist (the ERG has now done this).
ERG = Evidence Review Group; SLR = systematic literature review.	

Table 1.4: Key issue 3. Questionable validity of ITCs

Report Section	3.3 and 3.4
Description of issue and why the ERG has identified it as important	There is a lack of clarity and variability by comparator in analysis of RE-MIND2, the possibility of bias due to attempts to estimate the ATE, and questionable clinical validity of pola-BR extrapolations.
What alternative approach has the ERG suggested?	The MAIC has been selected instead of analysis of RE-MIND2 for the comparison with pola-BR in the CEA. The ERG would also like full reporting of all potentially suitable analyses, including the use of IPW (using propensity scores, and overlap weights) and RA for all relevant comparators. This should be accompanied by an assessment of overlap, including by use of SMDs as well as validation by clinical expert opinion and appropriate external data.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness is very difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The ERG recommends full reporting of all potentially suitable analyses, including the use of IPW (using propensity scores, and overlap weights) and RA for all relevant comparators. This should be accompanied by an assessment of overlap, including by use of SMDs as well as validation by clinical expert opinion and appropriate external data.
ATE = average treatment effect; CEA = cost effectiveness analysis; ERG = Evidence Review Group; IPW = inverse probability weighting; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect	

Report Section	3.3 and 3.4
comparison; pola-BR = polatuzumab vedotin with bendamustine and rituximab; RA = regression adjustment; SMD = standardised mean differences	

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness (CE) evidence review conclusions can be found in Section 6.4 of this report. The company's CE results are presented in Section 5, the ERG's summary and detailed critique are in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the CE evidence are discussed in Tables 1.5 and 1.6.

Table 1.5: Key issue 4: OS/PFS parametric extrapolations lack clinical validity

Report Section	4.2.6.9, 5.2 and 5.3
Description of issue and why the ERG has identified it as important	The ERG considered that there are issues with the validity of the OS/PFS extrapolations, especially (but not exclusively) for the pola-BR arm, which in turn resulted in cost effectiveness results very different to those obtained for example in TA649.
What alternative approach has the ERG suggested?	The ERG defined a new base-case with the purpose of mitigating some of the validation issues. However, it should be emphasised that this ERG "base-case" does not represent a best-case but a least-worse. A number of violations are still present in this ERG "base-case" that cannot be resolved with the current available evidence.
What is the expected effect on the cost effectiveness estimates?	Results for the pola-BR arm should be broadly in line with those in TA649.
What additional evidence or analyses might help to resolve this key issue?	The root of the problems causing these issues should be carefully re-investigated by the company and, if possible, corrected.
ERG = Evidence Review Group; OS =overall survival; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; TA =Technology Appraisal	

Table 1.6: Key issue 5: Lenalidomide list price should be used in the cost effectiveness analyses

Report Section	4.2.9.1
Description of issue and why the ERG has identified it as important	The company assumed a reduced price for lenalidomide [redacted].
What alternative approach	The ERG prefers to use the current list price for lenalidomide.

Report Section	4.2.9.1
has the ERG suggested ?	
What is the expected effect on the cost effectiveness estimates?	When the list price for lenalidomide is applied (i.e. in isolation of other changes), the pairwise ICERs that result from the company's base-case analysis increased from £[redacted] to £[redacted] vs. pola-BR, from £[redacted] to £[redacted] vs. BR and from £[redacted] to £[redacted] vs. R-GemOx.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is needed.
BR = bendamustine and rituximab; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin	

1.6 Other key issues: summary of the ERG's view

The ERG identified the evidence supporting the end-of-life criteria to have limited relevance to the population in the submission, see Table 1.7.

Table 1.7: Key issue 6. Evidence supporting the end-of-life criteria with limited relevance to the population in the submission

Report Section	7
Description of issue and why the ERG has identified it as important	The supporting literature for the company's claim for end-of-life criteria had limited relevance to the population in the submission. The references cited in support of the life expectancy estimates in patients with R/R DLBCL are of poor quality or limited relevance because of some participants being eligible for ASCT.
What alternative approach has the ERG suggested?	The ERG suggests that the company obtain more relevant evidence through targeted literature searches or by seeking statistics on life expectancy for relevant populations from UK-based registries of cancer patients.

Report Section	7
What is the expected effect on the cost effectiveness estimates?	Currently, there is uncertainty in terms of informing the ICER for end-of-life criteria.
What additional evidence or analyses might help to resolve this key issue?	The ERG would like to see citation of research literature that is more relevant and/or statistics from UK-based registries of cancer patients in order to better inform the estimates about life expectancy for patients with R/R DLBCL.
ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; R/R = relapsed or refractory; UK = United Kingdom	

1.7 Summary of the ERG's view

Table 1.8 summarises the pairwise ICERs the comparisons tafasitamab (TAFA) + lenalidomide (LEN) vs. polatuzumab vedotin with bendamustine and rituximab (pola-BR), rituximab in combination with bendamustine (BR) and rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) of both the company's and ERG's preferred base-cases, as well as the impact of each ERG assumption change applied individually to the company base-case.

The changes with the largest impact on the results were the assuming a constant hazard ratio from the matching-adjusted indirect comparison to extrapolate OS in the pola-BR arm, assuming a lognormal distribution (based on L-MIND data) to extrapolate PFS in the TAFA+LEN arm, using lenalidomide list price in the CE calculations, excluding CAR-T as subsequent treatment, and assuming the same disease management costs after progression for all treatments.

The full incremental results of the ERG's base-case analysis (not shown in Table 1.8) indicated that [redacted]. The ERG's probabilistic sensitivity analysis results were broadly in line with the deterministic ones, [redacted]. The cost effectiveness acceptability curve indicated that [redacted]. At the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that TAFA+LEN is a cost-effective alternative to the other comparators was [redacted].

The scenario analyses conducted by the ERG indicated that the ICER was reasonably stable for alternative choices of TAFA+LEN OS extrapolations. Results based on the alternative OS assumptions for pola-BR showed large differences with respect to the ERG base-case with QALYs varying from 1.16 to 1.47, values below what is expected from for example TA649. Most of the PFS extrapolations for TAFA+LEN and pola-BR seem highly implausible but overall, PFS assumptions do not seem to affect the ICER as much as OS. Time to treatment discontinuation assumptions for TAFA and LEN separately, or TAFA+LEN combined, can have a substantial impact on the total costs for the TAFA+LEN arm. The remaining scenarios had a moderate impact on the ICERs. From these, those that had the largest impact on the ICERs were assuming utility values as in TA567 (decreased all ICERs by approximately £[redacted]), including CAR-T as subsequent therapy (decreased the ICER for the comparison vs. pola-BR by approximately £[redacted]) and assuming disease management costs for all arms equal to those in TAFA+LEN (increased the ICER for the comparison vs. pola-BR by approximately £[redacted]).

Table 1.8: Summary of ERG's base-case results

Preferred assumption	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
Company's base-case (PAS price for TAFA)	[redacted]	[redacted]	[redacted]
+ OS for pola-BR based on MAIC with constant HR	[redacted]	[redacted]	[redacted]
+ PFS for TAFA+LEN using lognormal based on L-MIND	[redacted]	[redacted]	[redacted]
+ PFS for Pola-BR based on MAIC with constant HR	[redacted]	[redacted]	[redacted]
+ OS for BR based on MAIC with constant HR[a]	[redacted]	[redacted]	[redacted]
+ PFS for BR based on MAIC with constant HR			
+ Exclude CAR-T as subsequent treatment	[redacted]	[redacted]	[redacted]
+ 6 cycles of R-GemOx as subsequent treatment	[redacted]	[redacted]	[redacted]
+ Minimum between maximal and median durations for all other subsequent treatments	[redacted]	[redacted]	[redacted]
+ Same disease management costs in PD for all treatments	[redacted]	[redacted]	[redacted]
+ List price for lenalidomide	[redacted]	[redacted]	[redacted]
ERG's preferred base-case	[redacted]	[redacted]	[redacted]

[a] This change is included in '3 + PFS for BR based on MAIC with constant HR' since these changes cannot be applied in isolation.

BC = base-case; BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell therapy; ERG = Evidence Review Group; HR = hazard ratio; ICER = incremental cost effectiveness ratio; LEN = lenalidomide; MAIC = matching-adjusted indirect comparison; OS = overall survival; PAS = Patient Access Scheme; PD = progressed disease; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
Population	Adults with relapsed or refractory DLBCL and who are not eligible for ASCT	Patients with relapsed or refractory DLBCL who are not eligible for ASCT	N/A	The population is in line with the NICE scope
Intervention	Tafasitamab with lenalidomide followed by tafasitamab monotherapy	Tafasitamab (Minjuvi®) in combination with lenalidomide, followed by tafasitamab monotherapy	N/A	The intervention is in line with the NICE scope
Comparator(s)	Established clinical management without tafasitamab which may include: • chemotherapy with or without rituximab: R-GemOx (rituximab, gemcitabine oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine), (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (bendamustine, rituximab)	The following comparators are considered for the submission: • pola-BR • rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) • rituximab in combination with bendamustine (BR)	Although the scope identifies other rituximab and chemotherapy regimens, clinical experts interviewed as part of a UK advisory board confirmed that pola-BR, R-GemOx and BR were the most relevant comparators.	Some of the comparators listed in the NICE scope were addressed, see Section 2.3 for further details.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
	• pixantrone • polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR) • BSC			
Outcomes	The outcome measures to be considered include: • OS • PFS • response rates • adverse effects of treatment • HRQoL	Efficacy endpoints considered in the submission include: • OS • PFS • response rates (e.g. CR, PR) • adverse effects of treatment • HRQoL • time to treatment discontinuation or death (TTD) Safety Endpoints: • AEs • SAEs • AEs leading to a permanent discontinuation of study drug, a dose reduction or dose interruption	N/A. The outcomes specified in the scope are included in the submission, with the addition of TTD endpoint used to evaluate time on treatment for the economic model; additional data, e.g. DoR are also discussed as supportive clinical evidence.	The outcomes reported are in line with the NICE scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY.	NR	NR	The CEAs were conducted according to the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
	• The reference case stipulates 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 being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Other considerations	The availability and cost of biosimilar products should be taken into account.	NR	NR	N/A

Based on Table 1 of CS1 and the NICE final scope2

AE = adverse event; ASCT = autologous stem cell transplant; BSC = best supportive care; BR = rituximab in combination with bendamustine; CEAs = cost effectiveness analysis; CR = complete response; CS = company submission; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; ERG = Evidence Review Group; HRQoL = health related quality of life; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; OS = overall survival; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; PR = partial response; QALY = quality-adjusted life year; R-DECC = rituximab, dexamethasone, etoposide, chlorambucil, lomustine; R-Gem = rituximab in combination with gemcitabine; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; R-P-MitCEBO = rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine; SAE = serious adverse event; TTD = time to treatment discontinuation or death; UK = United Kingdom

2.1 Population

The population defined in the scope is: adults with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and who are not eligible for have autologous stem-cell transplantation.[2] The population in the company submission (CS) is in line with the population defined in the NICE final scope.

The population considered in the CS is also in line with the clinical trial for tafasitamab, the phase II L-MIND study (NCT02399085) which included adults with relapsed or refractory (R/R) DLBCL who were ineligible for high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) to receive tafasitamab + lenalidomide.

The proposed indication for tafasitamab is as follows: Tafasitamab is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT (CS, page 18).[1]

An application for marketing authorisation submitted to the European Medicines Agency (EMA) for tafasitamab was approved in August 2021, United Kingdom (UK) product license was granted on 08 October 2021, and the Medicines and Healthcare products Regulatory Agency (MHRA) also accepted the EMA Orphan Designation for tafasitamab.[1]

ERG comment: The population in this submission is in line with the National Institute for Health and Care Excellence (NICE) final scope.

2.2 Intervention

The intervention Tafasitamab (Minjuvi®) in combination with lenalidomide, followed by tafasitamab monotherapy is in line with the scope.

The recommended dosing regimen for tafasitamab is 12 mg/kg body weight administered as an intravenous (IV) infusion according to the following schedule (with each cycle consisting of 28 days):

- Cycle 1: Infusion on day 1, 4, 8, 15, and 22 of the cycle.
- Cycle 2: Infusion on day 1, 8, 15, and 22 of the cycle.
- Cycle 3: Infusion on day 1, 8, 15, and 22 of the cycle.
- Cycle 4: Infusion on day 1 and 15 of each cycle, until disease progression.

Alongside tafasitamab, lenalidomide is to be self-administered by patients with a recommended starting dose of 25 mg/daily on days 1 to 21 of each cycle (starting and subsequent dosing could be adjusted according to the lenalidomide summary of product characteristics [SmPC]).[1] The combination treatment of tafasitamab + lenalidomide is recommended for a maximum of 12 cycles after which patients would continue to receive tafasitamab as a single agent on day 1 and 15 of each cycle until disease progression or unacceptable toxicity.[1]

ERG comment: The intervention in the CS is in line with the NICE final scope.

2.3 Comparators

The description of the comparators in the NICE final scope[2] is as follows:

- Chemotherapy with or without rituximab: R-GemOx (rituximab, gemcitabine oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, mitoxantrone

cyclophosphamide, etoposide bleomycin, vincristine), (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (rituximab in combination with bendamustine)
- Pixantrone
- Pola-BR (polatuzumab vedotin in combination with bendamustine and rituximab)
- Best supportive care

The company considered R-GemOx, BR, and pola-BR, as the most relevant comparator treatments.

The single-arm L-MIND study provided clinical efficacy and safety evidence for tafasitamab + lenalidomide and an indirect comparison provided comparative evidence for the relative efficacy of tafasitamab + lenalidomide in the L-MIND study compared to pola-BR, BR, and R-GemOx (using data from six prospective studies).

ERG comment: In the request for clarification, the ERG asked the company to provide justification for the exclusion of several comparators listed in the NICE final scope, i.e. why R-Gem, R-P-MitCEBO, (R-)DECC, pixantrone, and best supportive care (BSC) were excluded as relevant comparators in the CS, and to discuss how the comparators selected align with the current UK clinical practice.[3]

In response, the company referred to three virtual interviews that were held on Microsoft Teams in September 2021 with UK clinical experts to seek advice on the relevant comparators for the population with transplant-ineligible R/R DLBCL in the UK stating that *"neither R-Gem, R-DECC or R-P-Mit-CEBO were referred to by the UK Experts during the interviews as being used in UK clinical practice for the population who would be eligible for TAFA+LEN. These variations of chemoimmunotherapy are therefore not considered to be relevant comparators for TAFA+LEN in England/the UK… pixantrone is available for use in the 3L and 4L treatment settings; however, the experts all advised that pixantrone is rarely used in the UK and is not a relevant comparator… furthermore, given the use of POLA+BR and chemoimmunotherapy for R/R DLBCL in patients ineligible for transplant, best supportive care/palliative care was not considered a suitable option"*.[4]

In discussing how the selected comparators aligned with current UK clinical practice, the company explained that *"the three experts all advised that POLA+BR, R-GemOx and BR would be the most relevant comparators for the UK for TAFA+LEN in transplant-ineligible R/R DLBCL"*.[4]

The ERG questioned the appropriateness of the conclusions that led to the exclusion of R-Gem, R-P-MitCEBO, (R-)DECC, pixantrone, and BSC as relevant comparators in this submission. This is highlighted as a key issue.

2.4 Outcomes

The NICE final scope[2] lists the following outcome measures:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rates
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

ERG comment: As all outcomes with the exception of HRQoL were assessed in the L-MIND study with the results being published in the CS, the ERG asked the company to provide results on the effects of tafasitamab + lenalidomide on HRQoL.[3]

In response, the company stated that further information on the systematic literature review (SLR) of HRQoL scores that informed the utility values presented in Table 28 of the CS were published in Appendix G and Appendix H of the CS.[4] Data on HRQoL and utility values are considered further in Section 4.2.8.

2.5 Other relevant factors

According to the company, *"the novel mechanism of action of tafasitamab with lenalidomide is an innovative treatment approach that has been demonstrated to be an effective, well-tolerated immunomodulatory, chemotherapy-free treatment option for patients with R/R DLBCL who are ineligible for ASCT or who have relapsed after ASCT"* (CS, Section B.1.3.6).[1] The company emphasised that the value of this new therapeutic combination to patients in this indication was highlighted by the Promising Innovative Medicines (PIM) designation awarded by the MHRA in the UK (January 2020 – PIM 2019/0012) and that it received accelerated approval from the United States (US) Food and Drug Administration (FDA) on 01 July 2020.[1]

Currently, the list price of a vial containing 200 mg tafasitamab powder for concentrate for solution for infusion is £705. The Patient Access Scheme (PAS) application to discount the list price to [redacted] per 200 mg vial of tafasitamab, was submitted to the Patient Access Schemes Liaison Unit (PASLU) and is pending approval.

End-of-life criteria are discussed in Section 7 of this report and the ERG identified a key issue regarding the evidence supporting the end-of-life criteria.

According to the company, there are no known equality issues related to the use of tafasitamab in patients with R/R DLBCL who are not eligible for ASCT (CS, Section B.1.4).[1]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the CS. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[5, 6] The CS was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[7] The ERG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS detailed the SLR undertaken to identify relevant literature relating to tafasitamab with lenalidomide for treating R/R DLBCL.[8] The SLR was conducted in two stages: an initial SLR in February 2021 and an update in June 2021. The same search strategies were used in the original SLR and updates.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE	PubMed	2011-4/2/21 4/2/21-28/6/21	4/2/21 28/6/21
Embase	Embase.com	2011-4/2/21 4/2/21-2/7/21	4/2/21 29/6/21
CENTRAL	Wiley	2011-4/2/21 2021-28/6/21	4/2/21 28/6/21
Additional resources			
ClinicalTrials.gov	Internet	2011-5/2/21 4/2/21-26/6/21	4/2/21 28/6/21
CADTH	Internet	Not stated	7/2/21 29/6/21
NICE			7/2/21 29/6/21
SMC			7/2/21 29/6/21
AWMSG			7/2/21 29/6/21
IQWiG			7/2/21 29/6/21
HAS			7/2/21 29/6/21
PBAC			7/2/21 29/6/21
ESMO			29/6/21

Resource	Host/Source	Date Ranges	Dates searched
ICER			29/6/21
AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; ESMO = European Society for Medical Oncology; HAS = Haute Autorité de Santé; ICER = Institute for Clinical and Economic Review; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium			

ERG comment:

- Searches were undertaken to identify relevant literature relating to tafasitamab with lenalidomide for treating R/R DLBCL. The CS provided sufficient details for the ERG to appraise the literature searches.[1]
- A good range of databases, clinical trials registers and additional grey literature resources were searched. Searches of conference proceedings were undertaken via Embase, although it is not clear if all relevant conferences are indexed by this database.
- Searches were well structured, transparent and reproducible, although there were issues with documentation in places, where the search strategies had been copied into a tabular format. The Cochrane Manual recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[9]
- The search strategies contained a population facet (R/R DLBCL), and for the searches of MEDLINE and Embase this was then combined with an additional facet of terms relating to treatments for the condition. The list of comparators was extensive, including many which were not listed in the NICE final scope,[2] and a good range of subject indexing terms (MeSH/EMTREE) and free text was used. However, the intervention, tafasitamab, was not among the drug names in the search strategy, so any studies referring to tafasitamab but not to its comparators will not have been retrieved by the MEDLINE or Embase searches. The Evidence Review Group (ERG) believes that this omission may have resulted in potentially relevant records being missed by the searches, however without re-running the searches, it is unclear what effect this may have had on recall. The abbreviation 'Pola-BR' was also missing from the strategies, although polatuzumab is included as subject indexing and free-text search terms.
- Results were limited by publication date from 2011 onwards, with a limit of 2016 to 2021 for conference abstracts. No language or study design limits were applied. No rationale appears to be provided as to the relevance of the date limit, which does appear overly restrictive, particularly in reference to tafasitamab's comparators.

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for the clinical effectiveness SLR is presented in Table 3.2.

Table 3.2: Study eligibility criteria for the systematic literature review of clinical effectiveness evidence

Included	Excluded
Patient population	
• Studies recruiting adult patients with transplant-ineligible, R/R DLBCL on at least second line treatment[*] • Studies recruiting patients with transformed lymphoma with DLBCL component, mixed presentation with either indolent and aggressive lymphoma or DLBCL • Studies including a mix of transplant-eligible and -ineligible patients or multiple indications were only included if separate results were available for eligible patients as described above.	• Studies recruiting only transplant-eligible or salvage therapy including ASCT-eligible patients • Studies including patients with a history of double-hit or triple-hit lymphoma • Studies recruiting patients with testicular lymphoma, bone lymphoma, primary CNS lymphoma, primary breast lymphoma, primary breast DLBCL, primary cutaneous DLBCL, DLBCL with CNS involvement, BL- and EBV-positive aggressive lymphoma • Studies recruiting patients with HIV-associated lymphoma, HIV with DLBCL or hepatitis B or C with DLBCL • Studies including only patients with prior history of malignancies other than DLBCL • Non-adult populations (<18 years of age) • Studies of animal subjects
Intervention	
Tafasitamab + lenalidomide as in the L-MIND study	NR
Comparators	
At least one of the following regimens in any study arm, derived from NCCN and ESMO guidelines, approved for use in either the US or EU: • ASHAP, ASHAP + rituximab (R-ASHAP) • ACVBP, ACVBP + rituximab (R-ACVBP) • Bendamustine, bendamustine + rituximab (R-BENDA) • Bendamustine + rituximab + polatuzumab vedotin (pola-BR) • Brentuximab vedotin • CEOP, CEOP + rituximab (R-CEOP) • CEPP, CEPP + rituximab (R-CEPP) • CHOP, CHOP + rituximab (R-CHOP), lenalidomide + R-CHOP (R2-CHOP) • DHAOx, DHAOx + rituximab (R-DHAOX) • DHAP, DHAP + rituximab (R-DHAP) • EPOCH, EPOCH + rituximab (R-EPOCH) • DA-EPOCH, DA-EPOCH + rituximab (DA-EPOCH-R)	Individual agents from within eligible comparator regimens unless specifically listed as a monotherapy

Included	Excluded
• ESHAP, ESHAP + rituximab (R-ESHAP) • GDP, GDP + rituximab (R-GDP) • Gemcitabine • Gemcitabine + rituximab • Gemcitabine + dexamethasone + carboplatin • Gemcitabine + dexamethasone + carboplatin + rituximab • Gemcitabine + vinorelbine • Gemcitabine + vinorelbine + rituximab • GemOx, GemOx + rituximab (R-GemOx) • Ibrutinib, ibrutinib + rituximab • ICE, ICE + rituximab (R-ICE) • IEV, IEV + rituximab (R-IEV) • Ifosfamide, ifosfamide + rituximab • IGEV, IGEV + rituximab (R-IGEV) • Lenalidomide • Lenalidomide + rituximab • Lenalidomide + obinutuzumab • Methylprednisolone, methylprednisolone + rituximab • MINE, MINE + rituximab (R-MINE) • BEAM, BEAM + rituximab (R-BEAM) • Pixantrone, pixantrone + rituximab • Polatuzumab vedotin + rituximab (R-POLA) • Rituximab • Vinorelbine, vinorelbine + rituximab • Axicabtagene ciloleucel (axi-cel) • Lisocabtagene maraleucel • Tisangenlecleucel • Best supportive care	
Outcomes	
Efficacy • Best overall response rate • End of treatment response rate • Duration of response • Progression-free survival • Event-free survival • Time to progression • Time to next treatment • Overall survival	NR

Included	Excluded
Safety • AEs, including SAEs • Laboratory findings	
Study designs	
• RCTs and non-RCTs • Open-label extensions • Observational studies (prospective, cross-sectional, and retrospective, including chart reviews, registries and surveys) • Single-arm trials • SLRs for hand-search	Studies indexed as case reports, case series, case studies, editorials, letters, comments, opinions or news
Setting	
Any setting relevant to the population of interest	NR
Country	
Any	N/A
Date range	
9 February 2021 to 28/29 June 2021	NR
Languages	
English and French	NR but presumably languages other than English and French

Based on Table 1 of the response to the request for clarification[4]

[*] Refractory is defined as disease that does not respond to initial treatment or that gets worse/stays the same within 6 months after the end of initial treatment. Relapsed is disease that responds to treatment but then returns. Patients must be on at least second line treatment.

ACVBP = doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisone; AE = adverse event; ASCT = autologous stem cell transplant; ASHAP = doxorubicin, solumedrol, cytarabine, and platinum; BEAM = carmustine, etoposide, cytarabine, and melphalan; BENDA = bendamustine; BL = Burkitt's lymphoma;; CEOP = cyclophosphamide, etoposide, vincristine, prednisone; CEPP = cyclophosphamide, etoposide, prednisone, procarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNS = central nervous system; DA EPOCH = dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DA EPOCH R = dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; DHAOx = dexamethasone, cisplatin, oxaliplatin; DHAP = dexamethasone, cisplatin, cytarabine; DLBCL = diffuse large B cell lymphoma; EBV = Epstein–Barr virus; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; ESMO = European Society for Medical Oncology; EU = European Union; GDP = gemcitabine, dexamethasone, cisplatin or carboplatin; GemOx = gemcitabine, oxaliplatin; HIV = human immunodeficiency virus; ICE = ifosfamide, carboplatin, etoposide; IEV = ifosfamide, etoposide, epirubicin; IGEV = ifosfamide, gemcitabine, vinorelbine, prednisone; MINE = mesna, ifosfamide, mitoxantrone, etoposide; N/A = not applicable; NCCN = National Comprehensive Cancer Network; NR = not reported; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R = rituximab; RCT = randomised controlled trial; R-pola = Rituximab and polatuzamab vedotin; R/R = relapsed or refractory; SAE = serious adverse event; SLR = systematic literature review; US = United States

ERG comment: The ERG believes that narrowing down the inclusion criteria to only studies published in English or French languages might have missed potentially relevant studies, i.e. has the potential to introduce bias. The date limitations shown in Table 3.2 (09 February 2021 to 28/29 June 2021) are as provided within the response to the request for clarification, however, they look incorrect and possibly amount to a typographical error.[4] The ERG notes that the search within the clinical effectiveness SLR was limited to studies published after 2010, see Table 3.1. This contrasts with the information in Table°3.2 and also with the date range within the CE SLR (20 years from 2000 to 2020), see Table 4.1. The consideration that economic evidence of tafasitamab may have been published prior to 2010 is inconsistent with the consideration that no evidence of clinical effectiveness was published prior to 2010.

3.1.3 Critique of data extraction

The initial information provided in the CS regarding data extraction was limited, e.g. no information was provided regarding whether a single reviewer extracted/entered the data, or if double data extraction was conducted by independent reviewers.[1]

In the response to the request for clarification, the company stated that data were extracted by a single reviewer and validated by a second reviewer. Any disagreements were resolved by consulting a third reviewer. The list of data elements that were extracted is shown as part of the response to clarification question B3.[4]

ERG comment: Extraction of study level details and baseline data by a single reviewer followed by independent checking by a second reviewer is acceptable. However, dual, independent data extraction with a pre-specified approach for achieving consensus is the recommended practice for extracting outcome data in order to minimise errors in estimates of effect.[10] The ERG considers that the outcome data and resulting estimates may be at risk of inaccuracies in light of the process employed by the company.[4]

3.1.4 Quality assessment

Section D.1.2 of Appendix D of the CS[8] mentioned the use of two adapted methodological quality assessment tools, one being based on Centre for Reviews and Dissemination's (CRD) checklist for randomised controlled trials (RCTs)[11] and the other informed by a checklist from the Critical Appraisal Skills Programme (CASP). The specific study design(s) were not described for the latter.[12]

Section B.2.5 of the CS included a presentation of the methodological quality assessment of the L-MIND and MOR208C201 studies using the aforementioned adapted RCT checklist.[1] Section D.1.2 of Appendix D of the CS showed use of the same tool for assessing other studies identified during the clinical effectiveness SLR.[8]

All of the studies assessed were single-arm, observational studies and it was not clear why the RCT checklist was used rather than a tool more suited to observational studies. The ERG asked for clarification on the approach used (question B3).[3] In response, the company outlined the same details as initially presented concerning the two adapted tools and also showed templates. This information did serve to clarify that the CASP checklist used was the one intended for cohort studies.[4]

ERG comment: The ERG believes that the CS used an inappropriate method of quality appraisal for the L-MIND and MOR208C201 studies. Within Appendix D, the CS states that *"in the case of single-intervention trials and open-label extensions, the application of the adapted CRD tool would have resulted in the majority of questions having a 'not applicable' response. Therefore, the adapted CASP (Critical Appraisal Skills Programme) tool was considered more informative and was used to*

evaluate these study designs".[8] It is unclear why the CS subsequently utilised the CRD checklist for RCTs for these studies. As a result, four of the seven quality assessment fields (randomisation, allocation concealment, similarity of baseline characteristics between groups and potential imbalances in dropouts between groups) were considered not applicable. Going by the information provided, it was difficult to judge the methodological assessment of the included studies.

Therefore, the ERG found it necessary to undertake another quality appraisal for the L-MIND (using the Salles et al. 2020 paper[13]) and MOR208C201[14] using an appropriate tool. The results of these assessments have been summarised in Table 3.3.

Table 3.3: Quality assessment of included studies

Question	L-MIND	MOR208C201
Was the cohort recruited in an acceptable way?	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes
Have the authors identified all important confounding factors?	Several potential confounding variables were indicated in the subgroup analyses for ORR (and some for DOR): age category; Ann Arbor stage; LDH level; IPI score; cell of origin phenotype; whether refractory to rituximab; whether refractory to last line of treatment; primary refractory; number of prior treatment lines	Yes: Baseline data were presented for several potential confounding factors for all patients and for the DLBCL subgroup in the safety population, including: age/age category; sex; body weight; race; time since first diagnosis; number of prior treatment lines; previous ASCT; ECOG grade; Ann Arbor stage at screening; number of patients rituximab refractory; whether refractory to last line of treatment; primary refractory; LDH level; IPI score; and biomarkers e.g., peripheral NK cell numbers at baseline and CD16 expression on NK cells
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes: a series of subgroup analyses were presented for ORR and DOR in the supplemental file	Yes: a series of subgroup analyses were presented for the DLBCL patients e.g., age category; IPI score; rituximab refractory; number of prior treatment lines; peripheral NK cell numbers at baseline; CD16 expression on NK cells
Was the follow-up of patients complete?	80/81 (98.8%) patients were followed up to the specified data cut-off (30 Nov 2018) for efficacy analyses. All 81 patients were followed up for the safety analyses.	No: 25/35 (71%) patients completed the study. Reasons for discontinuation: progressive disease (n=5), death (n=3), investigator decision (n=1), protocol violation (n=1). However, all 35 DLBCL patients were in the ITT population (having all received at least one dose of tafasitamab).

Question	L-MIND	MOR208C201
How precise (for example, in terms of confidence interval and p values) are the results	Confidence intervals tend to be broad, particularly for the estimates from the subgroup analyses	Where presented, the confidence intervals tended to be wide. This is not surprising given the small number of patients recruited and analysed.
The studies were appraised with the NICE methodological quality appraisal tool for non-randomised and non-controlled studies.[15] L-MIND was assessed from Salles et al. 2020[13] and MOR208C201 from the CSR[16] ASCT = autologous stem cell transplant; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; ITT = intention-to-treat; LDH = lactate dehydrogenase; N/A = Not applicable; NICE = National Institute for Health and Care Excellence; NK = natural killer; ORR = overall response rate		

3.1.5 Evidence synthesis

A meta-analysis was not presented, see Section B.2.8 of the CS.[1]

ERG comment: The CS provides a brief narrative synopsis of efficacy results. Due to the paucity of data available for synthesis, the CS presented results taken directly from the primary publication or related unpublished data.[1]

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Two single-arm, phase II studies were identified. One provided data on the effectiveness and safety of tafasitamab + lenalidomide dual therapy in patients with R/R DLBCL (the L-MIND study) and the other provided data from the MOR208C201 study on patients receiving tafasitamab monotherapy. Further details of these studies are outlined in this Section.

A third study, a retrospective, observational cohort, reported data on patients treated with lenalidomide monotherapy (the RE-MIND study), see Section 3.3.[1]

3.2.1 L-MIND phase II study

The only direct data regarding the safety and effectiveness of tafasitamab + lenalidomide dual therapy in patients with R/R DLBCL was provided in the L-MIND study.[1] This was an international phase II, open-label, single-arm study conducted at 35 academic and community centres.

The objective of this study was to ascertain the effectiveness of tafasitamab/lenalidomide dual therapy in adults with R/R DLBCL who were ineligible for HDC or ASCT. The primary outcome of interest was objective response rate (ORR), defined as complete response plus partial response (CR + PR). Further details regarding trial design and methodology are presented in Table 3.4.

Table 3.4: Trial design and methodology of the L-MIND (MOR208C203/NCT02399085) study

Parameter	Description
Study objective(s)	Primary objective: To determine the activity of a combination of TAFA+LEN in terms of ORR (ORR=CR + PR) in adults with R/R DLBCL.
Trial design	Phase II, single-arm, open-label, multicentre study (35 academic and community centres in Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, UK and US).
Trial drug	Tafasitamab (MOR00208) Anti-CD19 Antibody, 12 mg/kg, IV infusion, weekly (Cycle 1-3, with additional loading dose on day 4 of Cycle 1) to bi-weekly (Cycle 4 onwards), 4-week cycles. Treatment until disease progression or unacceptable toxicity or discontinuation due to any other reason. Lenalidomide 25 mg; PO, 4-week cycles (used daily for 3 of the 4 weeks). Up to 12 cycles in the absence of disease progression or unacceptable toxicity. To mitigate infusion-related reactions, premedication was administered between 30 minutes and two hours prior to the tafasitamab infusions: • Antipyretics (e.g. acetaminophen [paracetamol] 1000 mg per dose per mouth [p.o.] or IV or equivalent) • Histamine H1 receptor blockers (e.g. diphenhydramine 25 to 50 mg per dose IV or equivalent) • Histamine H2 receptor blockers (e.g. cimetidine 300 mg p.o., ranitidine 150 mg tablet p.o. or equivalent), glucocorticosteroids (methylprednisolone 80–120 mg per dose IV or equivalent) • Meperidine (25 mg per dose p.o. or IV) added as required for rigours or chills
Permitted and disallowed concomitant medication	**Permitted:** Concomitant medications were permitted to treat comorbidities or AEs during the study, as well as therapy to mitigate side effects of the study medication, and BSC. **Disallowed:** NR
Primary outcomes (including scoring methods and timings of assessments)	**Primary:** ORR, defined as PR + CR, as assessed by the independent radiology/clinical review committee (IRC). **Secondary:** Duration of response (DoR, defined as duration of CRs or PRs until progression or relace was evaluated); progression free survival (PFS); time to progression (TTP), defined as first dose of study drug until time of progression or death from lymphoma only; overall survival; time to next treatment (TTNT). **Safety endpoints:** Safety and tolerability assessed by evaluating the frequency, duration and severity of adverse events (AEs) **Additional endpoints:** Determination and characterisation of anti-tafasitamab antibody formation; Pharmacokinetic analysis of tafasitamab; Absolute and percentage change from baseline in B-, T-, and NK cell populations; Analysis of exploratory and diagnostic biomarkers from blood and tumour tissue (e.g. CD19, CD20, B-cell lymphoma-2, B-cell

Parameter	Description
	lymphoma-6 expression, CD16 expression on NK cells, and ADCC capacity), GEP for cell of origin subtyping and evaluation of AEs and ORR by FcγRIIIa and FcγRIIa polymorphism.
Pre-planned subgroups	Prespecified exploratory subgroup analysis of objective response by baseline characteristics
Eligibility criteria for participants	**Eligible:** Age ≥18 years Histologically confirmed diagnosis of: • DLBCL not otherwise specified • T-cell/histiocyte rich large B-cell lymphoma • EBV-positive DLBCL of the elderly (EBV-positive DLBCL) • Grade 3b follicular lymphoma • Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/WHO classification • Histological transformation to DLBCL from an earlier diagnosis of low-grade lymphoma (e.g. an indolent pathology such as follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukaemia) into DLBCL with a subsequent DLBCL relapse Available sample of fresh tumour tissue for central pathology review and correlative studies. If it was not possible to obtain a fresh tumour tissue sample from the patient, archival paraffin-embedded tumour tissue acquired ≤3 years prior to screening for the study had to be available for this purpose. Patients had to demonstrate: • R/R disease • ≥1 bi-dimensionally measurable disease site with a greatest transverse diameter of ≥1.5 cm and a greatest perpendicular diameter of ≥1.0 cm at baseline. The lesion had to be positive on PET scan • ≥1 but ≤3 previous systemic regimens for the treatment of DLBCL and one therapy line had to include a CD20-targeted therapy (e.g. rituximab) • ECOG performance status of 0–2 Patients not considered eligible in the opinion of the investigator, or patients unwilling to undergo intensive salvage therapy including ASCT because of, but not limited to, advanced age, comorbidities, impossibility or, refusal to perform ASCT. Documentation of the reason for a patient's ineligibility had to be provided in the patient's source data.

	Patients had to meet the following laboratory criteria at screening: • Absolute neutrophil count ≥1.5×10^9/l (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy) • Platelet count ≥90×10^9/l (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy) • Total serum bilirubin ≤2.5×ULN unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or with documented liver involvement by lymphoma may have been included if their total bilirubin was ≤5 × ULN (see exclusion criterion *'patients exhibiting history or evidence of severe hepatic impairment')* • ALT, AST and AP ≤3×ULN or <5×ULN in cases of documented liver involvement) serum creatinine clearance had to be ≥60 ml/minute either measured or calculated using a standard Cockcroft and Gault formula Females not pregnant or breastfeeding; ongoing pregnancy testing. Females (of any age) must refrain from donating blood or oocytes during the study and for three months after. Females must have committed to abstinence or effective uninterrupted contraception during the study and for 3 months after. Males had to use an effective barrier method of contraception without interruption and refrain from donating blood or sperm during the study and for three months after last dose. In the opinion of the investigator, patients must: • Be able and willing to receive adequate prophylaxis for thromboembolic events • Be able to understand, give written informed consent, and comply with all study-related procedures, medication use and evaluations • Not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative • Be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement **Ineligible:** Patients who had: • Any other histological type of lymphoma including primary mediastinal (thymic) large B-cell or Burkitt lymphoma • Primary refractory DLBCL* • A history of "double-/triple-hit" genetics DLBCL characterised by simultaneous detection of MYC with BCL-2 and/or BCL-6 translocation(s) defined by fluorescence in-situ hybridisation. MYC, BCL-2, BCL-6 testing prior to study enrolment was not required.

Parameter	Description
	Patients who had, within the 14 days prior to day 1 dosing: • Not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anti-cancer therapy or other lymphoma-specific therapy • Undergone major surgery or suffered from significant traumatic injury • Received live vaccines • Required parenteral antimicrobial therapy for active, intercurrent infections Patients who: • Had, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies • Were previously treated with CD19-targeted therapy or IMiDs (e.g. thalidomide, lenalidomide) • Had a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs and/or the excipients contained in the study drug formulations • Had undergone ASCT within the period ≤3 months prior to the signing of the informed consent form. Patients who had a more distant history of ASCT had to exhibit full haematological recovery before enrolment into the study • Had undergone previous allogeneic stem cell transplant • Had a history of deep venous thrombosis/embolism • Threatening thromboembolism or known thrombophilia or were at a high risk for a thromboembolic event in the opinion of the investigator and who were not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period Concurrently used other anti-cancer or experimental treatments Prior history of malignancies other than DLBCL, unless the patient had been free of the disease for ≥5 years prior to screening. Exceptions to the ≥5-year time limit included history of the following: • Basal cell carcinoma of the skin • Squamous cell carcinoma of the skin • Carcinoma in-situ of the cervix • Carcinoma in-situ of the breast • Carcinoma in-situ of the bladder • Incidental histological finding of prostate cancer (Tumour/Node/Metastasis stage of T1a or T1b) Patients exhibiting: • Positive hepatitis B and/or C serology

Parameter	Description
	• Known seropositivity for or history of active viral infection with human immunodeficiency virus • CNS lymphoma involvement–present or past medical history • History or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that in the investigator's opinion precluded participation in the study or compromised the patient's ability to give informed consent • History or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption • Gastrointestinal abnormalities including the inability to take oral medication, requiring IV alimentation, or prior surgical procedure affecting absorption • History or evidence of severe hepatic impairment (total serum bilirubin >3 mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion: *'laboratory criteria at screening, total serum bilirubin ≤2.5×ULN')*

Based on section B.2.3. of the CS[1] and NCT02399085[17]

* The definition of primary refractory DLBCL was revised (Protocol Amendment 2, Final Version 5.0 [27 Jun 2016]), (less than a PR to first line therapy or progression within six months from completion of 1L therapy) and removed the need to have DLBCL relapse/progression after at least three months from completion of prior CD20 containing therapy; exclusion criterion 1b was updated to reflect this.

ADCC = antibody-dependent cellular cytotoxicity; AE = adverse event; ALT = alanine transaminase; AP = alkaline phosphatase; ASCT = autologous stem cell transplant; AST = aspartate aminotransferase; BCL = B-cell lymphoma; BSC = best supportive care; CD = cluster of differentiation; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; EBV = Epstein Barr virus; ECOG = Eastern Cooperative Oncology Group; GEP = gastroenteropancreatic; ImiD = immunomodulatory drug; IRC = independent radiology/clinical review committee; IV = intravenous; LEN = lenalidomide; NK = natural killer; ORR = overall response rate; p.o. = taken orally; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; R/R = relapsed or refractory; TAFA = tafasitamab; TTNT = time-to-next treatment; TTP = time-to-progression; UK = United Kingdom; ULN = upper limit of normal; US = United States; WHO = World Health Organization

Relapsed disease was defined as the appearance of any new lesions or an increase in size of at least 50% of previously involved sites from nadir, according to the 2007 International Working Group response criteria, after the most recent systemic therapy. Refractory disease was defined as disease progression as per International Working Group response criteria, showing less than a partial response or disease recurrence or progression within less than 6 months from the completion of first-line therapy.[13]

Of the 156 patients screened, 81 were subsequently included in the trial. The primary reasons for ineligibility were lab criteria not met (n=31), no relapsed disease or absence of measurable disease (n=13) and medical history reasons, e.g. double hit lymphoma (n=10). No details were provided regarding the specific laboratory measures or values that resulted in the exclusion of these patients. The baseline characteristics of participants of the L-MIND study are reported in Table 3.5.

Table 3.5: Baseline characteristics of patients in the L-MIND study

	Overall; N=81 (100%)
Age (years)	
Median (range)	72 (62 to 76)
Sex, n (%)	
Male	44 (54%)
Female	37 (46%)
Race, n (%)	
Asian	2 (2%)
White	72 (89%)
Other	1 (1%)
Data missing	6 (7%)
Previous lines of systemic therapy	
Median (range)	2 (1-4)
1	40 (50%)
2	35 (43%)
3	5 (6%)
4	1 (1%)
Previous anti-CD20 therapy	
Yes	81 (100%)
No	0
Previous anthracycline therapy	
Yes	81 (100%)
No	0
Primary refractory	
Yes	15 (19%)
No	66 (81%)
Rituximab refractory	
Yes	34 (42%)
No	46 (57%)
Unknown	1 (1%)

	Overall; N=81 (100%)
Refractory to most recent previous therapy	
Yes	36 (44%)
No	45 (56%)
Previous ASCT	
Yes	9 (11%)
No	72 (89%)
Ann Arbor stage at screening	
I or II	20 (25%)
III or IV	61 (75%)
ECOG performance status	
0	29 (36%)
1	45 (56%)
2	7 (9%)
IPI score at screening	
0-2 (low and low-intermediate risk)	40 (49%)
3-5 (intermediate-high and high risk)	41 (51%)
Bulky disease*	
Present	15 (19%)
Absent	65 (80%)
Data missing	1 (1%)
Lactate dehydrogenase concentrations at screening	
Elevated	45 (56%)
Within reference range	36 (44%)
Cell of origin by immunohistochemistry	
Germinal centre B cell	38 (47%)
Non-germinal centre B cell	21 (26%)
Unknown	22 (27%)
Cell of origin by gene-expression profiling	
Germinal centre B cell	7 (9%)
Non-germinal centre B cell	19 (24%)
Unclassified	6 (7%)
Unknown	49 (60%)
DLBCL arising from a previous indolent lymphoma	
Yes	7 (9%)
Reasons for ASCT ineligibility	
Aged > 70 years	37 (46%)
Chemorefractory†	19 (23%)
Refusal	13 (16%)
Comorbidities‡	11 (14%)

	Overall; N=81 (100%)
Other[§]	1 (1%)

Based on Table 9 of the CS[1]
[*] Defined as having a longest lesion diameter of ≥7.5 cm (by central radiological assessment); [†] Patients without a partial or complete response with salvage therapy or who had ASCT before enrolment; [‡] All patients who are not chemorefractory and who have comorbidities (comorbidities are listed in appendix p 23); [§] Other reasons include inability to successfully collect stem cells
ASCT = autologous stem cell transplant; CD = cluster of differentiation; CS = company submission; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index

ERG comment: The primary publication for L-MIND provided sufficiently comprehensive details of relevant baseline characteristics and reflects the patient population in which the indication for treatment is being sought.[13] Information in the clinical study report (CSR) showed that 70/81 (86.4%) patients had a R/R DLBCL diagnosis confirmed by central pathology assessment. However, the remaining 11/81 (13.6%) patients had a diagnosis confirmed by local pathology assessment but this had not been confirmed by central pathology at the start of the study.[18]

In response to the request for the clarification, the company noted that *"the Baseline tumour assessment in the observational cohort study indicated 85% of the population had refractory disease.*[REF 13] *In L-MIND, 44% of patients were refractory to their last prior therapy,[13] indicating a lower proportion of patients with refractory disease for L-MIND than in the observational cohort study"*. However, the company stated that *"this is in alignment with clinical expert feedback regarding the population in routine clinical practice"*.[4] The ERG wanted to note this as a potential limitation of the generalisability to clinical practice in England and Wales.

3.2.1.1 Clinical effectiveness of tafasitamab/lenalidomide in the L-MIND study

The primary efficacy outcome for the L-MIND study was ORR. Secondary efficacy outcomes of interest consisted of DoR (months), PFS, time to progression (TTP) and time-to-next treatment (TTNT), and OS. As explained in Section B.2.4.1 of the CS, the full analysis set (FAS; the primary population for efficacy analyses) included all patients who received at least one dose of tafasitamab and at least one dose of lenalidomide, i.e. both study drugs had to be administered at least once. Of the 81 patients enrolled and treated in the study, one patient received tafasitamab only. This meant that whilst the presentation of baseline data included all 81 enrolled patients, the efficacy analyses were based on 80/81 (98.8%) patients. The safety population was defined differently, consisting of all patients who received at least one dose of tafasitamab or lenalidomide, i.e. either one or the other study drug had to be administered at least once, and included all 81 enrolled patients.[1]

3.2.1.1.1 Overall survival (OS)

A total of 41/80 participants (51.3%) died during follow-up; the Kaplan-Meier estimate for median OS was 33.5 months (95% confidence interval (CI) 18.3, upper CI not reached), with a median follow-up time of 42.7 months (95% CI 38.0 to 47.2). The remaining 39/80 patients were censored in the OS analysis, see Table 3.6.

Table 3.6: KM probability estimates for overall survival

	TAFA+LEN Z(N=80)
Full analysis set [95% CI]	
12 months (%)	[redacted]
18 months (%)	[redacted]

	TAFA+LEN Z(N=80)
24 months (%)	[redacted]
30 months (%)	[redacted]
36 /42 months (%)	[redacted]
48 /54 months (%)	[redacted]
Complete response [95% CI]	
Median OS (months)	Not reached [45.7, not reached]
18 months (%)	96.9 [79.8 to 99.6]
24 months (%)	90.6 [73.7 to 96.9]
36 months (%)	81.3 [62.9 to 91.1]
48 /54 months (%)	[redacted]
Partial response [95% CI]	
Median OS (months)	22.5 [8.5, not reached]
Based on Section B.2.6.4 of the CS[1] CI = confidence interval; CS = company submission; OS = overall survival	

3.2.1.1.2 Progression-free survival (PFS)

PFS was observed in 42 participants and the Kaplan-Meier estimate for median PFS was 11.6 months (95% CI 6.3 to 45.7) with a median follow-up of 33.9 months ([redacted]). Post-hoc analyses suggested a continued PFS benefit of tafasitamab monotherapy following discontinuation of lenalidomide (median PFS 12.7 months, 95% CI 2.3, upper CI not reached).

3.2.1.1.3 Objective response rate (ORR)

ORR was classified as the number of patients who experienced CR plus those who experienced PR. According to the CS, ORR was achieved by 46/80 participants (58%), 32 of which experienced a CR (40%) while 14 experienced a PR (18%) as of data cut-off (October 2020), see Table 3.7. Thirteen participants (16%) had stable disease at cut-off and an additional 13 (16%) participants had progressive disease. A total of eight participants were considered 'not evaluable', as there were no valid post-baseline radiological examinations available for which to assess response.

Table 3.7: Primary efficacy outcomes for L-MIND study

	TAFA+LEN (N=80)
Best objective response	
Complete response, n (%) [95% CI]	32 (40) [29 to 52]
Partial response, n (%) [95% CI]	14 (18) [10 to 28]
Stable disease, n (%)	13 (16)
Progressive disease, n (%)	13 (16)
Not evaluable, n (%)	8 (10)
Best ORR*, n (%) [95% CI]	46 (58) [46 to 69]
Based on Table 11 of the CS[1] * Complete response and partial response CI = confidence interval; CS = company submission; LEN = lenalidomide; ORR = objective response rate; TAFA = tafasitamab	

3.2.1.1.4 Health-related quality of life (HRQoL)

HRQoL was not addressed in L-MIND.

3.2.1.1.5 Other outcomes

The CS reported other outcomes, not covered in the NICE final scope, namely TTP, TTNT, and duration of response (DoR).

- The median TTP was 16.2 months (95% CI 17.4, upper CI not reached).
- The median TTNT was 15.4 months (95% CI 7.6 months, upper CI not reached), and 43/80 (54%) patients received subsequent treatment.
- At the time of data cut-off (October 2020), the median duration of response was 43.9 months (95% CI 26.1 to not reached). Of the 80 participants included in the intention-to-treat (ITT) analysis, there were 46 responders (58%); of which 13 participants (28.3%) progressed, two (4.3%) died, and 31 (67.4%) were censored.
  The CS provides Kaplan-Meier plots for duration of response by best objective response CR or PR for patients in the full analysis set. The median duration of response for PR patients was 5.6 months, whereas the estimate of the median duration of response for CR patients was not reached, see Table 3.8.

Table 3.8: Kaplan-Meier probability estimates for duration of response

	TAFA+LEN (N=80)
Full analysis set [95% CI]	
12 months (%)	73.7 [57.4 to 84.5]
18 months (%)	[redacted]
24 months (%)	[redacted]
30 /36 /42 months (%)	[redacted]
Complete response [95% CI]	
Median DoR (months)	[redacted]
12 months (%)	[redacted]
18 months (%)	[redacted]
24 months (%)	[redacted]
30 /36 /42 months (%)	[redacted]
Partial response [95% CI]	
Median DoR(months)	[redacted]

Based on Section B.2.6.4 of the CS[1]
CI = confidence interval; CS = company submission; OS = overall survival

3.2.1.2 Safety outcomes

As explained in Section B.2.4.1 of the CS (and outlined in Section 3.2.1.1), the safety population consisted of all patients who received at least dose of tafasitamab or lenalidomide, i.e. either one or the other study drug had to be administered at least once, and included all 81 enrolled patients. This differed to the FAS for the efficacy analyses (defined as all patients who received at least one dose of tafasitamab and at least one dose of lenalidomide) which included 80/81 (98.8%) patients.[1]

Treatment emergent adverse events (TEAEs) occurred in all 81 participants included within the L-MIND trial, neutropenia being the most common AE (40/81 patients, 49%). Common adverse events (AEs) of grade 3 or worse included neutropenia, anaemia, thrombocytopenia, leukopenia, febrile neutropenia, and pneumonia. AEs are presented in Table 3.9.

Ten participants discontinued the study during the combination therapy phase due to AEs, and 20 participants discontinued treatment with one or both study drugs due to AEs. None of the grade 5 AEs were considered of special interest or were suspected to be related to tafasitamab or lenalidomide.

Table 3.9: Treatment emergent adverse events reported in the L-MIND study

Adverse event	Adverse event grades			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological events, n (%)				
Neutropenia	1 (1)	22 (27)	17 (21)	0
Anaemia	22 (27)	6 (7)	0	0
Thrombocytopenia	11 (14)	10 (12)	4 (5)	0
Leukopenia	5 (6)	6 (7)	1 (1)	0
Febrile neutropenia	0	8 (10)	2 (2)	0
Lymphopenia	2 (2)	2 (2)	1 (1)	0
Agranulocytosis	0	0	1 (1)	0
Non-haematological events, n (%)				
All rash[*]	22 (27)	7 (9)	0	0
Diarrhoea	26 (32)	1 (1)	0	0
Asthenia	17 (21)	2 (2)	0	0
Cough	17 (21)	1 (1)	0	0
Peripheral oedema	18 (22)	0	0	0
Pyrexia	16 (20)	1 (1)	0	0
Decreased appetite	16 (20)	0	0	0
Hypokalaemia	10 (12)	4 (5)	1 (1)	0
Back pain[†]	11 (14)	2 (2)	0	0
Fatigue	12 (15)	2 (2)	0	0
All urinary tract infection[*]	9 (11)	3 (4)	1 (1)	0
Constipation	13 (16)	0	0	NR
Muscle spasms	12 (15)	0	0	0
Nausea	12 (15)	0	0	0
Bronchitis	10 (12)	0	1 (1)	0
Vomiting	11 (14)	0	0	0
Dyspnoea	9 (11)	1 (1)	0	0
Abdominal pain	7 (9)	1 (1)	0	0
Upper respiratory tract infection	6 (7)	2 (2)	0	0
Hypertension	4 (5)	3 (4)	0	0
Increased blood creatinine[†]	5 (6)	1 (1)	0	0
Mucosal inflammation	5 (6)	1 (1)	0	0
Pneumonia	1 (1)	5 (6)	0	0
Hypocalcaemia	4 (5)	1 (1)	0	0
Hypogammaglobulinemia	4 (5)	1 (1)	0	0

Adverse event	Adverse event grades			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Increased γ-glutamyl transferase	4 (5)	1 (1)	0	0
Atrial fibrillation	1 (1)	2 (2)	1 (1)	0
Pulmonary embolism	0	2 (2)	2 (2)	0
Sinusitis	3 (4)	1 (1)	0	0
Deep vein thrombosis	2 (2)	0	1 (1)	0
Hyperbilirubinemia	2 (2)	1 (1)	0	0
Increased blood bilirubin	2 (2)	1 (1)	0	0
Increased transaminases	1 (1)	2 (2)	0	0
Lower respiratory tract infection	2 (2)	1 (1)	0	0
Renal failure	1 (1)	2 (2)	0	0
Syncope	2 (2)	1 (1)	0	0
Tumour flare	2 (2)	1 (1)	0	0
Cataract	1 (1)	1 (1)	0	0
Congestive cardiac failure	0	2 (2)	0	0
Muscular weakness	1 (1)	1 (1)	0	0
Urinary incontinence	1 (1)	1 (1)	0	0
Arthritis	0	1 (1)	0	0
Atrial flutter	0	1 (1)	0	0
Biliary colic	0	1 (1)	0	0
Bronchopulmonary aspergillosis	0	0	1 (1)	0
Cardiac failure	0	0	1 (1)	0
Cerebrovascular accident	0	0	0	1 (1)
Cervicobrachial syndrome	0	1 (1)	0	0
Cranial nerve infection	0	1 (1)	0	0
Cytomegalovirus infection	0	1 (1)	0	0
Device-related thrombosis	0	1 (1)	0	0
Enterobacter bacteraemia	0	1 (1)	0	0
Febrile infection	0	0	1 (1)	0
Femur fracture	0	1 (1)	0	0
Haematuria	0	1 (1)	0	0
Hyperkalaemia	0	1 (1)	0	0
Hypersensitivity	0	1 (1)	0	0
Hyponatraemia	0	1 (1)	0	0
Infected bite	0	1 (1)	0	0
Klebsiella sepsis	0	1 (1)	0	0
Lower limb fracture	0	1 (1)	0	0
Lung infection	0	1 (1)	0	0
Myocardial ischaemia	0	0	1 (1)	0

Adverse event	Adverse event grades			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Myositis	0	1 (1)	0	0
Nephrolithiasis	0	1 (1)	0	0
Neutropenic sepsis	0	1 (1)	0	0
Osteonecrosis	0	1 (1)	0	0
Peripheral sensorimotor neuropathy	0	1 (1)	0	0
Progressive multifocal leukoencephalopathy	0	0	0	1 (1)
Recurrent marginal zone Lymphoma	0	1 (1)	0	0
Respiratory failure	0	0	0	1 (1)
Respiratory syncytial virus infection	0	1 (1)	0	0
Sepsis	0	0	1 (1)	0
Soft tissue infection	0	1 (1)	0	0
Streptococcal sepsis	0	0	1 (1)	0
Sudden death	0	0	0	1 (1)
Varicella zoster virus Infection	0	0	1 (1)	0
Wound complication	0	0	1 (1)	0

Based on Table 17 of the CS[1]
The Table shows treatment-emergent AEs of grade 1 or 2 occurring in at least 10% of patients and all grade 3, 4, and 5 events.
* Defined by customised Medical Dictionary for Regulatory Activities query; † One report of back pain and one report of increased blood creatinine had no toxicity grading
AEs = adverse events; CS = company submission

At of the initial data cut-off (November 2018), treatment emergent serious adverse events (SAEs) had occurred in 41/80 (51%) patients. The most frequent (in two or more patients) were pneumonia (5/81, 6%), febrile neutropenia (5/81, 6%), pulmonary embolism (3/81, 4%), bronchitis (2/81, 2%), atrial fibrillation (2/81, 2%) and congestive cardiac failure (2/81, 2%). As of the October 2020 data cut-off, this had increased to 43/81 (53.1%) patients.

As of the initial data cut-off (November 2018), 30 patients had died (30/81, 37%); eight during study treatment and 22 after treatment. The majority of these were related to lymphoma progression (30/81, 77%). The remaining seven (23%) were not related to disease progression. As of the October 2020 data cut-off, this had increased to 42 patients (51.9%). No deaths were considered related to study treatment.

ERG comment: Of the 45 participants who discontinued both tafasitamab and lenalidomide during cycles 1 to 12, 32 of these did so due to progressive disease (Figure 5 of the CS).[1] An additional four participants discontinued tafasitamab monotherapy after cycle 12 prior to data cut-off due to progressive disease. Therefore, of the 80 patients within the intention-to-treat (ITT) population (patients who received at least one dose of tafasitamab), almost half (36/80) of these discontinued due to progressive disease by the point of data cut-off.

Table 11 of the CS provides alternative information regarding best ORR as of data cut-off, and states that of the 80 participants within the ITT cohort, 13 of these had progressive disease (32 had complete response, 14 had partial response and 13 had stable disease).

There are inconsistencies in the presentation of PFS events within the clinical effectiveness data; specifically, within the PFS subheading on page 49, the CS states that *"PFS events were observed in 42 patients (52.5%)"*; however in the following section (Time to progression and time-to-next treatment, page 50), the CS states that *"PFS events occurred in 35 of 80 patients (44%)"*.[1] It is unclear whether this is an error, or whether there are differences in the nature of PFS specified within each section.

The ERG notes that, although comprehensive details were provided regarding all AEs experienced during the follow-up of the L-MIND study, limited details were provided regarding serious adverse events (SAEs). Specifically, Table 17 in the CS lists 85 different AEs, many of which had only a single occurrence (i.e. <2% of patients), whereas SAEs were reported narratively and were limited to those that occurred in two or more patients (i.e. >2%). As 41 patients experienced one or more SAEs, it is concerning that more details of these events were not provided.[1]

The ERG notes that HRQoL was not assessed in L-MIND although being an outcome listed in the NICE final scope, see Section 2.4.[2]

3.2.2 MOR208C201 phase IIa study

The CS includes supportive data from the MOR208C201 study (NCT01685008), specifically the DLBCL cohort who received tafasitamab monotherapy.[1, 19] Table 3.10 presents select baseline characteristics from the MOR208C201 study.

Table 3.10: Baseline characteristics of DLBCL cohort within MOR208C201 study

Characteristics	DLBCL cohort (N=35)
Age, (years)	
Median (range)	71 (35–90)
Sex, n (%)	
Male	24 (69)
Female	11 (31)
Race, n (%)	
Asian	1 (3)
White	33 (94)
Black/African American	0 (0)
Other	1 (2.9)
Median time since first DLBCL diagnosis, months	23 (2–120)
Ann Arbor Disease Staging dichotomised, n (%)	
Stage I and II	4 (11)
Stage III and IV	30 (86)
Unknown	1 (3)
ECOG performance status, n (%)	
0	19 (54)
1	15 (43)
2	1 (3)

Based on Table 10 of the CS
CS = company submission; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group

3.2.2.1 Clinical effectiveness of tafasitamab/lenalidomide in the MOR208C201 study

Clinical efficacy outcomes within the MOR208C201 study were limited to objective response rate and disease control rate (Table 3.11).

Table 3.11: Primary efficacy outcomes for MOR208C201 study

Outcome, n (%)	DLBCL cohort (N=35)
Complete response	2 (5.7)
Partial response	7 (20)
Objective response rate [95% CI]	9 (25.7) [12.5 to 43.3]
Stable disease	5 (14.3)
Disease control rate [95% CI]	14 (40.0) [23.9 to 57.9]
Progressive disease	11 (31.4)
Not estimable	0
No response assessment	10 (28.6)

Based on Table 12 of the CS
CI = confidence interval; CS = company submission

3.2.2.2 Safety outcomes

As detailed in Table 3.12, the most frequently reported AEs of any grade within the DLBCL cohort were neutropenia and peripheral oedema, both of which occurred in 6/35 participants (17%). Other frequently occurring adverse events included dyspnoea (5/35, 14%) and thrombocytopenia, infusion-related reactions, upper respiratory tract infections and headaches, each of which occurred in 4/35 participants (11%). SAEs occurred in two of the DLBCL patients, both of which had a suspected relationship to tafasitamab; one case of febrile neutropenia and one of genital herpes.[20]

Table 3.12: Adverse events of Grade 3 or higher reported in the MOR208C201 DLBCL cohort

Outcome, n (%)	DLBCL, n=35	Total, N=92
Any grade ≥3[*], n (%)	19 (54)	37 (40)
Haematological[#], n (%)		
Neutropenia	6 (17)	8 (9)
Thrombocytopenia	2 (6)	4 (4)
Anaemia	3 (9)	3 (3)
Non-haematological[#], n (%)		
Dyspnoea	2 (6)	4 (4)
Pneumonia[§]	3 (9)	3 (3)
Fatigue	1 (3)	2 (2)
Hypokalaemia	1 (3)	2 (2)
Infusion-related reaction,[$] n (%)		
Any, n (%)	4 (11)	11[ß] (12)
Grade 1/2	4 (11)	10 (11)
Grade 4	0	1 (1)

Based on Table 18 of the CS[1]
[*] TEAEs including PT disease progression; [#] TEAEs reported at grade 3 in two or more patients overall; [§] In two patients, pneumonia started during the extended treatment phase (days 706 and 468, respectively), both

Outcome, n (%)	DLBCL, n=35	Total, N=92
patients recovered within two weeks. One patient developed pneumonia with cardiorespiratory failure (unrelated to tafasitamab treatment) in cycle 1 (day 23) with a fatal outcome; [$] TEAEs according to the Medical Dictionary for Regulatory Activities preferred term (PT); [ß] No grade 3 or grade 5 infusion-related reactions were reported. CS = company submission; DLBCL = diffuse large B-cell lymphoma; PT = preferred term; TEAE = treatment emergent adverse event		

ERG comment: The CS did not include any information regarding SAEs. The study by Jurczak et al. 2018 states that two of the 35 DLBCL patients experienced a SAE with a suspected relationship to tafasitamab; one case of febrile neutropenia and one of genital herpes.[20]

Clinical efficacy outcomes within the MOR208C201 study were limited to objective response rate and disease control rate, i.e. did not report any results for OS, PFS, or HRQoL, all of which were listed as outcomes of interest in the NICE final scope.[2]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

According to the CS, *"as the pivotal L-MIND study of TAFA+LEN in R/R DLBCL (...) was a single-arm trial, the comparative efficacy of TAFA+LEN was assessed via 1:1 nearest-neighbour (NN) matching with external (synthetic) control arms. These data were generated in two retrospective cohort studies (RE-MIND [MOR208C206] and RE-MIND2 [MOR208C213]),[21, 22] and a matching-adjusted indirect comparison (MAIC) against the published clinical studies of key comparators[23]"*.[1]

ERG comment: RE-MIND *"is an observational, retrospective cohort study designed to characterise the effectiveness of LEN monotherapy in the treatment of patients with R/R DLBCL who were not eligible for HDC following ASCT"*. [1] As detailed in Section 2.3, this is outside the scope of the NICE final scope and will not be discussed in this report.[2]

It should be noted that relevant details on RE-MIND2 (Section 3.3.1) and the MAIC (Section 3.3.2) were reported in various documents submitted by the company, including the CS, CS Appendix D, the response to the request for clarification as well as statistical analysis plans and CSRs.[1, 4, 8, 22, 24]

Please see Section 3.4 for a detailed critique of the indirect comparison and/or multiple treatment comparison.

3.3.1 RE-MIND2

According to the CS, *"RE-MIND2 was a large, real-world, retrospective cohort study of patients with R/R DLBCL (N=3,454)), based on a pre-specified design, aimed at characterising the effectiveness and tolerability of TAFA+LEN (in L-MIND; data cut-off 30 October 2020) with a 1:1 NN-matched population treated with systemic regimens administered in routine clinical care as recommended by NCCN/ESMO guidelines.[22] The RE-MIND2 cohort included patients treated with the following regimens: BR, R-GemOx, pola-BR, rituximab (R)+lenalidomide (LEN), CAR-T therapies, and pixantrone; in the second, third, or fourth-line treatment settings.[22] Based on feedback from UK clinical experts,[25] BR, R GemOx and pola-BR were considered the most relevant comparators for patients with R/R DLBCL who are ineligible for ASCT in the UK"*.[1]

Inclusion and exclusion criteria for RE-MIND2 were reported in Table 14 of the CS.[1] The *"non-randomised cohorts were balanced with the L-MIND population on nine baseline covariates using estimated propensity score"*, namely:[1]

1. Age (as categorical variable with subgroups <70 vs. ≥70 years of age)
2. Ann Arbor stage (I/II vs. III/IV)
3. Refractoriness status to last therapy line (yes vs. no)
4. Number of prior lines of therapy (1 vs. 2/3)
5. History of primary refractoriness (yes vs. no)
6. Prior ASCT (yes vs. no)
7. Neutropenia (<1.5×109/l; conversion formula (g/dl×0.621=mmol/l); yes vs. no)
8. Anaemia (<10 g/dl [=6.21 mmol/l]; *) (yes vs. no)
9. Elevated lactate dehydrogenase (LDH>upper limit of normal [ULN]; yes vs. no)

Two additional factors were used in sensitivity analyses, namely:[8]

10. History of early relapse (yes vs. no) and history of primary progressive disease (yes vs. no)
11. ECOG (0 to 1 vs. ≥2)

"Data from the L-MIND study (…) were compared with the following observational cohorts in RE-MIND2":[1]

- Systemic therapies pooled cohort
- BR cohort
- R-GemOx cohort
- R + LEN (R2) cohort
- CD19 CAR-T cohort (pre-specified sensitivity analysis)
- Pola-BR cohort (pre-specified sensitivity analysis)
- Pixantrone monotherapy cohort

Primary endpoint was OS while ORR, CR rate, DoR, event-free survival, PFS, TTNT, treatment discontinuation rate due to AEs, and duration of treatment exposure were reported as secondary end points.[1]

In line with the comparators defined in the NICE final scope, see Section 2.3, results are presented for BR (Section 3.3.1.1), R-GemOx (Section 3.3.1.2), pola-BR (Section 3.3.1.3), and pixantrone (Section 3.3.1.4).[2]

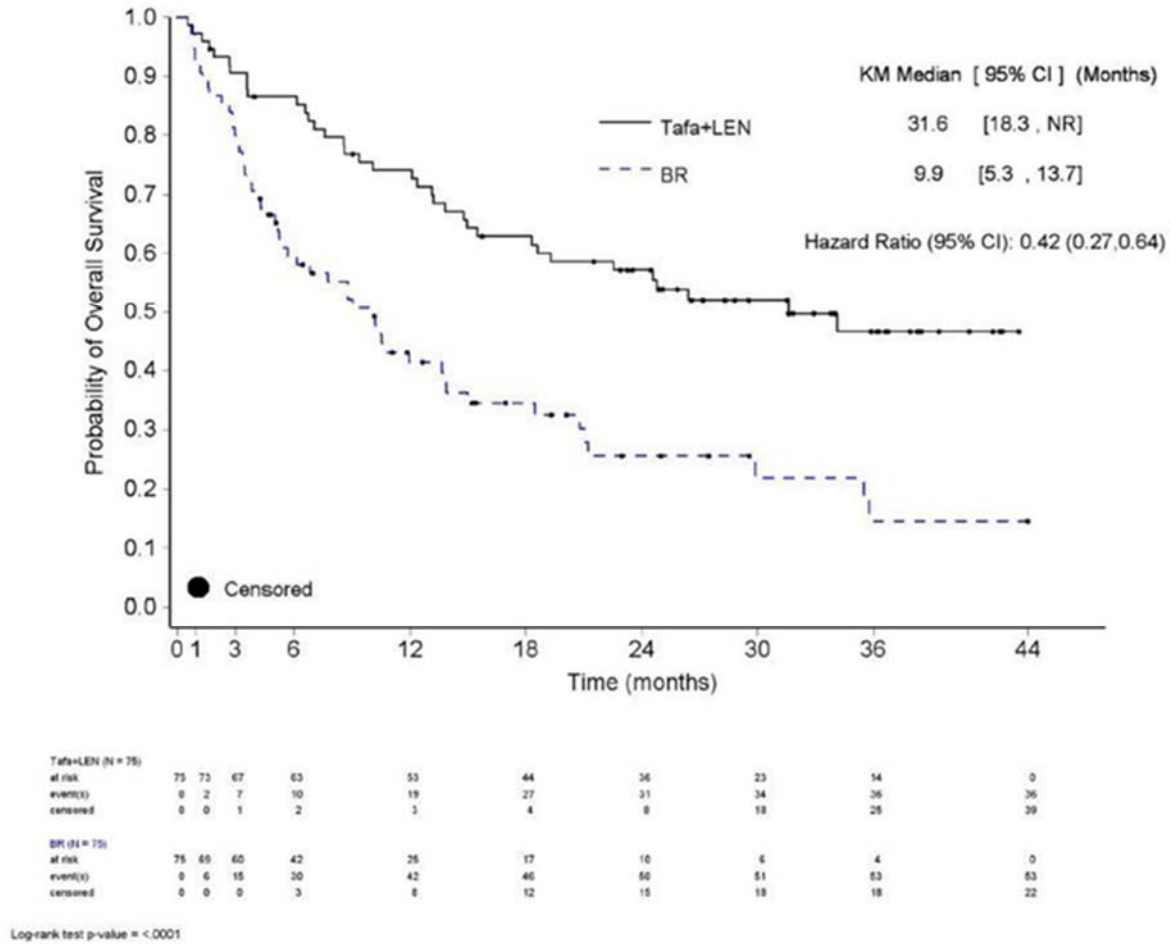
3.3.1.1 BR

The difference in OS between cohorts was statistically significant in favour of TAFA+LEN vs. BR (hazard ratio (HR) 0.418, 95% CI 0.272 to 0.644; Cox proportional hazards (PH) model P<0.0001), see Figure 3.1.[1]

A sensitivity analysis, using 11 covariates, showed a *"a less pronounced difference in OS between treatments compared with the primary analysis"* and did not reach statistical significance (HR 0.652, 95% CI 0.403 to 1.054; Cox PH model P=0.0809).[8]

Another sensitivity analysis, using overlap weights, was in line with the primary analysis (HR 0.433, 95% CI 0.256 to 0.732, [redacted]).[4, 22]

Figure 3.1: KM plot for OS: BR



Based on Figure 11a of the CS[1]
BR = rituximab in combination with bendamustine; CI = confidence interval; CS = company submission; KM = Kaplan-Meier; LEN = lenalidomide; OS = overall survival

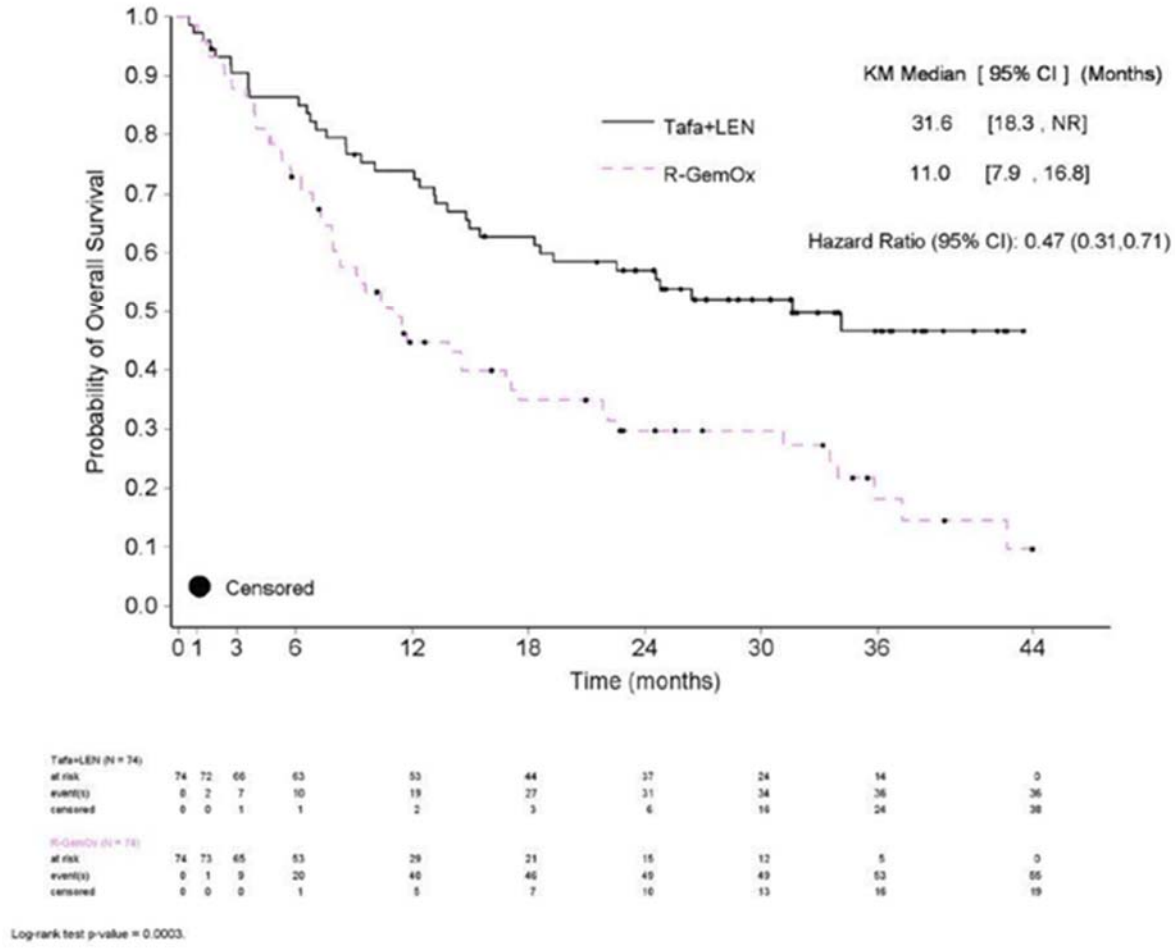
3.3.1.2 R-GemOx

The difference in OS between cohorts was statistically significant in favour of TAFA+LEN vs. R-GemOx (HR 0.467, 95% CI 0.305 to 0.714; Cox PH model P=0.0004), see Figure 3.2.[1]

A sensitivity analysis, using 11 covariates, confirmed the findings of this analysis (HR 0.535, 95% CI 0.337 to 0.850; Cox PH model P=0.0081).[8]

[redacted][22]

Figure 3.2: KM plot for OS: R-GemOx



Based on Figure 11b of the CS[1]
CI = confidence interval; CS = company submission; KM = Kaplan-Meier; LEN = lenalidomide; NR = not reached; OS = overall survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin

3.3.1.3 Pola-BR

In response to a request for clarification, the company provided results for TAFA+LEN vs. pola-BR. In brief, [redacted], see Figure 3.3.[4] The ERG noticed that these results were for the nine covariate model with multiple imputation.[24]

A sensitivity analysis, [redacted].[24]

According to the response to request for clarification, there were concerns regarding *"the observational cohort treated with POLA+BR with patients observed to be worse off compared to L-MIND enrolled patients"* and *"as a result, due to this lack of overlap in the populations the post-hoc analyses were*

conducted by matching L-MIND patients to POLA+BR treated patients as no overlap concerns were raised in the reverse matching. It should be noted however that the reverse matching led to a departure from the L-MIND original population".[4]

Figure 3.3: KM plot for OS: Pola-BR

Based on Figure 7 of the response to the request for clarification[4]
CI = confidence interval; KM = Kaplan-Meier; LEN = lenalidomide; NR = not reached; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

3.3.1.4 Pixantrone

According to the response to the request for clarification, *"because of the small accrual of patients treated with pixantrone in the RE-MIND2 study (n=17), no comparative efficacy analyses of TAFA+LEN versus pixantrone could be conducted".*[4]

3.3.2 Match-adjusted indirect comparisons

According to the CS, the population from L-MIND was matched with the published comparator populations via a matching-adjusted indirect comparison (MAIC).[1] Relevant studies were selected based on a SLR and interview with clinical experts[25].[1] Further details are provided in Appendix D of the CS.[8]

As detailed in Table 3.13, six prospective studies were selected for inclusion in the MAIC.[1]

Table 3.13: Studies identified for the MAIC

Comparator	Study	Data sources
Pola-BR	GO29365[26, 27]	Sehn et al. 2018 Blood[28]
BR	GO29365[a26, 27]	Sehn et al. 2018 Blood[28]
	Ohmachi et al. 2013[29]	Ohmachi et al. 2013 (no OS or DoR results) [29]

Comparator	Study	Data sources
	Vacirca et al. 2014[30]	Vacirca et al. 2014 (no OS results reported) [30]
R-GemOx	Mounier et al. 2013[31]	Mounier et al. 2013 (only median DoR without CI reported)[31]
Based on Table 16 of the CS[1] [a] [redacted] BR = bendamustine and rituximab; CI = confidence interval; CS = company submission; DoR = duration of response; IRC = independent radiology/clinical review committee; MAIC =matched adjusted indirect comparison; OS = overall survival; pola-BR = polatuzumab, bendamustine, and rituximab; R-GemOX = rituximab, gemcitabine, oxaliplatin		

3.3.2.1 BR

According to the CS, *"an overview of the relative efficacy estimates for TAFA+LEN compared with all comparators (pola-BR, BR) across all efficacy outcomes is also provided in Appendix D"*.[1]

It should be noted that results for OS, based on the pooled estimate, could not be located in any of the documents provided by the company. Other results of the MAIC are presented in Table 3.14.

Table 3.14: Relative Efficacy Estimates for Observed and Weighted TAFA+LEN vs. BR

Outcome	Unadjusted Comparison (95% CI, P-value)	Population-adjusted Comparison (95% CI, P-value)
OS[a]	HR 0.27 (0.16 to 0.44; <0.001)	HR 0.39 (0.18 to 0.82; 0.014)
PFS-IRC[b]	HR 0.40 (0.23 to 0.71; 0.002)	HR 0.39 (0.29 to 0.53; <0.001)
DoR-IRC[b]	HR 0.30 (0.23 to 0.41; <0.001)	HR 0.35 (0.25 to 0.50; <0.001)
ORR-IRC[b]	OR 1.69 (0.69 to 4.14; 0.252)	OR 1.59 (0.94 to 2.69; 0.086)
CRR-IRC[b]	OR 2.05 (1.00 to 4.17; 0.049)	OR 2.43 (1.33 to 4.41; 0.004)
Based on Table 20 of MAIC technical report[23] [a] GO29365 only; [b]pooled estimate using GO29365, Vacirca et al. and Ohmachi et al. BR = rituximab in combination with bendamustine; CI = confidence interval; CRR = complete response rate; CS = company submission; DoR = duration of response; HR = hazard ratio; IRC = independent review committee; MAIC = matching-adjusted indirect comparison; LEN = lenalidomide; NR = not reported; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TAFA = tafasitamab		

3.2.3.2 R-GemOx

Results of the MAIC are presented in Table 3.15.

Table 3.15: Relative Efficacy Estimates for Observed and Weighted TAFA+LEN vs. GemOx

Outcome	Unadjusted Comparison (95% CI, P-value)	Population-adjusted Comparison (95% CI, P-value)
OS	HR 0.54 (0.35 to 0.83; 0.006)	HR 0.55 (0.28 to 1.06; 0.073)
PFS-INV	HR 0.58 (0.39 to 0.88; 0.010)	HR 0.59 (0.30 to 1.17; 0.133)
DoR-INV	Ratio of medians 4.39	Ratio of medians 4.39

Outcome	Unadjusted Comparison (95% CI, P-value)	Population-adjusted Comparison (95% CI, P-value)
ORR-INV	OR 1.22 (0.57 to 2.58; 0.609)	OR 1.42 (0.46 to 4.38; 0.543)
CRR-INV	OR 0.73 (0.35 to 1.54; 0.409)	OR 1.09 (0.34 to 3.54; 0.882)

Based on Table 60 of Appendix D of the CS[8]
CI = confidence interval; CRR = complete response rate; CS = company submission; DoR = duration of response; HR = hazard ratio; INV = investigator assessed; LEN = lenalidomide; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

3.3.3.3 Pola-BR

Results of the MAIC are presented in Table 3.16.

Table 3.16: Relative Efficacy Estimates for Observed and Weighted TAFA+LEN vs. pola-BR

Outcome	Unadjusted Comparison (95% CI, P-value)	Population-adjusted Comparison (95% CI, P-value)
OS	HR 0.59 (0.36 to 0.97; 0.039)	HR 0.68 (0.35 to 1.34; 0.268)
PFS-IRC	HR 0.79 (0.49 to 1.30; 0.354)	HR 0.88 (0.45 to 1.73; 0.719)
DoR-IRC	HR 0.49 (0.23 to 1.04; 0.062)	HR 0.34 (0.12 to 0.98; 0.045)
ORR-IRC	OR 0.81 (0.37 to 1.80; 0.607)	OR 0.68 (0.25 to 1.86; 0.450)
CRR-IRC	OR 0.67 (0.31 to 1.46; 0.309)	OR 0.74 (0.27 to 2.07; 0.571)

Based on Table 9 of Appendix D of the CS[8]
CI = confidence interval; CRR = complete response rate; CS = company submission; DoR = duration of response; HR = hazard ratio; IRC = independent review committee; LEN = lenalidomide; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; TAFA = tafasitamab

3.4 Critique of the indirect comparison and/or multiple treatment comparison

ERG comment: There was generally a lack of clarity as to the justification for the choice of comparators and studies for the indirect comparisons. The ERG notes that lenalidomide is not listed as a relevant comparator in the NICE final scope (see Section 2.3) thus can accept that the comparison with lenalidomide might be of little clinical relevance, particularly since it was not included in the original NICE scope (see Section 2.3) and so this critique will focus on RE-MIND2 as opposed to RE-MIND. The company chose to focus only on comparisons of R-GemOx and BR using RE-MIND2 as opposed to pixantrone, CAR-T therapy, and pola-BR, although analyses for the latter two therapies were conducted and a short summary provided.[1] The ERG appreciates that CAR-T was not included in the NICE scope, but pola-BR was and the company also stated that clinical experts considered it to be relevant.[1]

Also, it was unclear why MAIC results were presented in the CS only for pola-BR and BR, even though a MAIC was conducted and results presented in Appendix D for a comparison with R-GemOx.[1, 8] As set out in technical support documents (TSDs) 17 and 18, there are multiple methods available for adjusting for confounding in the absence of studies that include both intervention and comparator.[32, 33] According to TSD 17, analysis of pooled individual participant data (IPD) is preferable to populations adjustment, e.g. using a MAIC, whereby only the IPD for the intervention are adjusted to better match the summary characteristics of the patients in the comparator study.[33] There are two main reasons for this: pooling comparator and intervention IPD affords greater ability to reduce the risk of bias, and the adjustment of the data is likely to be more generalisable to the population likely to receive the intervention. The latter can be explained simply by the fact that because only the intervention data can

be adjusted to better match the comparator population when only summary statistics are available for the comparator, as is the case with a MAIC. Of course, this would not be a problem if the comparator population corresponds to that where the intervention would be prescribed in clinical practice. However, if there are differences between intervention and comparator populations, which there must be a suspicion of to warrant any adjustment, then it is likely that the intervention population bears a closer resemblance to clinical practice, not least because those are the patients who were actually given the intervention. This population mismatch is compounded when there are multiple comparators each with outcomes estimated from a different data source. This means that to estimate the treatment effect of the intervention versus each comparator, the intervention data are adjusted differently for each comparator. This is therefore likely to lead to a bias in implied treatment effects between comparators. On the other hand, estimating the treatment effect of the intervention and comparators from the same pooled IPD and adjusting the data for all comparators to better match the characteristics of those who received the intervention is liable to lead to greater comparability. This implies that in principle the ERG prefers RE-MIND2 to the MAICs.

Of course, even if the pooled IPD approach were to be preferred in principle, there is the question as to how well implemented the analyses were in practice. For RE-MIND2 the company stated in the CS that 1:1 nearest neighbour matching was employed based on the propensity score estimated using nine covariates, with 11 used in a sensitivity analysis.[1] In fact, for pola-BR, CAR-T and R2 the main analysis used six covariates with nine used in combination with multiple imputation in a sensitivity analysis.[24] Matching is one of the approaches recommended in TSD 17.[33] However, there are other methods that could be used including IPW and regression adjustment (RA) or combinations of approaches, i.e. so-called a doubly robust method. The company were requested in the clarification letter to refer to TSD 17 to justify the choice of methods.[3, 33] In response to the request for clarification, the company stated that *"in a sensitivity analyses, average treatment effect (ATE) was also derived through the use of propensity score weighting in the RE-MIND2 primary analyses. Results obtained through these means were aligned with the results reported in the base case. In the RE-MIND2 post-hoc analyses, average treatment effect on the treated (ATT) was evaluated using inverse probability of treatment weighting to extract as much information by a limited dataset and ensure specific results were not driven by a specific methodological choice"*.[4] The ERG would point out that IPW also uses the propensity score, the weight being the inverse of the propensity score, which is the probability of receiving the treatment. Also, the only mention of the propensity score in the CS or the appendices was in relation to matching, but the ERG did note that a statistical report of a post-hoc analysis (also mentioned in the clarification letter response) did mention the application of IPW, but only for comparisons with pola-BR, CAR-T and rituximab and lenalidomide (R2).[24] The ERG noted difficulty in locating this statistical methods information, normally expecting this to be located in Document B of the CS or in one of the accompanying appendices. A formula for the IPWs which indicates that it is the ATT that has been estimated, p/(1-p), was given as the weight for the comparator data then the equivalent weight for the intervention is p/p=1. This implies that the ATT was estimated in the post-hoc analyses of comparisons with pola-BR, CAR-T and R2 because only the comparator data are adjusted (the intervention has a weight of 1, i.e. no adjustment). In fact, when matching as opposed to IPW was used, the baseline characteristics of the TAFA+LEN cohort varied depending on which comparator was being matched (BR, R-GemOx, pola-BR, CAR-T or R2), which suggests difference estimates of the ATE. As explained in TSD 17, the estimation of the ATE might be the ideal, assuming that there are patients who received the comparator who might be the sort of patients who would receive the intervention in clinical practice and vice versa.[33] However, although the characteristics of the comparator and intervention cohorts might be different, the estimation of the ATE still requires sufficient overlap in characteristics between intervention and comparator patients to ensure that the probability of receiving

the other treatment is not zero. The additional problem is that, as explained above in relation to a MAIC, matching that involves selecting intervention patients to better match comparator ones necessarily changes the resulting cohort characteristics so that if there are several comparators then there can be a bias in treatment effect between comparators. This does not happen when estimating the ATT because only the comparator cohorts are adjusted in order to better match the intervention cohort characteristics. Therefore, given the need to compare to several comparators, the ERG in principle would prefer a method of adjusting for confounding that estimates the ATT which suggests different estimates of the ATE. Also, although the differences in baseline characteristics were small, and sample size only varied by 1, the fact that an "adjustment factor" was considered if the KM plots suggested that the original and matched TAFA+LEN patients were different in terms of OS or PFS, indicates a more substantial difference between the matched and unmatched TAFA + LEN data. It is therefore unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Although not explicitly stated, if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the *average treatment effect on those treated with the comparator*.

The company were also asked to explain why they did not consider RA.[3] In response to the request for clarification, the company stated that *"regression analyses were not considered because of the observed differences in the L-MIND and observational cohorts that could have led to quasi separation of the data in the estimation of the models, particularly in the analyses against POLA+BR, and concerns over the possibility of finding good models to fit the outcomes of interest (PFS and OS)"*.[4] It is unclear to the ERG what is meant by this as *"quasi separation"* suggests that there was very little overlap between intervention and comparator patients such that one or more characteristics might predict treatment almost perfectly, i.e. propensity score = 1 or 0. However, this would have also affected the validity of IPW. *"Overdispersion"* of weights is mentioned in relation to pola-BR in the response to request for clarification, which suggests that some propensity scores might be regarded as too close to 1 or 0, but this was not mentioned in any of the documents provided by the company, including the CS, appendices or study reports.[1, 4, 8] The statistical report for the post-hoc analysis did mention that, for IPW, trimming of extreme weights (threshold of 30) was applied and that there was still a lack of balance as measured by standardised mean differences (SMDs) in covariates, although the distribution of weights was not reported in any document for the ERG to assess the need for trimming.[24] Appendix D also stated that *"comparative analysis with the L-MIND cohort was performed only if a certain balance of baseline characteristics had been achieved (i.e., standardised mean difference [SMD] ≤0.2 for all covariates)"*.[8] Although it is reasonable to consider an arbitrary threshold for checking for sufficient overlap, the value mentioned in TSD 17 is 0.25 and there is no recommendation to not perform the analysis at all should the threshold be exceeded for a single covariate.[33] The ERG can confirm that the SMDs for pola-BR for four of the nine covariates used in the company base-case statistical model did appear to be high (above 0.25), although all but one (prior ASCT) were below 0.25 for the six covariate model.[24]

The statistical report for the post-hoc analysis also mentioned that *"overlap weights"* could be used to mitigate the problem of extreme weights: although not referred to in TSD 17, these are essentially the propensity scores themselves as opposed to the inverse of them and so are more tightly bounded (0 to 1).[24, 33, 34] Appendix D also states that as sensitivity analysis used overlap weights with a stricter calliper for matching to reduce the SMDs to no more than 0.1, although the only sensitivity analysis results that were presented were for an 11 covariate model that appeared not to employ overlap weights and with a limit of SMD of 0.2.[8] The only results using overlap weights were those versus BR and R-GemOx, which were presented for OS in the QuEENS checklist provided with the clarification letter and also in a CSR for RE-MIND2.[4, 22] Although no baseline characteristics were provided to confirm this, the

response to clarification stated that the overlap weights method was used to estimate the average treatment effect (ATE).[4, 22]

In conclusion, in principle the ERG prefers the RE-MIND2 IPD analyses to the MAICs for the reasons given above. However, there was generally a lack of clarity in the methods used for indirect comparisons: Inferring from all documents provided by the company and the clarification letter response, it appears that matching using the propensity score based on nine covariates was used in the base-case for comparison with the following comparators using RE-MIND2:

- R-GemOx (Section 3.3.1.2)
- BR (Section 3.3.1.1)
- Pola-BR (Section 3.3.1.3)
- R2
- CAR-T

It is unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Although not explicitly stated, if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the *average treatment effect on those treated with the comparator*.

IPW to estimate the ATT appeared to be only used for the following comparators:

- Pola-BR (Section 3.3.1.3)
- R2
- CAR-T

Overlap weights to estimate the ATE appeared to be only used for the following comparators:

- R-GemOx (Section 3.3.1.2)
- BR (Section 3.3.1.1)

Various other sensitivity analyses were also conducted and variously reported across the company supplied documents, including the use of multiple imputation and six or 11 as opposed to nine covariates. Finally, RA was not attempted. However, as shown by clinical expert opinion and comparison to trial data of the economic model extrapolations of the data from these analyses summarised in Section 4.2.6.4.1, the method that provides the better external (clinical) validity for pola-BR is not the use of RE-MIND2: the MAIC is superior. By contrast, if the MAIC is selected for R-GemOx, OS results seem to be overestimated. For BR, either the MAIC or the RE-MIND2 approaches lead to similar results (1.04 vs. 1.13 quality-adjusted life years (QALYs), respectively). Therefore, given the lack of clarity and variability by comparator in analysis of RE-MIND2, the possibility of bias due to attempts to estimate the ATE, and the questionable clinical validity of pola-BR extrapolations, the ERG questions the validity of the ITC results generally. This constitutes a key issue, which might be mitigated by full reporting of all potentially suitable analyses, including the use of IPW, overlap weights and RA for all relevant comparators. This should be accompanied by an assessment of overlap, including by use of SMDs as well as validation by clinical expert opinion and appropriate external data.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG conducted quality assessment of the studies identified in the CS, see Section 3.1.5 for details.

3.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on tafasitamab with lenalidomide for treating relapsed or refractory diffuse B-cell lymphoma. Searches were conducted in February 2021 and updated in June 2021. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and grey literature resources were searched. Strategies included an extensive list of search terms for comparators, but the ERG believes that search terms should also have been included for tafasitamab. A publication date range of longer than the last ten years may have been beneficial.

Study selection was restricted according to language, with only studies reported in English or French being eligible. The stated date limitation for study selection was very narrow (09 February 2021 to 28/29 June 2021) and this may be an error in light of the date restrictions for the literature searches (post 2010 for clinical effectiveness studies and post 2000 for CE evaluations. This in itself is also discrepant since clinical evidence would need to be available concurrently (if not earlier) than the CE data.

Data were not extracted according to best recommended practice for systematic reviews. Whilst extraction of study-level details and baseline data by a single reviewer with independent checking by a second reviewer is acceptable, it is recommended that outcome data are extracted by two independent reviewers. The risk of inaccuracies in outcome data (and therefore ensuing estimates) cannot be discounted.[9]

The company used an inappropriate methodological quality assessment checklist for assessing the L-MIND and MOR208C201 studies, i.e. one that did not account for the single-arm design of both studies. The ERG have carried out additional work and have assessed both studies using a more suitable tool namely, the NICE checklist for assessing non-randomised and non-controlled studies.[15]

The ERG notes that the only direct evidence comparing tafasitamab plus lenalidomide dual therapy with lenalidomide therapy alone comes from one prospective cohort consisting of 81 patients. These data were subsidised with additional data from an additional prospective cohort study focused on tafasitamab monotherapy.

A meta-analysis was not presented and the CS provides a brief, narrative summary of the efficacy results for the two studies: L-MIND (MOR208C203; assessed efficacy and safety of tafasitamab and lenalidomide dual therapy) and MOR208C201. In the L-MIND study, it was apparent that 11/81 (13.6%) patients had a diagnosis made only by local pathology assessment and not confirmed by central pathology at the start of the study. This may call into doubt the eligibility of some patients in the cohort. The FAS for efficacy analyses comprised 80/81 (98.8%) patients. Efficacy outcomes included OS, PFS, and ORR. HRQoL data were not available from L-MIND. Outcomes additional to the NICE Final Scope were TTP, TTNT and DoR. The safety population included all enrolled patients (N=81). Data were provided on TEAEs and discontinuation due to AEs.

Of concern is the lack of details regarding serious adverse events in both the L-MIND and MOR208C201 studies; the L-MIND study only provides data regarding those SAEs that occurred in two or more patients, even though data regarding less important adverse events were reported for all patients. The CS does not mention serious adverse events that occurred in the MOR208C201 study, indeed the publication by Jurczak et al. 2018 specifies that "*four of 92 patients experienced an SAE with a suspected relationship to MOR208 (tafasitamab)*", two of which occurred in the DLBCL group included within the CS (febrile neutropenia and genital herpes).[20] No information was provided regarding total SAEs; i.e. SAEs that did not have a suspected relationship to tafasitamab.

There was generally a lack of clarity in the methods used for indirect comparisons and some were conducted for comparators outside of the NICE scope. Inferring from all documents provided by the company and the clarification letter response, it appears that matching using the propensity score based on nine covariates to estimate the ATE was used in the base-case for comparison with the following in-scope comparators using RE-MIND2: R-GemOx, BR and pola-BR. It is unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Although not explicitly stated, if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the *average treatment effect on those treated with the comparator*. IPW to estimate the ATT appeared to be only used for pola-BR. Overlap weights to estimate the ATE appeared to be only used for R-GemOx and BR. Various other sensitivity analyses were also conducted and variously reported across the company supplied documents, including the use of multiple imputation and six or 11 as opposed to nine covariates. RA was not attempted. In addition, MAICs were conducted for comparison with R-GemOx, BR and pola-BR. Although in principle the ERG prefers the RE-MIND2 analyses to the MAICs, as shown by clinical expert opinion and comparison to trial data of the economic model extrapolations of the data from these analyses, the method that provides the better external (clinical) validity for pola-BR is the MAIC. By contrast, if the MAIC is selected for R-GemOx, OS results seem to be overestimated. For BR, the MAIC and RE-MIND2 approaches lead to similar results. Therefore, given the lack of clarity and variability by comparator in analysis of RE-MIND2, the possibility of bias due to attempts to estimate the ATE, and the questionable clinical validity of pola-BR extrapolations, the ERG questions the validity of the ITC results generally. This constitutes a key issue, which might be mitigated by full reporting of all potentially suitable analyses, including the use of IPW, overlap weights and RA for all relevant comparators. This should be accompanied by an assessment of overlap, including by use of SMDs as well as validation by clinical expert opinion and appropriate external data.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to CE presented in the CS. The CADTH evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[5, 6] The CS was checked against the STA specification for company/sponsor submission of evidence.[7] The ERG has presented only the major limitations of each search strategy in the report.

Appendices G and H of the CS detail a literature review using systematic methodology undertaken to identify relevant literature relating to economic and HRQoL data on tafasitamab with lenalidomide for treating R/R DLBCL.[35, 36] Searches relating to costs, health economics, HRQoL and utilities were conducted simultaneously. The searches were conducted in two stages: an initial search in June 2020 and an update in July 2021. The same search strategies were used in the original search and updates.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the cost effectiveness literature review (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE	PubMed	2000-7/6/20 7/6/20-1/7/21	7/6/20 13/7/21
Embase	Embase.com	2000-7/6/20 7/6/20-14/7/21	7/6/20 13/7/21
CENTRAL CDSR	Wiley	2000-7/6/20 Last year to 13/7/21	7/6/20 13/7/21
HTA Database NHS EED DARE	CRD website	2000-7/6/20	7/6/20
INAHTA HTA database	Not stated	Not stated	13/7/21
PsycINFO	Not stated	2000-7/6/20 2020-13/7/21	7/6/20 13/7/21
EconLit	Not stated	Not stated 2020-13/7/21	7/6/20 13/7/21
CEA Registry	Not stated	Not stated	7/6/20 13/7/21
Additional resources			
CADTH	Internet	Not stated	7/6/20

Resource	Host/Source	Date Ranges	Dates searched
			13/7/21
NICE			7/6/20 13/7/21
SMC			7/6/20 13/7/21
AWMSG			7/6/20 13/7/21
IQWiG			7/6/20 13/7/21
HAS			7/6/20 13/7/21
PBAC			7/6/20 13/7/21

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDSR = Cochrane Database of Systematic Reviews; CEA = cost effectiveness analysis; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EED = Economic Evaluation Database; HAS = Haute Autorité de Santé; HTA = health technology assessment; INAHTA = International Network of Agencies for Health Technology Assessment; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium

ERG comment:

- Searches were undertaken to identify economic and HRQoL data on tafasitamab with lenalidomide for treating R/R DLBCL, with searches relating to costs, health economics, HRQoL and utilities conducted simultaneously. The CS provided sufficient details for the ERG to appraise the literature searches.[1]
- A good range of databases, clinical trials registers and additional grey literature resources were searched.
- Searches were well structured, transparent and reproducible, although there were issues with documentation in places, where the search strategies had been copied into a tabular format. The Cochrane Manual recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[9]
- The search strategies contained a population facet (R/R DLBCL), and for the searches of MEDLINE and Embase this was then combined with an additional facet of terms relating to treatments for the condition. The list of comparators was extensive, including many which were not listed in the NICE final scope,[2] and a good range of subject indexing terms (MeSH/EMTREE) and free text was used. Tafasitamab was not among the drug names in the search strategy, so any studies referring to tafasitamab but not to its comparators will not have been retrieved by the MEDLINE or Embase searches. This may be because the aim of the searches was to identify cost/resource utilisation evidence only for pharmacological treatments which are currently available for transplant-ineligible R/R DLBCL, however without re-running the searches and assessing the results, it is unclear what effect this may have had. The abbreviation 'Pola-BR' was also missing

from the strategies, although polatuzumab is included as subject indexing and free-text search terms.

- Search filters were applied to the MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) results to limit the results to economic/cost and HRQoL studies. The filters used were cited as those developed and maintained by the CADTH Information Services Filters Working Group.
- Results were limited by publication date from 2000 onwards. No language limits were applied.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on CE studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with R/R DLBCL that meet all of the following criteria: **For refractory DLBCL:** • No response to initial treatment • Stable or progressing disease within 6 months after end of initial treatment **For relapsed DLBCL:** • Response on initial treatment but disease returns • On second or later line treatment • Be ineligible for ASCT • Be ineligible for allogenic stem cell transplantation Studies with a mixed population of transplantation eligible/ ineligible patients were included (even when results were not reported separately for these groups). Studies with a mixed population with respect to indication were included if results were presented separate for the DLBCL patient group. Transformed lymphoma with DLBCL component, mixed presentation with either indolent and aggressive lymphoma or DLBCL was included. Double hit lymphoma, triple hit lymphoma (in the absence of clear information in the title or abstract if it was clearly DLBCL related) was included.	• Animal subjects • Non-adult populations • Testicular lymphoma • Bone lymphoma • Primary CNS lymphoma • Primary breast lymphoma • Primary breast DLBCL • Primary cutaneous DLBCL • DLBCL with CNS involvement • BL- and EBV-positive aggressive lymphoma • HIV-associated lymphoma • DLBCL in HIV patients • DLBCL in hepatitis B and C patients
Intervention (economic evaluations)	Tafasitamab + lenalidomide	N/A
Intervention (cost and resource use)	Tafasitamab + lenalidomide	N/A

	Inclusion criteria	Exclusion criteria
Comparator	All treatment regiments for the indication described in NCNN and ESMO guidelines and approved for use in the US or the EU, including: • ASHAP, ASHAP + rituximab (R ASHAP) • ACVBP, ACVBP + rituximab (R ACVBP) • Bendamustine, bendamustine + rituximab (BR) • Bendamustine + rituximab + polatuzumab vedotin (pola-BR) • Brentuximab vedotin • CEOP, CEOP + rituximab (R CEOP) • CEPP, CEPP + rituximab (R CEPP) • CHOP, CHOP + rituximab (R CHOP), R2 CHOP • DHAOx, DHAOx + rituximab (R DHAOX) • DHAP, DHAP + rituximab (R DHAP) • EPOCH, EPOCH + rituximab (R EPOCH) • DA EPOCH, DA EPOCH + rituximab (DA EPOCH R) • ESHAP, ESHAP + rituximab (R ESHAP) • GDP, GDP + rituximab (R GDP) • Gemcitabine • Gemcitabine + rituximab • Gemcitabine + dexamethasone + carboplatin • Gemcitabine + dexamethasone + carboplatin + rituximab • Gemcitabine + vinorelbine • Gemcitabine + vinorelbine + rituximab • GemOx, GemOx + rituximab (R GemOx) • Ibrutinib, ibrutinib + rituximab • ICE, ICE + rituximab (R ICE) • IEV, IEV + rituximab (R IEV) • Ifosfamide, ifosfamide + rituximab • IGEV, IGEV + rituximab (R IGEV) • Lenalidomide • Lenalidomide + rituximab • Lenalidomide + obinutuzumab • Methylprednisolone, methylprednisolone + rituximab • MINE, MINE + rituximab (R MINE) • BEAM, BEAM + rituximab (R BEAM) • Pixantrone, pixantrone + rituximab	Studies related to nonpharmacological treatment

	Inclusion criteria	Exclusion criteria
	• Polatuzumab vedotin + rituximab (R-pola) • Rituximab • Vinorelbine, vinorelbine + rituximab • Axicabtagene ciloleucel (axi cel) • Lisocabtagene maraleucel • Tisagenlecleucel • Best supportive care	
Outcomes(s) 1 (Published economic evaluations)	HRQoL outcomes measured by: • Utility instruments (e.g. EQ-5D, HUI-3, SF-6D) • Direct utility elicitation (e.g. time trade-off, standard gamble, rating scale) • Generic HRQoL questionnaires (e.g. SF 36, SF 12) • Disease specific questionnaires and patient reported outcomes (e.g. EORTC QLC C30, FACT G, FACT Lym, etc) Economic evaluation outcomes (e.g. ICER's)	Studies only reporting clinical efficacy and safety data
Outcomes(s) 2 (Cost/resource use studies)	Any cost or healthcare resource use information (e.g. direct medical costs, direct nonmedical costs, indirect costs).	N/A
Study design 1 (Economic evaluations)	• Cost utility analysis • Cost effectiveness analysis • Cost benefit analysis • Cost minimisation analysis	N/A
Study design 2 (Cost/resource use studies)	Any	N/A
Publication type (economic evaluations)	• Journal articles presenting original research • Reports published by HTA agencies	• Case repots, case series, or case study • Editorials • Letters, comments, opinions, or news
Publication type (cost and resource use)	• Journal articles presenting original research • Reports published by HTA agencies	• Case repots, case series, or case study • Editorials • Letters, comments, opinions, or news
Other (Economic evaluations)	• Published between 2000 and 2020 • Published in the English language	N/A
Other (cost and resource use)	• Published between 2000 and 2020 • Published in the English language	N/A

Based on Table 1 in Appendix G of the CS[35]

ACVBP = doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisone; ASCT = autologous stem cell transplant; ASHAP = doxorubicin, solumedrol, cytarabine, and platinum; BEAM = carmustine, etoposide,

	Inclusion criteria	Exclusion criteria
cytarabine, and melphalan; BL = Burkitt's lymphoma; BR = rituximab in combination with bendamustine; CEOP = cyclophosphamide, etoposide, vincristine, prednisone; CEPP = cyclophosphamide, etoposide, prednisone, procarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNS = central nervous system; CS = company submission; DA EPOCH = dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DA EPOCH R = dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; DHAOx = dexamethasone, cisplatin, oxaliplatin; DHAP = dexamethasone, cisplatin, cytarabine; DLBCL = diffuse large B cell lymphoma; EBV = Epstein–Barr virus; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; EQ-5D = European Quality of Life-5 Dimensions; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; ESMO = European Society for Medical Oncology; EU = European Union; FACT G = Functional Assessment of Cancer Therapy General; FACT Lym = Functional Assessment of Cancer Treatment Lymphoma; GDP = gemcitabine, dexamethasone, cisplatin or carboplatin; GemOx = gemcitabine, oxaliplatin; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; HTA = health technology assessment; HUI = Health Utility Index; ICE = ifosfamide, carboplatin, etoposide; ICER = incremental cost effectiveness ratio; IEV = ifosfamide, etoposide, epirubicin; IGEV = ifosfamide, gemcitabine, vinorelbine, prednisone; MINE = mesna, ifosfamide, mitoxantrone, etoposide; N/A = not applicable; NCCN = National Comprehensive Cancer Network; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R = rituximab; R2 CHOP = lenalidomide plus rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone; R-pola = Rituximab and polatuzamab vedotin; R/R = relapsed or refractory; SF 6D = Short Form Six Dimensions; SF 12 = 12 Item Short Form Health Survey; SF 36 = 36 Item Short Form Health Survey; US = United States		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify CE studies.

4.1.3 Identified studies

In total, 40 economic publications were identified from the CE SLR. A total of four publications reported CEAs which included the comparators included in the NICE final scope for this appraisal.[2] These studies were considered to some extent relevant for the decision problem by NICE and are discussed further. The study by Neubauer et al. 2019, explored the CE of TAFA+LEN compared to existing treatment pathways in terms of cost per life years gained (LYG).[37] The model used was a discrete event simulation model. However, the exact comparators considered in the study were not clearly stated in the study abstract. The other three studies (Betts 2019, Betts 2020 and Patel 2020) compared pola-BR vs. BR for transplant-ineligible R/R DLBCL patients, from a US payer perspective. Both Betts 2019 and Betts 2020 were based on a partitioned survival model approach, whereas Patel 2020 was based on a Markov model.[38-40] A summary of the four studies is provided in Table 4.3 below.

Table 4.3: Summary of included studies in the economic evaluations SLR

Study name Country	Patient population	Interventions and comparators	Model settings	QALYs (Interventions, comparator)	Costs (currency) (Intervention, comparator)	ICER (per QALY gained)
Neubauer 2019[37] USA	Transplant-ineligible R/R DLBCL	TAFA+LEN DLBCL treatment pathway	Perspective: payer Time horizon: NR Discrete event simulation	NR	NR	NR Cost per LYG: between $60,000 and $330,000 (depending on a hypothetical drug cost range of $200,000–$600,000)
Betts 2019[38] USA	Transplant-ineligible R/R DLBCL	pola-BR BR	Perspective: payer Time horizon: NR Partitioned survival model	**Incremental QALYs:** pola-BR vs. BR: 2.49	**Total cost (USD):** pola-BR: $232,358 BR: $118,874 **Incremental cost:** Pola-BR vs. BR: $113,484	pola-BR vs. BR: $45,535
Betts 2020[39] USA	Adults with R/R DLBCL, after ≥1 prior therapy, who were ineligible for HSCT	pola-BR BR	Perspective: payer Time horizon: lifetime Partitioned survival model	**QALYs:** pola-BR: 3.31 BR: 0.73 **Incremental QALYs:** pola-BR vs. BR: 2.57	**Total cost (USD):** pola-BR: $210,418 BR: $118,088 **Incremental cost:** pola-BR vs. BR: $92,329	pola-BR vs. BR: $35,864
Patel 2020[40] USA	Transplant ineligible R/R DLBCL	pola-BR BR	Perspective: payer Time horizon: lifetime Markov model	**QALYs:** pola BR: 2.35 BR: 0.59	**Total cost (USD):** pola-BR: $200,905 BR: $108,265	pola-BR vs. BR: $52,519

Study name Country	Patient population	Interventions and comparators	Model settings	QALYs (Interventions, comparator)	Costs (currency) (Intervention, comparator)	ICER (per QALY gained)
				Incremental QALYs: pola-BR vs. BR: 1.76	**Incremental cost:** pola-BR vs. BR: $92,641	

Based on Table 22 of the CS[1]

AE = adverse event; BR = bendamustine and rituximab; CS = company submission; DLBCL = diffuse large B cell lymphoma; HSCT = haematopoietic stem cell transplantation; ICER = incremental cost effectiveness ratio; LY = life year; PD = progressive disease; pola-BR = polatuzumab vedotin with bendamustine, and rituximab; QALY = quality adjusted life year; R/R = relapsed or refractory; TAFA+LEN = tafasitamab + lenalidomide; USA = United States of America; USD = United States dollar

4.1.4 Conclusions of the cost effectiveness review

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify economic and HRQoL data on tafasitamab with lenalidomide for treating R/R DLBCL.[1, 4] Searches were conducted in June 2020 and updated in July 2021. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and grey literature resources were searched. Strategies included an extensive list of search terms for the population and comparators, and validated search filters for study design. Overall, the ERG has no major concerns about the literature searches conducted.

The review was generally well reported and identified a range of CE, HRQoL, cost/resource use evidence relevant to the indication and potentially useful for the CEA. One of the identified studies was investigating TAFA+LEN, specifically. However, the study by Neubauer et al. 2019, explored the CE of TAFA+LEN compared to existing treatment pathways in terms of cost per LYG and the exact comparators included in the study were not clearly stated in the study abstract.[37] Therefore, the identified evidence did not negate the necessity to develop a de novo economic model.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	As per the reference case.
Perspective on costs	NHS and PSS.	As per the reference case.
Type of economic evaluation	Cost utility analysis with full incremental analysis.	As per the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	As per the reference case.
Synthesis of evidence on health effects	Based on systematic review.	As per the reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects expressed in QALYs. HRQoL measured using the EQ-5D-5L (mapped to EQ-5D-3L).
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	HRQoL reported by R/R DLBCL patients in a previous trial (treatments differ).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Representative sample of UK population. Van Hout mapping algorithm used to translate EQ-5D-5L utility values to EQ-5D-3L values.[41]

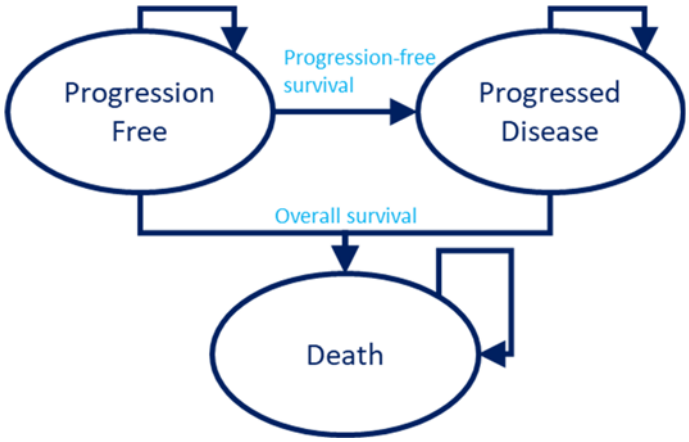
Element of health technology assessment	Reference case	ERG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	As per the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	As per the reference case.

DLBCL = diffuse large B-cell lymphoma; EQ-5D = EuroQoL-5 Dimensions; EQ-5D-3L = EuroQoL-5 Dimensions, 3 levels; EQ-5D-5L = EuroQoL-5 Dimensions, 5 levels; ERG = Evidence Review Group; HRQoL = health related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; R/R = relapsed or refractory; UK = United Kingdom

4.2.2 Model structure

The company developed in Microsoft Excel® a partitioned survival model to assess the CE of tafasitamab for the treatment of patients with DLBCL who are ineligible to receive SCT. As usual, partitioned survival models contain three health states, as shown in Figure 4.1. All patients start in the progression-free state and they remain there until progression or death. Transitions between health states are determined by PFS and OS survival curves calculated from the L-MIND trial data, with the proportion of patients in the progressed disease health state calculated as the difference between OS and PFS at any given time point. The proportion of the patients that are on treatment, while in progression-free, was informed by TTD data. The model has a cycle length of four weeks and half-cycle correction was applied to account for events happening at any time during the cycle. Costs and utilities are applied to each health state to calculate total costs and QALYs per model cycle. The input values of the model, and their underlying assumptions, are further elaborated in the remaining of Section 4 of the ERG report.

Figure 4.1: Schematic representation of the model structure



Based on Figure 17 of the CS[1]
CS = company submission

ERG comment: Partitioned survival models are commonly used in oncology in general and in NICE technology appraisals (TAs) for R/R DLBCL in particular, e.g. the same modelling approach was used for example in TA649 (polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma).[42] The model structure therefore appears appropriate.

4.2.3 Population

The population in the final scope by NICE was defined as "*Adults with relapsed or refractory diffuse large B-cell lymphoma and who are not eligible for have autologous stem-cell transplantation"*, in line with the conditional marketing authorisation by the EMA for the use of tafasitamab.[2] This is the same population included in the economic evaluation, which is also in line with the population enrolled in the L-MIND study, see Section 3.2.1. Patients included in the economic model were assumed to have an average baseline age of 69.3 years, 54.5% male, a mean weight of [redacted] and a mean height of [redacted], based on the L-MIND population characteristics.

ERG comment: As detailed in Section 2.1, the population is in line with the NICE final scope.[2]

4.2.4 Interventions and comparators

The intervention considered in the model was tafasitamab in combination with lenalidomide (TAFA+LEN), administered in four weekly treatment cycles (28 days). Tafasitamab is assumed to be administered by IV infusion at a dose of 12 mg/kg. For the first three treatment cycles, tafasitamab is administered weekly on days 1, 8, 15 and 22 of each 28-day treatment cycle, with an additional loading dose administered on day 4 of the first treatment cycle. After the first three treatment cycles, tafasitamab is administered on days 1 and 15 (bi-weekly) of each 28-day treatment cycle until disease progression. Lenalidomide is assumed to be administered orally at a dose of 25 mg per day for days 1 to 21 of each 28-day treatment cycle, up to a maximum of 12 treatment cycles.

The company included three comparators in the economic model, based on the R/R DLBCL patient pathway and feedback from clinical experts.[25] The chosen comparators were the following:

- Polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR). Dosing for pola-BR was based on TA649,[42] and consisted of polatuzumab vedotin 1.8 mg/kg IV once every three-week treatment cycle (day 2 of cycle 1, day 1 of cycles 2 to 6) up to a maximum of six total treatment cycles, bendamustine 90 mg/m^2 IV on two consecutive days for each three-week treatment cycle (days 2 and 3 of cycle 1, days 1 and 2 of cycles 2 to 6) up to a maximum of six total treatment cycles, and rituximab 375 mg/m^2 IV on day 1 for each three-week treatment cycle up to a maximum of six total treatment cycles
- Bendamustine and rituximab (BR). Dosing for BR was also based on TA649,[42] with BR dosing as defined in the pola-BR regimen.
- Rituximab, gemcitabine and oxaliplatin (R-GemOx). Dosing for R-GemOx was based on Mounier 2013,[31] whereas the maximum number of treatment cycles for R-GemOx was based on UK lymphoma guidelines.[43] These consisted of rituximab 375 mg/m^2 IV on day 1 of every 15-day treatment cycle up to a maximum of six treatment cycles, and gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 IV on day 2 of every 15-day treatment cycle up to a maximum of six treatment cycles.

ERG comment: As explained in Section 2.3 of this report, not all comparators included in the final scope issued by NICE were considered in this CS which has been identified as a key issue.[2]

4.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS). The model has a time horizon of 45 years, which is considered appropriate as a lifetime horizon given that the average age of patients at baseline is 69.3 years, as in the L-MIND study.[13] Costs and QALYs were discounted at 3.5% per annum according to the NICE method guidance.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Survival analysis - General approach: TAFA+LEN

Survival analyses for the TAFA+LEN arm, were conducted using L-MIND data. The company followed the recommendations by the NICE Decision Support Unit (DSU) on survival data extrapolation. Six parametric distributions (exponential, Weibull, Gompertz, lognormal, log-logistic and generalised Gamma) were fitted to extrapolate OS, PFS, and TTD data from the L-MIND study.[44] Analyses were performed using the LIFEREG procedure in SAS version 9.4, with a specialised macro used for the Gompertz distribution (since this is not a standard option in SAS 9.4).

The following criteria were considered by the company when selecting the most appropriate parametric distributions:

- Akaike information criterion (AIC) or corrected AIC (AICC) and Bayesian Information Criterion (BIC), with the best fit to the observed data given by the lowest AIC(C)/BIC values.
- Visual inspection of the parametric curves compared to the observed data.
- Clinical plausibility of the long-term extrapolations (confirmed in discussions with clinical experts).
- Validity of long-term extrapolations in relation to external data (where available).
- Modified Burnham/Anderson rules for AIC/AICC (similar to those adopted by the ERG in NICE TA612 and NICE TA640)[45, 46]:
    - Distributions within 4 points from the lowest AICC were classified as ‘good’ relative statistical fit.
    - Distributions within 4 to 7 points were classified as ‘neutral’.
    - Distributions within 7 to 10 points were considered as ‘inferior’.
    - Distributions with more than 10-point difference were considered as ‘poor’.
- Modified Kass/Raftery rules for BIC:
    - Distributions within 10 points from the lowest BIC were considered as ‘reasonable’ relative statistical fit.
    - Distributions with more than 10-point difference were classified as ‘poor’.
- Assessment of the plausibility of the hazard profiles (using smoothed hazard plots).

Finally, OS was capped by general population mortality using data from UK life tables, and PFS was capped by OS to prevent PFS from exceeding OS over time.[47]

4.2.6.2 Survival analysis - General approach: comparators

In the absence of head-to-head data to compare the (clinical) effectiveness of TAFA+LEN against any of the three comparators included in the CEA (pola-BR, BR and R-GemOx), the company relied on indirect treatment comparisons to estimate PFS and OS in the comparator arms of the model. Two approaches were selected by the company:

- A 1:1 nearest-neighbour (NN) matching with external (synthetic) control arms, using RE-MIND2 data.[22]
- A MAIC against the published clinical studies of key comparators.[23]

Details on these matching methods are provided and discussed in Sections 3.3 and 3.4, respectively. Details specific to the model implementation are explained below.

4.2.6.2.1 Use of the ITC

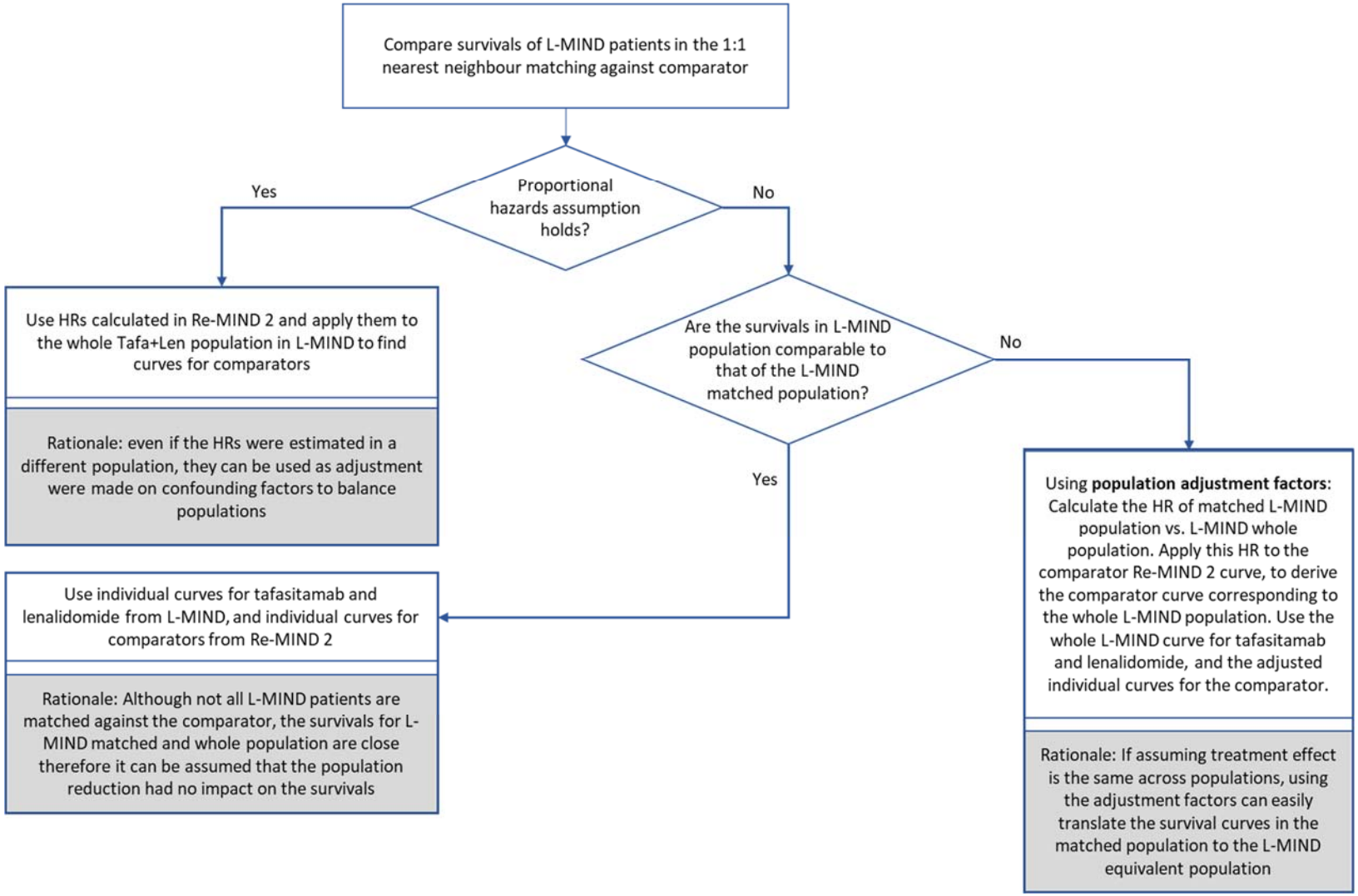
An ITC using RE-MIND2, 1:1 NN matching based on the PS estimated from nine covariates was used in the base-case for comparison with several comparators, including R-GemOx, BR and pola-BR, see Sections 3.3 and 3.4. After the matching was conducted, the company proceeded as follows:

1. For each comparator, the PH assumption was tested to determine whether a HR could be estimated from a comparison of the matched patients in L-MIND and the comparator arm.
2. If the PH assumption was deemed plausible, the estimated HR would be applied to the original L-MIND data.
3. When the PH assumption (between TAFA+LEN and a comparator) was considered to be violated, individual parametric fits to the matched patient data for the comparators would be required.
    a. OS and PFS Kaplan-Meier (KM) plots for the matched TAFA+LEN patients were overlaid with the original L-MIND data to assess whether the two populations were sufficiently similar.
    b. If the KM curves were deemed to be similar, "*unadjusted*" parametric fits for the comparator data from RE-MIND2 were used to model OS and PFS, and the parametric fits for the original L-MIND patients were used to model OS and PFS in the TAFA+LEN, as explained above (see Section 4.2.6.1).
    c. If the KM plots suggested that the original and matched TAFA+LEN patients were different in terms of OS or PFS, the company estimated an "*adjustment factor*" (similar to a constant HR) between the matched and unmatched TAFA+LEN patients, and applied the inverse of this estimate (1/adjustment factor) to the matched comparator arm data with the purpose to make it more comparable with the original L-MIND population.
    d. The "*adjustment factor*" was calculated as follows. For each comparator matched populations, OS and PFS Cox regression models were fitted to data from all TAFA+LEN patients appending data from the L-MIND matched patients. The Cox model assessed the effect of a *"dummy"* covariate defined as 1 if the records identified where from one of the matched sets, and 0 if they were from the L-MIND overall population. Note that this approach double counted some patients since the L-MIND matched patients were also included in the L-MIND enrolled population. The company indicated that while the result of the Cox regression model cannot be interpreted as an HR (due to double counting some patients), it provides a measure of the relationship between the overall L-MIND population against a subset of matched patients, that was further assumed to be applicable to the comparators. The inverse of this HR-like measure was applied to the OS and PFS curves obtained from the comparators matched subset to produce outcomes in an *"L-MIND-like"* population. This approach also relied on the PH assumption between L-MIND whole population and matched population. The company indicated that this assumption was tested for all comparator PFS and OS data, and the PH assumption was considered appropriate in each case. Finally, note that this "*adjustment*" was only needed for the comparison against pola-BR, because 42 out of the 81 participants in L-MIND were not possible to match,

which resulted in clear differences between the matched TAFA+LEN and the overall TAFA+LEN populations.

A schematic representation of the survival model selection process used for RE-MIND2 data is shown in Figure 4.2.

Figure 4.2: Schematic representation of RE-MIND2 survival model selection process



Based on Figure 64 in Appendix M of the CS[48]
CS = company submission; HR = hazard ratio

ERG comment: As explained above in Section 3.4, matching that involves selecting intervention patients to better match comparator ones necessarily changes the resulting patient cohort characteristics so that if there are several comparators then there can be a bias in treatment effect between comparators. Further comments on the critique of the ITC can be found in Section 3.4 of this report. The ERG comments in this section refer to the assumptions made by the company after the matching was conducted.

The PH assumption was first tested separately for each comparator against TAFA+LEN. However, the ERG would prefer to follow the general recommendation in DSU TSD 14 that when patient-level data are available, "*it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach – the assumption should be tested which will indicate whether it may be preferable to separately fit parametric models to each treatment arm, or to allow for time-varying hazard ratios. Fitting separate parametric models to each treatment arm involves fewer assumptions*".[44]

When KM plots suggested that the original and matched TAFA+LEN patients were different in terms of OS or PFS, the company estimated an "*adjustment factor*" between the matched and unmatched TAFA+LEN patients. It is worth noting here in addition to in Section 3.4 that the reason there is a difference is because of the ITC method employed, i.e. adjustment that appears to estimate the average treatment effect on those treated with the comparator instead of the ATT. If only comparator patients had been selected to match the TAFA+LEN cohort or IPW had been used for all comparators then the TAFA+LEN data would not have been adjusted as part of the ITC and no *"adjustment factor"* would be required.

The assessment of the *"difference"* seems subjective. The "*adjustment factor*" was calculated by a Cox regression model fitted to data from all TAFA+LEN patients appending data from the L-MIND matched patients. This approach double counted some patients since the L-MIND matched patients were also included in the L-MIND enrolled population. It is unclear why the original L-MIND dataset adding a covariate matched/not matched was not be used for the analysis. This would have avoided double counting patients. The inverse of this adjustment factor provided a measure of the relationship between the overall L-MIND population against a subset of matched patients, that was further assumed to be applicable to the comparators. This means that the adjustment factor between matched and unmatched patients in TAFA+LEN arm would be the same as the adjustment factor between the matched and unmatched patients in all comparators.

Since patient-level data were available for all comparators, the ERG considers that such adjustment factors might have been calculated for each arm, in order to test the assumption of equal adjustment factor across all arms. The adjustment approach relied on the proportional hazard assumption between the L-MIND and matched populations, however it is unclear how this was tested and if some violations were present in the analyses since the company indicated that the adjustment factor was not really a HR.

4.2.6.2.2 MAIC

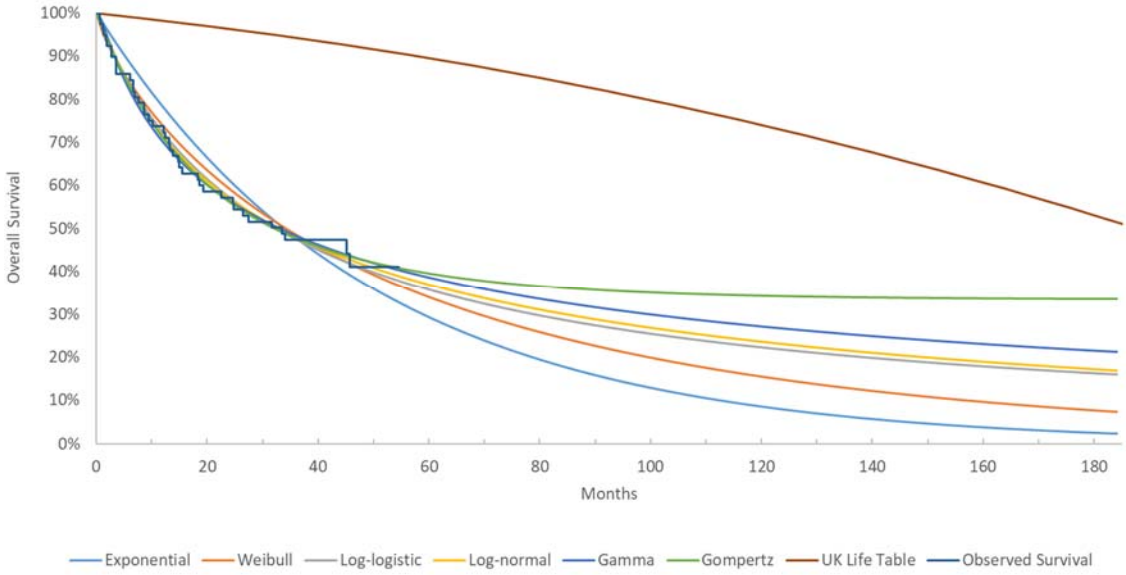
The methodology used in the MAIC is described and discussed in Sections 3.3 and 3.4 of this report, respectively. Details about how the MAIC results were implemented in the model (OS and PFS) are provided below.

4.2.6.3 Overall survival: TAFA+LEN

The company provided the AICC and BIC goodness of fit estimates for the parametric functions used to model OS for TAFA+LEN in L-MIND in Tables 133 and 134 of Appendix M of the CS.[48] The lognormal distribution resulted in the lowest AICC and BIC values, suggesting the best statistical fit to the observed data. However, all distributions resulted in AICC values differing in less than 4 points from the lognormal AICC value, with the exception of the exponential distribution (4.74 points), and all distributions resulted in BIC values differing in less than 10 points from the lognormal BIC value.

Visual inspection of the OS extrapolations for the TAFA+LEN arm, as shown in Figure 4.3, indicated, according to the company, that the exponential distribution resulted in the poorest visual fit to the data by overestimating most of the KM curve until the tail. To a lower extent, the Weibull distribution seemed to overestimate the middle section of the KM curve before appearing to underestimate the tail. All other distributions were practically indistinguishable in terms of visual fit to the observed KM data, but differences are observed in the tails. According to the company, the generalised Gamma and Gompertz distributions appeared to generate the closest fit.

Figure 4.3: OS extrapolations for TAFA+LEN



Based on Figure 60 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; TAFA+LEN = tafasitamab + lenalidomide; UK = United Kingdom

Therefore, the assessment of the long-term extrapolations, i.e. the curve tails, was crucial to determine what distributions are appropriate to model OS in the TAFA+LEN arm. The company presented the estimated median OS and the percentage of alive patients at two, five, and ten years, and validated these estimates with three UK clinical experts, see Table 4.5.[25] Based on this, it was concluded that the Gompertz distribution resulted in an unrealistic long-term plateau and was deemed implausible for OS. In terms of OS at year 5, the first expert interviewed by the company expressed an expectation of less than 30% survival, the second expert suggested that this would be between the Weibull and lognormal distributions (34% and 37%) and the third one indicated a value between 37% and 40%. In terms of OS at year 10, the first expert expected OS to be in the *"high-teens"*, the second one between the exponential and lognormal models (9% and 24%) and the third one between 20% and 25%.

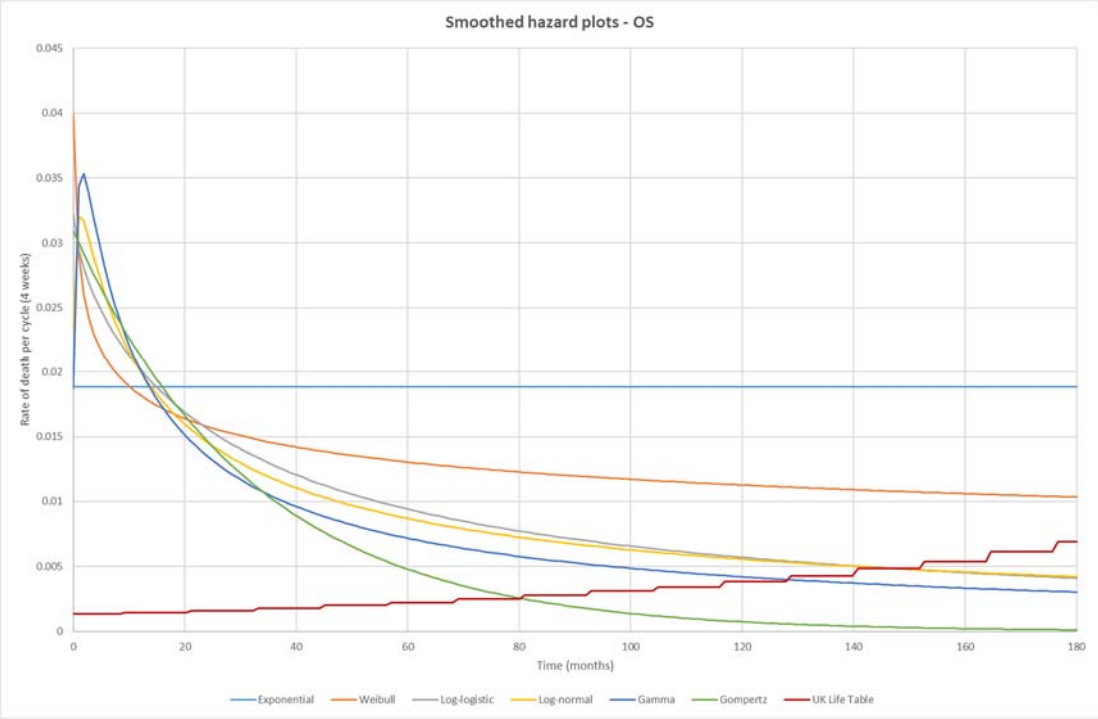
Table 4.5: Median OS and percentage survived for TAFA+LEN

Distribution	Median (months)	2-year OS	5-year OS	10-year OS
Exponential	33.9	61%	29%	9%
Weibull	34.2	59%	34%	16%
Log-logistic	32.5	57%	36%	22%
Lognormal	33.0	57%	37%	24%
Gamma	33.1	57%	39%	27%
Gompertz	35.0	56%	40%	34%

Based on Table 135 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; TAFA+LEN = tafasitamab + lenalidomide

The assessment of the tails resulted in no clear candidate. At this stage, Weibull, log-logistic and lognormal are still potential candidates. Thus, the company further explored hazard plots for OS. These can be seen in Figure 4.4. This plot showed that the generalised Gamma and the lognormal distributions had short-term increasing risk of death (up to 3 and 2 model cycles, respectively) after it starts to decline (the generalised Gamma resulted in a sharper short-term increase and decline in mortality risk). For the Weibull, log-logistic and Gompertz distributions, the risk of death was decreasing over time, and it was constant for the exponential distribution. The clinical experts interviewed by the company indicated that they would expect an increasing then decreasing hazard as the most plausible profile for the OS hazard. The first clinical expert indicated a preference for the generalised Gamma hazard profile, the second expert preferred the lognormal and the third expert suggested that the hazard profiles from the lognormal and log-logistic may be the most plausible (even though the log-logistic hazard was a monotone decreasing function). Based on all the evidence presented above, the company selected the lognormal distribution to model OS in the base-case analysis. Other distributions were explored in scenario analyses.

Figure 4.4: OS smoothed hazard plots for TAFA+LEN



Based on Figure 61 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; TAFA+LEN = tafasitamab + lenalidomide; UK = United Kingdom

ERG comment: The AICC and BIC values estimated by the company cannot be used to discriminate between distributions, with the exception of the exponential (even though this might be seen as borderline, the AICC rule can be strictly applied).

Visual inspection of the OS extrapolations (Figure 4.3) can be used to rule out the exponential distribution. Given the apparent uncertainty in the curves after approximately 30 months, the ERG prefers a more cautious assessment regarding the Weibull distribution, which would be included as a potential candidate at this point. The company claimed that the generalised Gamma and Gompertz distributions appeared to generate the closest fit, but based on Figure 4.3, the ERG is unable to assess whether this is the case or not.

Based on the assessment of the long-term extrapolations, it seems that the Gompertz and generalised Gamma distributions (together with the exponential) could be deemed as the least plausible extrapolations for OS, even though this was based on expert opinion and no experts provided the same range of survival estimates.

Hazard plots for OS (Figure 4.4) were used to assess how the risk of death changes over time. The clinical experts interviewed by the company expected an increasing then decreasing hazard as the most plausible profile for the OS hazard. However, there was no consensus among the experts about which profile was the preferred one (one expert suggested the log-logistic may be the most plausible even though the hazard was decreasing). Note that the time points at which the hazard curves cross with that of the UK general population, can be interpreted as the time at which the risk of death equals that of the general population. This happened at approximately 130 months (10.83 years) for the generalised Gamma distribution and at 140 months (11.67 years) for the lognormal and log-logistic distribution.

The company selected the lognormal distribution to model OS in the base-case analysis. Despite the uncertainty, the ERG agrees with the selection made by the company and considers the lognormal distribution the most plausible to model OS in the TAFA+LEN arm when RE-MIND2 data are used for the survival analysis, given the evidence presented. However, as discussed below, a different distribution could be chosen if for example it is assumed that the same type of distribution should be used for all treatment arms, as recommended in DSU TSD14.[44]

4.2.6.4 Overall survival: comparators (RE-MIND2)

The company's approach to modelling OS based on RE-MIND2 data in the comparator arms is described above, e.g. Figure 4.2. Details for specific comparators are provided below.

4.2.6.4.1 Pola-BR

The company assessed the plausibility of assuming a PH model between TAFA+LEN and pola-BR OS by inspecting the log cumulative hazard and the Schoenfeld residuals test plots as presented in Figures 86 and 87, respectively, in Appendix M of the CS.[48] Based on these, the company concluded that a PH assumption was not appropriate. Therefore, individual parametric fits to the matched patient data for the pola-BR arm were explored. As mentioned above, for the comparison against pola-BR, only 39 patients of the original L-MIND population could be matched with pola-BR patients. An overlaid plot of the KM curves for the matched TAFA+LEN patients and the original L-MIND data was presented in Figure 88 in Appendix M of the CS.[48] The company concluded that the curves were substantially different, most likely caused by the impossibility of matching approximately half of the original L-MIND patients. Therefore, as explained above, the company estimated an *"adjustment factor"* of 1.13 between the matched and unmatched TAFA+LEN population. The inverse of this factor (0.88) was applied to the unadjusted OS parametric curves for pola-BR obtained from RE-MIND2 data with the idea of making these curves more comparable to the original L-MIND population.

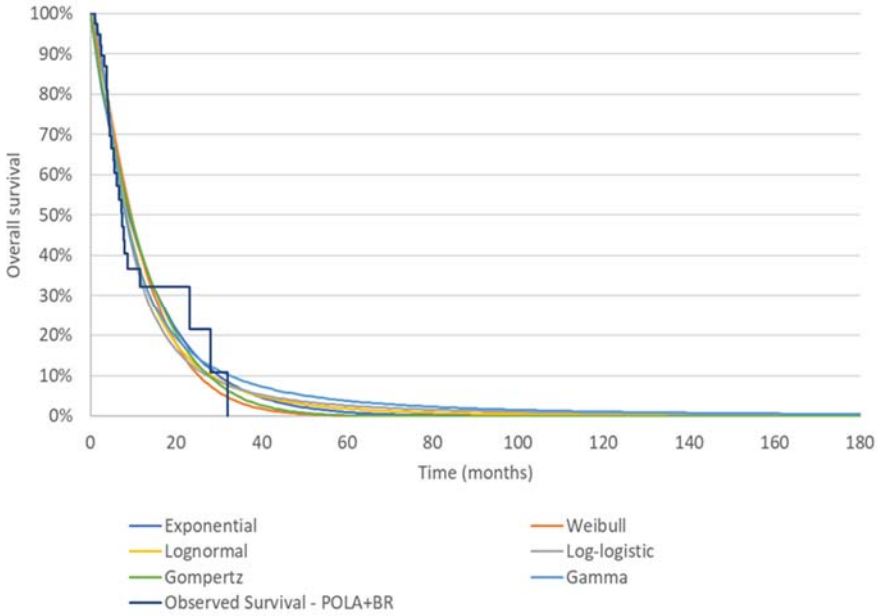
From this point forward, the methodology used by the company to select the most plausible OS extrapolations for the pola-BR arm was the same as the one described in Section 4.2.6.3 for the TAFA+LEN arm. Therefore, the steps taken by the company are described briefly.

AICC/BIC estimates for the unadjusted parametric curves were presented in Tables 149 and 150 in Appendix M of the CS.[48] The lognormal distribution resulted in the lowest AICC and BIC values. All distributions resulted in AICC values differing in less than 4 points from the lognormal AICC value, with the exception of the Weibull and the Gompertz distribution (4.49 and 5.92 points, respectively), and all distributions resulted in BIC values differing in less than 10 points from the lognormal BIC value.

Visual inspection of the OS *unadjusted* extrapolations for the pola-BR arm are shown in Figure 4.5. According to the company, all distributions resulted in a similar extrapolations and visual fit to the first half of the KM curve, after which all distributions seem to underestimate survival in the middle to late part of the curve. The Weibull and the Gompertz distributions appeared to produce the closest fit to the data at the end of the KM curve. However, it should be noted that a sharp drop after approximately 20 months was observed in the KM curve for OS, which fell to 0% at approximately 30 months. The company explained that this is likely caused by a small number of patients at risk remaining on treatment. Finally, the company concluded that the generalised Gamma distribution appeared to potentially over predict OS at the tail of the curve. However, since this distribution produced the closest fit prior to the sharp drop, it was still deemed as a plausible fit.

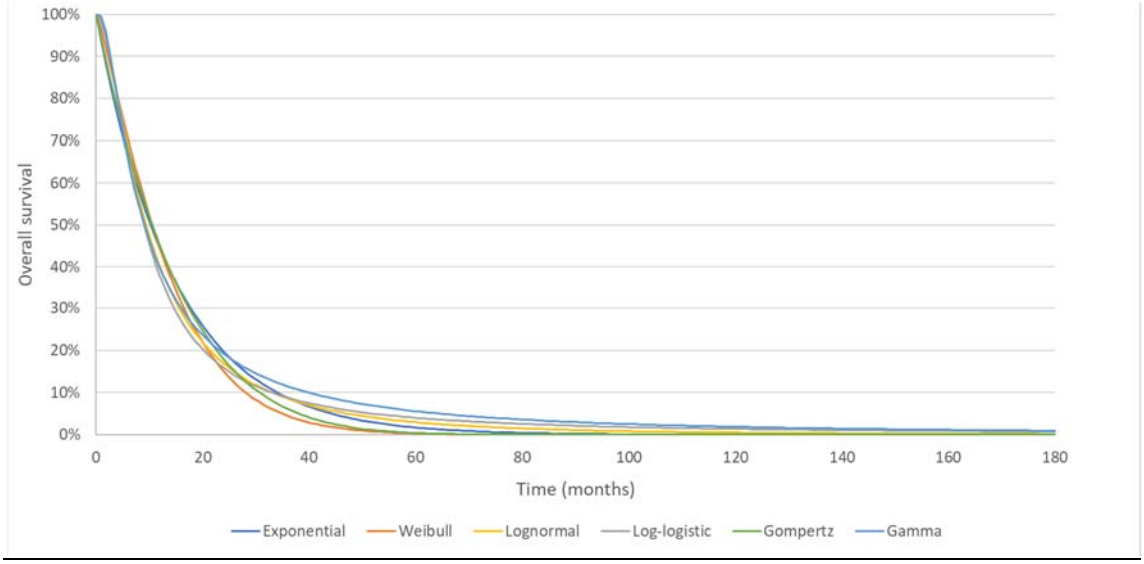
The OS *adjusted* extrapolations for the pola-BR arm (i.e. the ones used in the economic model) are shown in Figure 4.6. The survival curves were adjusted upwards by applying an adjusting factor of 0.88 to their unadjusted counterparts. No further interpretation of visual fit of the adjusted curves was provided in the CS.

Figure 4.5: Unadjusted OS extrapolations for pola-BR



Based on Figure 89 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Figure 4.6: Adjusted OS extrapolations for pola-BR



Based on Figure 90 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Table 4.6 presents the estimated percentage of alive patients at two, five, and ten years based on the *unadjusted* OS curves. As expected from Figure 4.5, predictions were fairly similar across all models, with the generalised Gamma distribution resulting in the highest OS overall.

Table 4.6: Expected (unadjusted) OS per distribution for pola-BR

Distribution	2-year OS	5-year OS	10-year OS
Weibull	12%	0%	0%
Lognormal	13%	2%	0%
Log-logistic	12%	3%	1%
Exponential	16%	1%	0%
Generalised gamma	15%	4%	1%
Gompertz	14%	0%	0%

Based on Table 151 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Table 4.7 presents the estimated percentage of alive patients at two, five, and ten years based on the *adjusted* OS curves, and validated these estimates with three UK clinical experts.[25] The experts concluded that all the adjusted parametric distributions resulted in *"overly pessimistic"* OS extrapolations for pola-BR in relation to what should be expected in clinical practice. It was suggested that the *"pessimistic nature of the data may reflect the recent entry of pola-BR onto the market and a lack of experience with its use in clinical practice at the time of RE-MIND2 data collection"*.[25]

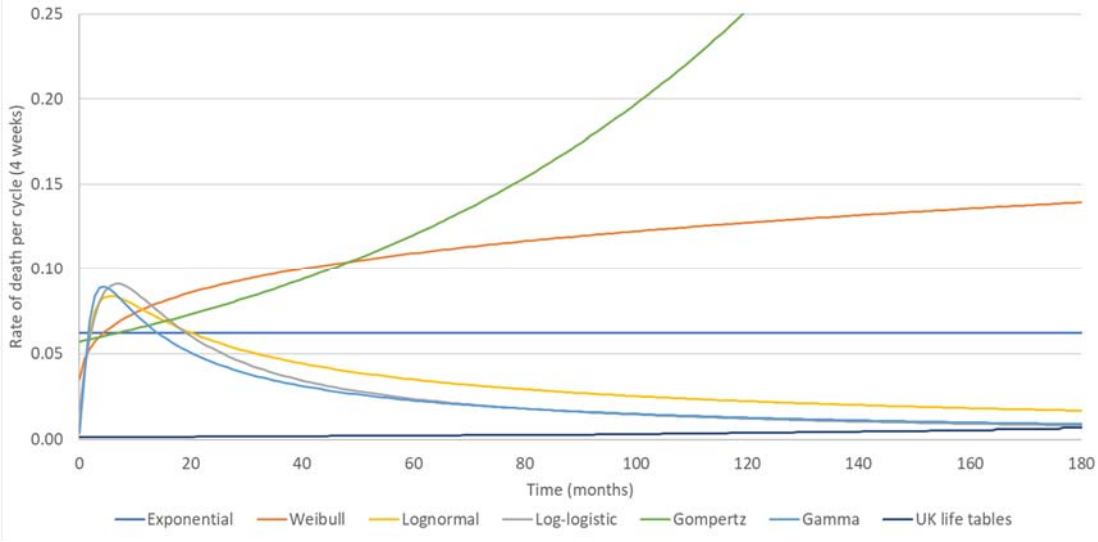
Table 4.7: Expected (adjusted) OS per distribution for pola-BR

Distribution	2-year OS	5-year OS	10-year OS
Weibull	15%	0%	0%
Lognormal	17%	3%	0%
Log-logistic	16%	4%	1%
Exponential	20%	2%	0%
Generalised gamma	19%	6%	2%
Gompertz	18%	0%	0%

Based on Table 152 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Despite the lack of (clinical) validity of the long-term OS extrapolations for the pola-BR arm, the company still explored hazard plots for OS. These can be seen in Figure 4.7. The clinical experts interviewed by the company indicated that they would expect an increasing then decreasing hazard as the most plausible profile for OS. The generalised Gamma, lognormal and log-logistic distributions presented this type of hazard profile. However, the company did not select any distribution for their base-case at this point and explored the validity of the OS extrapolations by comparing them with available (external) data.

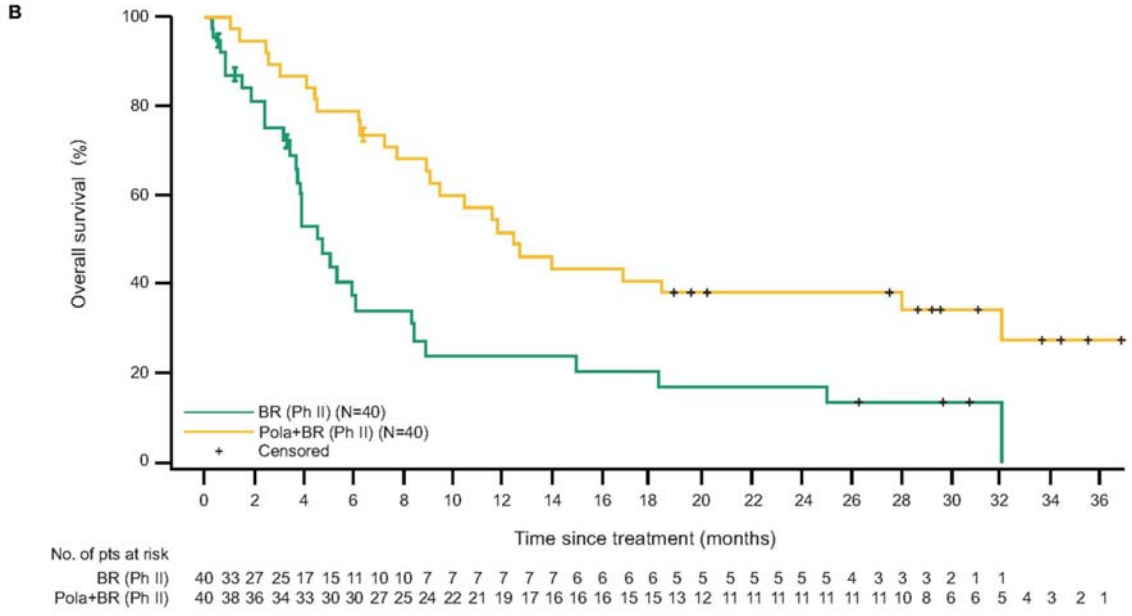
Figure 4.7: OS smoothed hazard plots for pola-BR



Based on Figure 91 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; UK = United Kingdom

Predictions from the parametric OS extrapolations for the pola-BR arm were compared to available clinical trial data from Sehn et al. 2019 and real-world data from Northend et al. 2021.[49, 50] As shown in Figure 4.8, Sehn 2019 data estimated approximately 38% of two-year OS for pola-BR, which is considerably higher than those produced by any of the parametric models (for example, the adjusted generalised Gamma distribution predicted 19% OS at two years).[50] This confirms that the parametric extrapolations estimated by the company may have largely underestimated OS in relation to the Sehn 2019 data. However, the company argued that these differences may have been related to underlying differences in the study populations but no attempt to address this question in the CS was made.

Figure 4.8: OS estimates for pola-BR, Sehn 2019

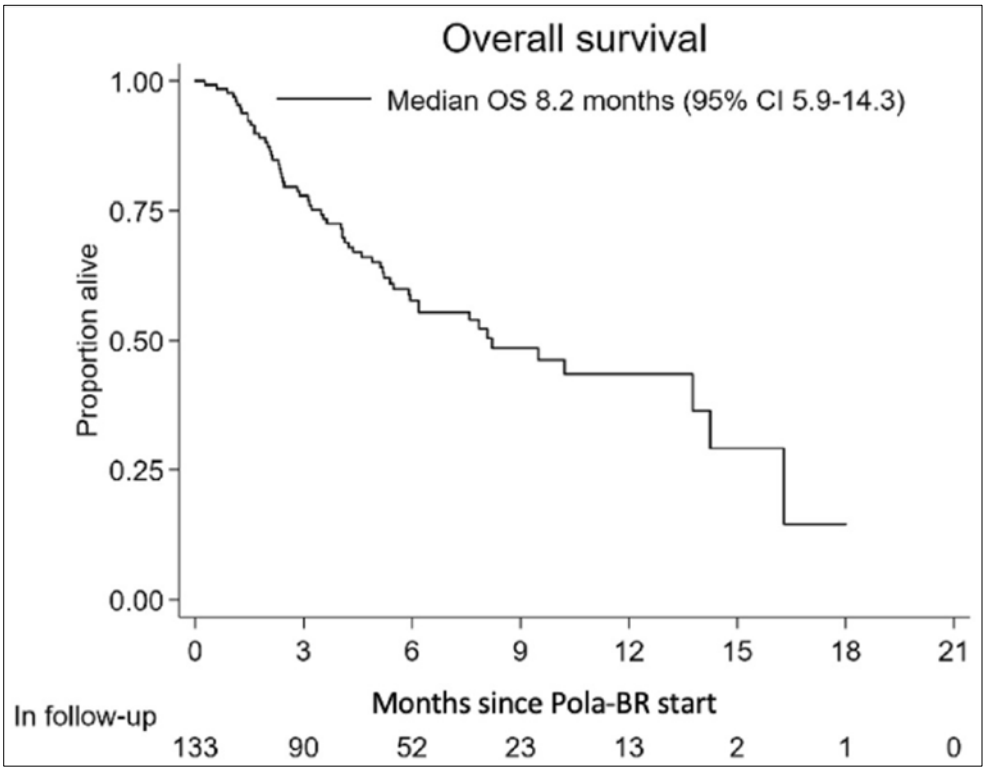


Based on Figure 92 in Appendix M of the CS[48] and Sehn et al. 2019[50]

BR = bendamustine + rituximab; CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Figure 4.9 shows OS estimates for pola-BR from Northend et al. 2021.[49] The Northend study estimated approximately 43% of one-year OS for pola-BR, compared to 52% in the Sehn 2019 study.[50] However, the company argued that this may be related to differences in the study design (RCT vs. retrospective analysis of real-world data) and the underlying patient populations, with a relatively high proportion of patients (39.9%) in the Northend study using pola-BR as a bridging therapy to SCT or chimeric antigen receptor T-cell therapy (CAR-T) rather than as a standalone treatment. In terms of one-year OS, predicted estimates from the parametric distributions varied from 37.8% to 45.1%, which were closer to the Northend estimate than to the Sehn 2019.

Figure 4.9: OS estimates for pola-BR, Northend 2021



Based on Figure 93 in Appendix M of the CS[48] and Northend 2019[49]
BR = bendamustine + rituximab; CS = company submission; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Based on all the evidence presented above, the company selected the (adjusted) generalised Gamma distribution as the most plausible candidate to model OS for pola-BR. It should be noted that NICE DSU TSD14 recommends in general selecting the same type of parametric distribution for each treatment.[44]

The company selected the lognormal distribution to model OS in the TAFA+LEN arm but argued that since the mechanism of action of polatuzumab is different to that of both tafasitamab and rituximab plus chemotherapy regimens, selecting a different type of distribution for the pola-BR arm was considered reasonable.

ERG comment: Visual inspection of the OS unadjusted extrapolations for the pola-BR arm should be done with caution. All distributions resulted in similar extrapolations and visual fit in general, but as the company noted, a sharp drop in the KM curve for OS after approximately 20 months, which fell to

0% at approximately 30 months, was observed. The potential implications of this characteristic of the data were not discussed. The ERG considers that fitting standard parametric distributions to these data could be a difficult exercise and that more complex models might have provided a better fit. However, it might also be argued that since OS data were *"complete"* (all patients died at approximately 30 months) extrapolation might not be needed at all, following the company's approach in TTD. The company explained the sharp drop in the OS KM curve is likely caused by the small number of patients at risk remaining on treatment. The ERG cannot judge this because the number of patients at risk were not reported. However, the OS KM curve shows that at 30 months the survival probability is 0% for pola-BR *matched* patients. Seeing the data presented by the company; e.g. Sehn et al. 2019 and Northend et al. 2021,[49, 50] and the results in TA649,[42] this seems highly unrealistic.

The OS *adjusted* extrapolations for the pola-BR arm were calculated by applying an adjusting factor of 0.88 to their unadjusted counterparts. The ERG questions the validity of this adjustment factor, which is only applied because of the method of confounding as described above. Had a method of adjustment for confounding been implemented that estimated the ATT, whereby there was no change in the TAFA+LEN cohort, but instead in the comparator cohort, then no further adjustment would need to be considered.

The estimated percentage of alive patients at two, five, and ten years based on these curves was presented to three UK clinical experts and it was consensus that all the adjusted parametric distributions resulted in *"overly pessimistic*" OS extrapolations for pola-BR.[42]

The adjusted OS extrapolations for the pola-BR arm were also compared to clinical trial data from Sehn et al. 2019[27, 51], and confirmed that the company analyses may have largely underestimated OS in relation to the Sehn 2019 data.[50] The company argued that these differences may have been related to underlying differences in the study populations.

This raised concerns as to whether the sub-population of matched patients in the pola-BR arm (or the complete population in L-MIND) is representative for UK patients who are expected to be treated with pola-BR. It should be noted that the population in the Sehn study is the population in the GO29365 trial, which was the key trial in TA649 (pola-BR submission to NICE).[42] In Section 3.4 of the Final Appraisal Determination (FAD) document for TA649, the Appraisal Committee concluded that the trial GO29365 was generalisable to UK clinical practice.[42] Therefore, if as the company argues, the (large) differences between the OS extrapolations for the pola-BR arm in this appraisal and the OS data from Sehn et al. 2019 are related to underlying differences in the study populations, it could also be argued that the study population in this appraisal may not be generalisable to the UK. A comparison between the two populations was requested by the ERG in clarification question C23.[3, 4] This was discussed in Section 4.2.3 of this report.

Parametric OS extrapolations for the pola-BR arm were also compared to real-world data from Northend 2021.[49] OS predicted estimates from the parametric distributions were closer to those in the Northend study. However, given the shorter duration of the Northend study (18 months), these estimates were compared at 12 months only. It should also be noted the small number of patients at risk in the Northend study at (and after) one year (13/133, 10%), which suggests a high degree of uncertainty towards the end of the study period. The Northend study estimated approximately 43% of 1-year OS for pola-BR, compared to 52% in the Sehn 2019 study.[49, 50] The company argued that the differences in OS between the Northend and Sehn studies may be related to differences in the study design (RCT vs. retrospective analysis of real-world data) and the underlying patient populations (with a proportion of patients in the Northend study receiving Pola-BR as a bridging therapy prior to SCT or CAR-T). There was also no discussion as to what extent the population in Northend et al. 2021 is representative to the

UK patient population, although the study is based on retrospective analysis of patients from 28 UK hospitals.[49] Therefore, it is uncertain whether a comparison between the modelled and Northend OS for pola-BR is appropriate.

The company selected the (adjusted) generalised Gamma distribution as the most plausible candidate to model OS for pola-BR. Based on all the evidence presented by the company, the ERG would agree with this choice. However, it should be emphasised that even in this case, model outcomes for pola-BR are unlikely to produce (clinically) valid results.

It should also be noted that the company selected the lognormal distribution to model OS in the TAFA+LEN arm and the generalised Gamma in the pola-BR arm, which in principle is not in line with NICE DSU TSD14 recommendations: *"when parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model", which would not allow the modelled survival for each treatment arm to follow "drastically different"* distributions.[44] TSD14 concludes then that if "*different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis"*.[44] In this respect, the company argued that since the mechanism of action of polatuzumab is different to that of both tafasitamab and rituximab plus chemotherapy regimens, selecting a different type of distribution for the pola-BR arm was considered reasonable.

In response to clarification question C8, the company explained that the selection of the generalised Gamma distribution for modelling OS in the pola-BR arm was mainly justified by its *"most optimistic long-term predictions"*.[4] It was also argued that a potential rationale *"in terms of biological plausibility was provided based on differences in mechanism of action between polatuzumab and other modelled therapies, with polatuzumab an antibody drug conjugate targeting the CD79b antigen compared to CD19 and CD20 for tafasitamab and rituximab, respectively"*.[4] In addition, the company explained that both polatuzumab and rituximab are given in combination with chemotherapy agents, but tafasitamab is given in combination with an immunomodulatory agent (lenalidomide). Also, in pre-clinical studies, lenalidomide caused both direct cell death and enhanced the action of tafasitamab.[52] Therefore, the chemotherapy-free combination of tafasitamab (given until disease progression) and lenalidomide can be considered to be biologically different to polatuzumab or rituximab combined with chemotherapy (given for fixed treatment durations).

The ERG acknowledges that TSD14 recommendations regarding the selection of different type of survival models for different treatment arms are not very specific.[44] Recommendations focussed on not allowing *"drastically different"* distributions per treatment arm. Whether the lognormal (two-parameter function) and the generalised Gamma (three-parameter function) distributions can be deemed as drastically different is unclear to the ERG. Furthermore, based on TSD14 recommendations, justification should be provided on biological plausibility, clinical expert judgement and robust statistical analysis.

According to the ERG, the company provided justification based on biological plausibility only, but cannot judge whether this biological plausibility would imply that using different probability distributions to model OS in different treatment arms is appropriate. Therefore, while it is acknowledged the uncertainty around this aspect of the modelling, the ERG prefers, whenever possible, following the general TSD14 recommendations and considers that the same type of distributing should be selected for modelling OS in all treatment arms. The ERG would also speculate that, given that the pola-BR cohort are likely to have more severe disease than the TAFA+LEN cohort, then if a method of adjustment for confounding were implemented that only adjusted the pola-BR cohort, this would

probably also have made any survival curve for pola-BR more clinically plausible. How much more plausible is difficult to predict.

4.2.6.4.2 BR

The company assessed the plausibility of assuming a PH model between TAFA+LEN and BR OS by inspecting the log cumulative hazard and the Schoenfeld residuals test plots as presented in Figures 78 and 79, respectively, in Appendix M of the CS.[48] The company concluded that a PH assumption appeared to hold. Therefore, a constant HR (1/0.418 = 2.392) generated from the matched TAFA+LEN and BR RE-MIND2 populations was applied to the TAFA+LEN overall population from L-MIND.

ERG comment: The log cumulative hazard curves for TAFA+LEN and BR crossed at the beginning of the plot. After that, the company considered that the curves appeared parallel. While this might be the case, the interpretation of these plots is subjective and it could also be argued that almost up to the first half of the curves, these seem to converge, which would suggest that the PH assumption would not hold.

Similarly, the linear regression for the scaled Schoenfeld residuals was broadly parallel to the 0 line. The P-value of 0.9489 generated from the Schoenfeld residuals test was interpreted by the company as suggestion that the PH assumption was appropriate. The ERG would like to emphasise that failing to reject a null hypothesis (PH in this case) is not the same as accepting the hypothesis as true. An example of this is provided by the company in the assessment of the PH assumption for PFS in pola-BR in Section 4.2.6.7.1.

In Appendix M to the CS, the company mentioned that although *"the global test of proportionality from the Schoenfeld residuals test generated a non-statistically significant p value (p-value=0.1676), visual inspection of the Schoenfeld residual plot (Figure 95) showed a downward trend in the residuals over time which was non-parallel to the 0 line, suggesting that a proportional hazards assumption was not appropriate"*.[48] This shows that relying on the P-value only can be misleading. Thus, while the PH assumption between TAFA+LEN and BR might hold, the ERG would prefer to see a plot of the HR over time. If this resulted in a constant line, this would be a clearer indication of PH. However, also in this case the ERG prefers to follow the general recommendations in TSD 14 and since patient-level data are available, relying upon the PH assumption seems unnecessary.[44]

4.2.6.4.3 R-GemOx

Based on the log cumulative hazard and the Schoenfeld residuals test plots presented in Figures 65 and 66, respectively, in Appendix M of the CS, the company concluded that a PH assumption between TAFA+LEN and R-GemOx OS was not appropriate.[48] Individual parametric fits to the matched patient data for the R-GemOx arm were explored.

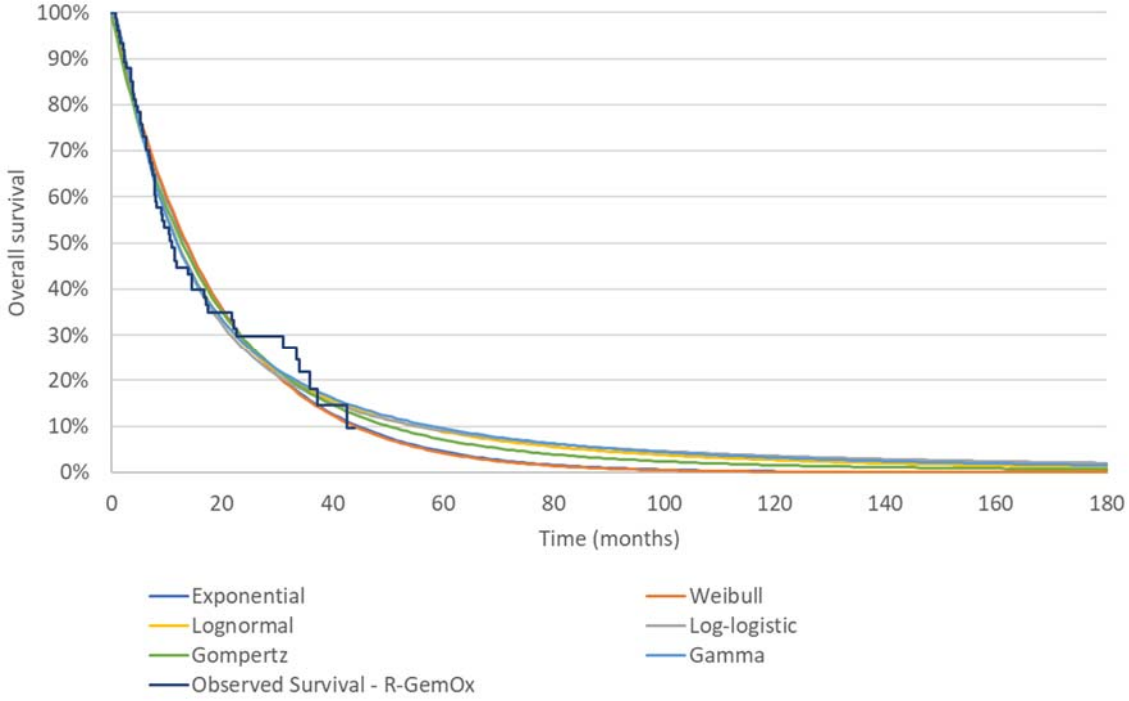
For the comparison against R-GemOx, 74 patients out of the original 80 L-MIND population could be matched. An overlaid plot of the KM curves for the matched TAFA+LEN patients and the original L-MIND data was presented in Figure 67 in Appendix M of the CS.[48] The company concluded that the curves overlapped considerably and, therefore, unadjusted OS extrapolations were used to model the R-GemOx arm.

AICC/BIC estimates for the unadjusted parametric curves were presented in Tables 140 and 141 in Appendix M of the CS.[48] The lognormal distribution resulted in the lowest AICC and BIC values. However, all distributions resulted in AICC values differing in less than 4 points from the lognormal AICC value, with the exception of the Weibull and the Gompertz distribution (5.38 and 4.95 points,

respectively), and all distributions resulted in BIC values differing in less than 10 points from the lognormal BIC value.

Visual inspection of the OS *unadjusted* extrapolations for the R-GemOx arm are shown in Figure 4.10. According to the company, all distributions resulted in a similar extrapolations and visual fit to the first half of the KM curve, after which all distributions seem to underestimate survival in the middle to late part of the curve. According to the company, the Weibull and the exponential distributions appeared to produce the closest fit to the data at the end of the KM curve. However, given the step downwards at the end of the KM curve, where a relatively small number of patients were at risk, the company concluded that the other models may still be deemed as reasonable candidates to modelling OS in the R-GemOx arm.

Figure 4.10: Unadjusted OS extrapolations for R-GemOx



Based on Figure 68 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin

The company presented in Table 4.8 the estimated percentage of alive patients at two, five, and ten years based on the unadjusted OS curves for R-GemOx. Predictions were similar across all models at two years. The lognormal, log-logistic and generalised Gamma distributions resulted in the highest OS probabilities estimated at 5 and 10 years. Two of the clinical experts consulted by the company expressed their preference for the lognormal and log-logistic extrapolations (based on 5 and 10-year predictions), while the other clinical expert, expected lower long-term OS for R-GemOx (of around 5% at 5 years) and indicated a preference for the Gompertz and Weibull models.

Table 4.8: Expected (unadjusted) OS per distribution for R-GemOx

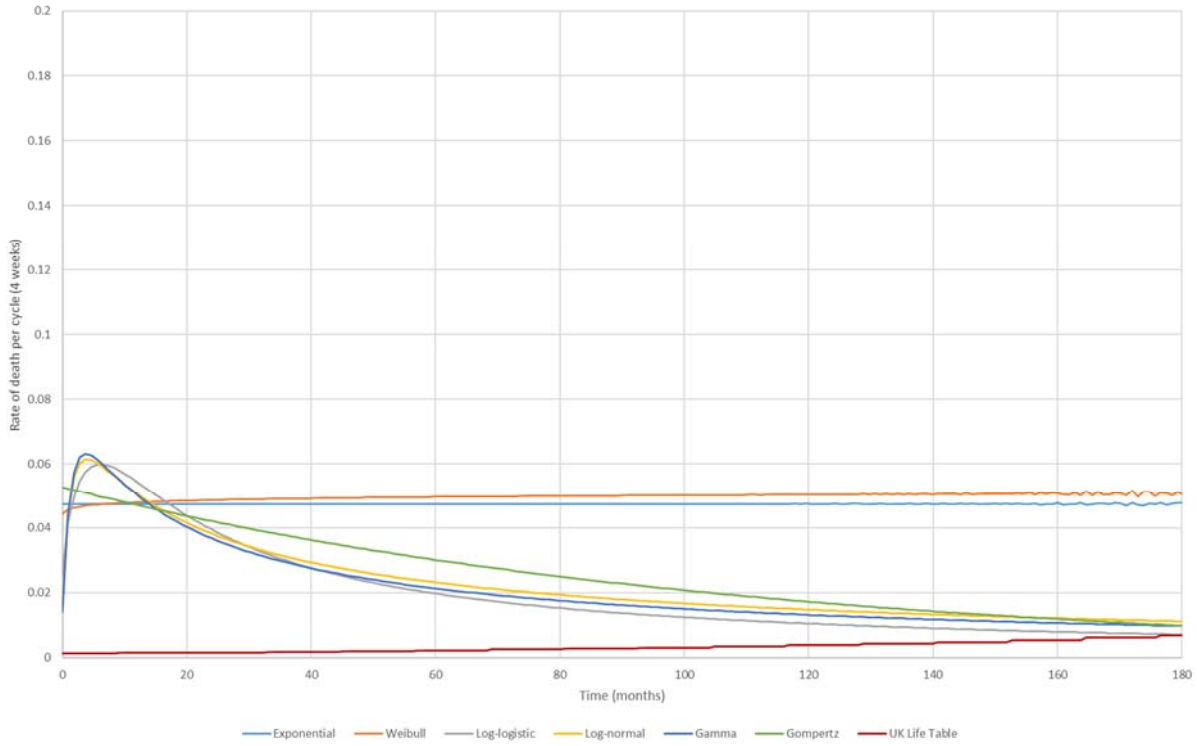
Distribution	2-year OS	5-year OS	10-year OS
Weibull	29%	4%	0%
Lognormal	28%	9%	3%
Log-logistic	27%	9%	4%

Distribution	2-year OS	5-year OS	10-year OS
Exponential	29%	5%	0%
Generalised gamma	28%	10%	3%
Gompertz	29%	7%	2%

Based on Table 142 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin

The company explored then the hazard plots for OS (these can be seen in Figure 4.11) and discussed these with the clinical experts, who also here indicated that they would expect an increasing then decreasing hazard as the most plausible profile for OS. The generalised Gamma, lognormal and log-logistic distributions presented this type of hazard profile. One expert indicated a preference for the log-logistic model, and another one for the lognormal model.

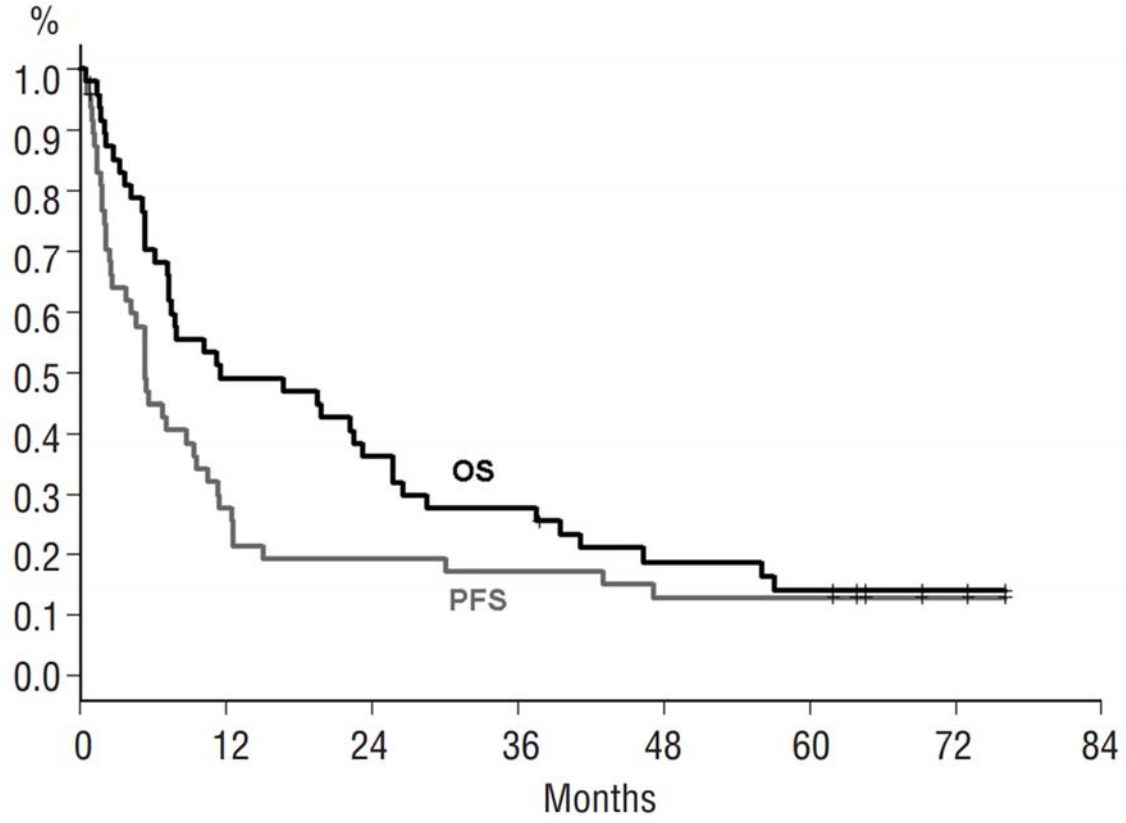
Figure 4.11: OS smoothed hazard plots for R-GemOx



Based on Figure 69 in Appendix M of the CS[48]
CS = company submission; OS = overall survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; UK = United Kingdom

Predictions from the parametric OS extrapolations for the R-GemOx arm were compared to available clinical trial data from Mounier et al. 2013.[31] Note that Mounier 2013 was also used for the MAIC. As shown in Figure 4.12, Mounier 2013 data estimated OS approximately at 36% and 14% at two and five years, respectively. Compared to Mounier 2013 data, all parametric curves estimated by the company underestimated the 2-year OS (ranged from 27% to 29%) and 5-year OS (ranged 4% to 10%). Based on the 5-year predictions, the lognormal, log-logistic and generalised Gamma resulted in the closest probabilities to those observed in Mounier 2013, although they were still lower than the 14% in Mounier 2013.[31] The company noted that potential differences in the underlying characteristics of the R-GemOx population from RE-MIND2 and the Mounier 2013 trial population, as noted for the MAIC analysis, should be taken into account when directly comparing outcomes from the two studies.

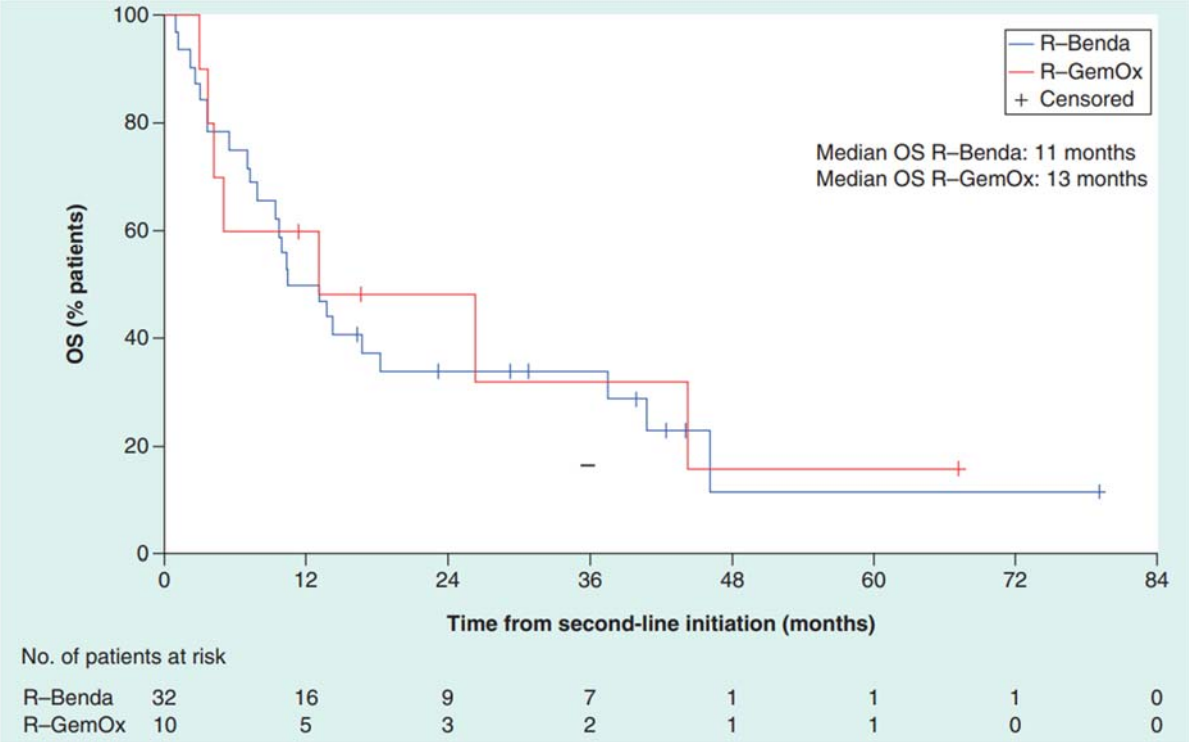
Figure 4.12: OS and PFS estimates for R-GemOx, Mounier 2013



Based on Figure 70 in Appendix M of the CS[48] and Mounier et al. 2013[31]
CS = company submission; OS = overall survival; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin

Figure 4.13 shows OS estimates for R-GemOx from Ionescu-Ittu 2019.[53] This study estimated approximately 48% and 16% OS for R-GemOx at 2 and 5 years, respectively, which is even higher than the ones observed in Mounier 2013, and thus higher than those predicted by the company.[31] However, the company noted that Ionescu-Ittu 2019 included only 10 patients receiving R-GemOx, with very few patients at risk at 2 and 5 years (3 and 1 patients, respectively). Based on all the evidence presented above, the company concluded that the lognormal, log-logistic and generalised Gamma distributions are the most plausible candidate to model OS for R-GemOx, and based on the clinical experts' preference, the lognormal distribution was selected for the base-case.

Figure 4.13: OS estimates for R-GemOx, Ionescu-Ittu 2019



Based on Figure 71 in Appendix M of the CS[48] and Ionescu-Ittu 2019[53]
CS = company submission; OS = overall survival; R-GemOx = rituximab in combination with gemcitabine; R-Benda = rituximab + bendamustine

ERG comment: The OS extrapolations for the R-GemOx arm were compared to data from Mounier 2013 and Ionescu-Ittu 2019.[27, 31, 51, 53] Both comparisons suggested that the company analyses may have underestimated OS in relation to these two studies, even though to a lower extent than in the pola-BR arm.

The company also argued that these differences may have been related to underlying differences with the Mounier population and the small sample size in Ionescu-Ittu 2019 (10 patients in R-GemOx). Again, this raised concerns as to whether the sub-population of matched patients in the R-GemOx is representative for UK patients who are expected to be treated with R-GemOx.

4.2.6.5 Overall survival: MAIC

MAIC methodology and results are presented in Sections 3.3 and 3.4, respectively. The main purpose of the MAIC was to match the population from L-MIND with published comparator populations. According to the company, successful matching was achieved for all comparators. The studies included in the MAIC for OS are summarised in Table 3.12.

The MAIC for BR and R-GemOx relied on the assumption of a constant HR. For pola-BR, however, the company presented log-cumulative OS hazard plots for TAFA+LEN and pola-BR in Figure 102 in Appendix M of the CS.[48] Since both curves crossed over the follow-up time, the company concluded that assuming OS PH in between TAFA+LEN and pola-BR was not appropriate. The company noted a change in the trend of the hazards at approximately four months. Based on this, the company modelled for OS in the pola-BR arm a time-varying HR using a split at four months, which was assumed in the company's base-case. The company also noted that a 4-month time period

[redacted].

As an alternative assumption, a split at 11 months was also modelled since this corresponds [redacted]. Despite considering the PH assumption as inappropriate, a constant HR was included in the model too. An overview of the HR's estimated for OS from the MAIC are summarised in Table 4.9.

Table 4.9: MAIC HRs for OS

Comparator	HR (vs. TAFA+LEN)	Notes
R-GemOx	1.82	Calculated from MAIC outputs (1/0.55)
BR	2.56	Calculated from MAIC outputs (1/0.39)
Pola-BR: 4-month split - first 4 months	0.55	Calculated from MAIC outputs (1/1.82)
Pola-BR: 4-month split - after 4 months	2.44	Calculated from MAIC outputs (1/0.41)
Pola-BR: 11-month split - first 11 months	1.08	Calculated from MAIC outputs (1/0.93)
Pola-BR: 11-month split - after 11 months	3.03	Calculated from MAIC outputs (1/0.33)
Pola-BR: constant HR	1.47	Calculated from MAIC outputs (1/0.68)
Pola-BR: 3-month split - first 3 months	0.53 (0.15-1.89)	Sensitivity analysis
Pola-BR: 3-month split - after 3 months	2.17 (1.03-4.55)	Sensitivity analysis
Pola-BR: 9-month split - first 9 months	0.93 (0.42-2.08)	Sensitivity analysis
Pola-BR: 9-month split - after 9 months	3.03 (1.19-7.69)	Sensitivity analysis

Based on Table 157 in Appendix M of the CS[48]
BR = rituximab in combination with bendamustine; CS = company submission; HR = hazard ratio; LEN = lenalidomide; MAIC = matching-adjusted indirect comparison; pola-BR = polatuzumab vedotin with bendamustine and rituximab; OS = overall survival; R-GemOx = Rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

ERG comment: The MAIC methodology is discussed in detail in Section 3.4 of this report. The ERG comments in this Section refer to the assumptions made by the company after the MAIC was conducted.

The MAIC for BR and R-GemOx relied on the assumption of a constant HR, which means that the treatment effect of TAFA+LEN compared to BR and R-GemOx is constantly maintained over time. If this is assumed as a plausible scenario, it might contradict the assumptions derived from the analyses based on RE-MIND2 data, from which, for example, a PH model for R-GemOx was deemed inappropriate, meaning that the treatment effect of TAFA+LEN compared to R-GemOx is *not* constantly maintained over time. When the PH assumption was deemed appropriate with both methods, as in the case of BR, it would have been illustrative to compare both HRs to see what differences are observed between the two approaches and whether these can be deemed as comparable.

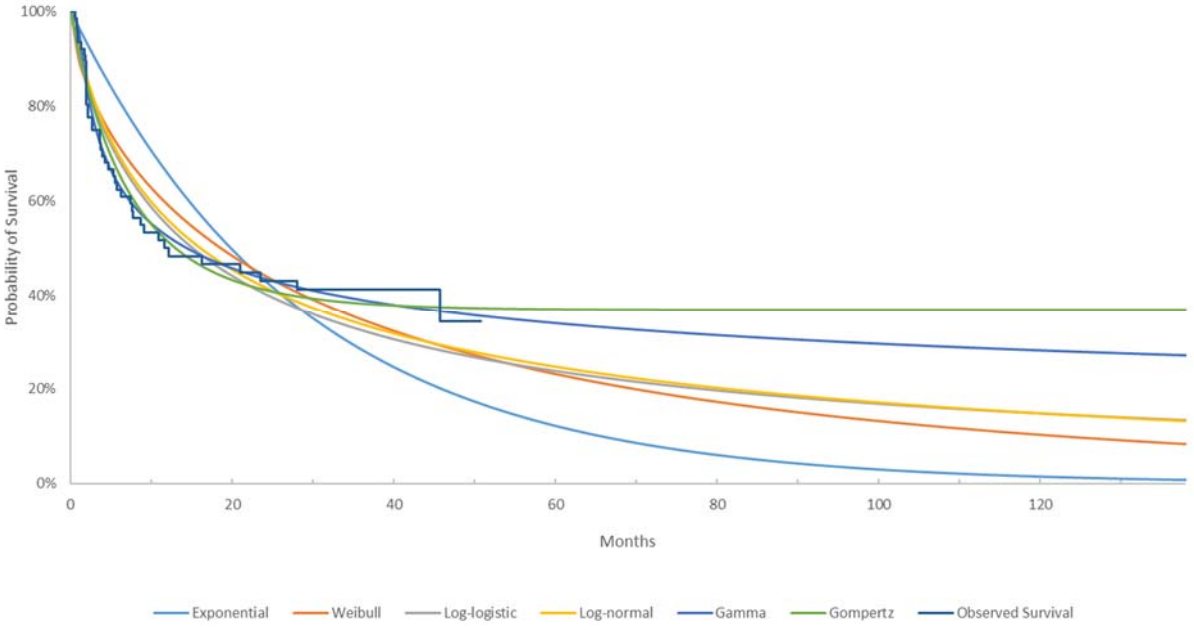
The ERG agrees with the company that assuming OS PH between TAFA+LEN and pola-BR was not appropriate. However, it is not clear from Figure 102 in Appendix M of the CS that there is a change in the trend of the hazards at approximately four months, as noted by the company.[48] First, the scale on the X-axis is not presented with sufficient detail to judge what happens at approximately four months. It could also be argued that, based on the plots, OS for TAFA+LEN is worse than OS for pola-BR at the beginning, then both are approximately equal, and finally TAFA+LEN is better.

4.2.6.6 Progression free survival: TAFA+LEN

Based on AICC and BIC values shown in Tables 136 and 137 in Appendix M of the CS, the generalised Gamma distribution was expected to have the best statistical fit to the observed data.[48] All distributions resulted in AICC values differing in more than 10 points from the generalised Gamma AICC value, with the exception of the Gompertz distribution (9.22 points), which could be considered as borderline between inferior and poor fit. All distributions resulted in BIC values differing in more than 10 points from the generalised Gamma BIC value, except the Gompertz (6.99 points) and the lognormal (9.28 points).

Based on visual inspection of the PFS extrapolations for the TAFA+LEN arm, as shown in Figure 4.14, the company considered that the generalised Gamma provided the best visual fit followed by the Gompertz model. However, it was noted that the Gompertz distribution seemed to underpredict the middle to late section of the KM curve before generating a likely high and unrealistic plateau (due to a statistical artefact of the parametric fitting where a gamma parameter <0 was estimated). All other distributions seem to overestimate most of the initial half of the KM curve and underestimate the tail, with the exponential distribution resulting in the poorest visual fit to the KM data.

Figure 4.14: PFS extrapolations for TAFA+LEN



Based on Figure 62 of Appendix M of the CS[48]
CS = company submission; LEN = lenalidomide; PFS = progression-free survival; TAFA = tafasitamab

Table 4.10 presents the estimated median PFS and the percentage of alive patients at two, five, and ten years, and validated these estimates with three UK clinical experts.[25] Based on this, it was concluded that the Gompertz distribution resulted in an unrealistic long-term plateau and was deemed implausible for PFS. The first clinical expert suggested 25% PFS probability at 5 years, the second expert preferred

the Weibull predictions (23% and 10% PFS probability at 5 and 10 years, respectively) followed by lognormal distribution (25% and 15% PFS probability at 5 and 10 years, respectively) and the third expert preferred the lognormal or log-logistic distributions (24%-25% and 10% PFS probability at 5 and 10 years, respectively).

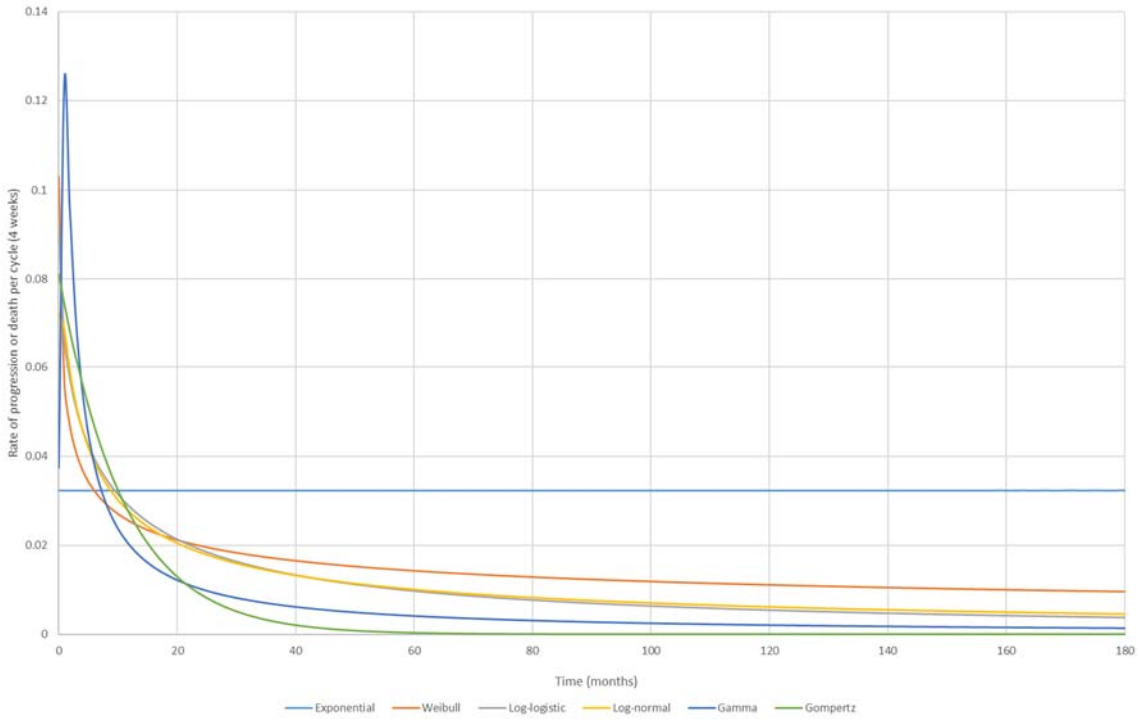
Table 4.10: Median PFS and percentage survived for TAFA+LEN

Distribution	Median (months)	2-year PFS	5-year PFS	10-year PFS
Exponential	19.8	43%	12%	2%
Weibull	18.5	44%	23%	10%
Log-logistic	15.1	40%	24%	15%
Lognormal	16.0	42%	25%	15%
Gamma	14.3	44%	34%	28%
Gompertz	14.0	41%	37%	37%

Based on Table 138 of Appendix M of the CS[48]
CS = company submission; LEN = lenalidomide; PFS = progression-free survival; TAFA = tafasitamab

Finally, the company explored hazard plots for PFS, as can be seen in Figure 4.15. The clinical experts interviewed by the company indicated that they would expect decreasing hazard (of progression or death) as the most plausible profile for the PFS hazard. However, there was no consensus regarding the best candidate since the first expert chose the lognormal, the second expert chose the Weibull (followed by lognormal) and the third expert chose the lognormal or log-logistic distributions.

Figure 4.15: PFS smoothed hazard plots for TAFA+LEN



Based on Figure 63 of Appendix M of the CS[48]
CS = company submission; LEN = lenalidomide; PFS = progression-free survival; TAFA = tafasitamab

Based on all the evidence presented above, the company selected the generalised Gamma distribution to model PFS in the base-case analysis, based on the best statistical fit and visual fit to the observed

data. The lognormal distribution resulted in a poor statistical and visual fit to the data, but it was explored in scenario analysis as it most closely aligned with clinical expert expectations in terms of long-term PFS and hazard profiles for TAFA+LEN.

ERG comment: The ERG considers that there is no "statistical artefact" associated to the estimation of the parameters of the Gompertz distribution. These parameters should be positive by definition. It is likely that the procedure used by the company to estimate the parameters of the Gompertz distribution failed to converge to a valid solution. Therefore, the ERG considers that the Gompertz distribution should not be used.

Based on the assessment of the long-term extrapolations, clinical experts considered the lognormal, log-logistic and Weibull as the most plausible PFS extrapolations. It should be noted then that the distributions with the most plausible tails according to the experts, seem to overestimate PFS in the TAFA+LEN for approximately 20 months at least. Also, long-term predictions by the Gompertz and generalised Gamma distributions seem unrealistically high, since these are higher than the corresponding OS probabilities at 10 years (see Table 4.5).

The clinical experts interviewed by the company expected a decreasing hazard as the most plausible profile for the PFS hazard. However, there was no consensus among the experts about which profile was the preferred one.

The company selected the generalised Gamma distribution to model PFS in the base-case analysis. The ERG acknowledges the uncertainty regarding the modelling of PFS, but does not agree with the selection made by the company. Despite resulting in the best fit to the data, the generalised Gamma distribution seems to overpredict PFS in the long-term, as confirmed by the clinical experts consulted by the company. Also, the hazard profile of the generalised Gamma distribution does not match with the experts' expectations of a hazard declining over time. Even though the lognormal, loglogistic and Weibull distributions seem to overestimate PFS for TAFA+LEN at least for 20 months, it is likely that the impact of this overestimation on the results is less than overestimating PFS in the long-term. The ERG prefers then the distribution with the smallest overestimation, which seems to be either the lognormal or the log-logistic distribution.

4.2.6.7 Progression free survival: comparators (RE-MIND2)

The company's approach to modelling PFS based on RE-MIND2 data in the comparator arms is the same as the one described in Section 4.2.6.4 for OS. Details for specific comparators are provided below.

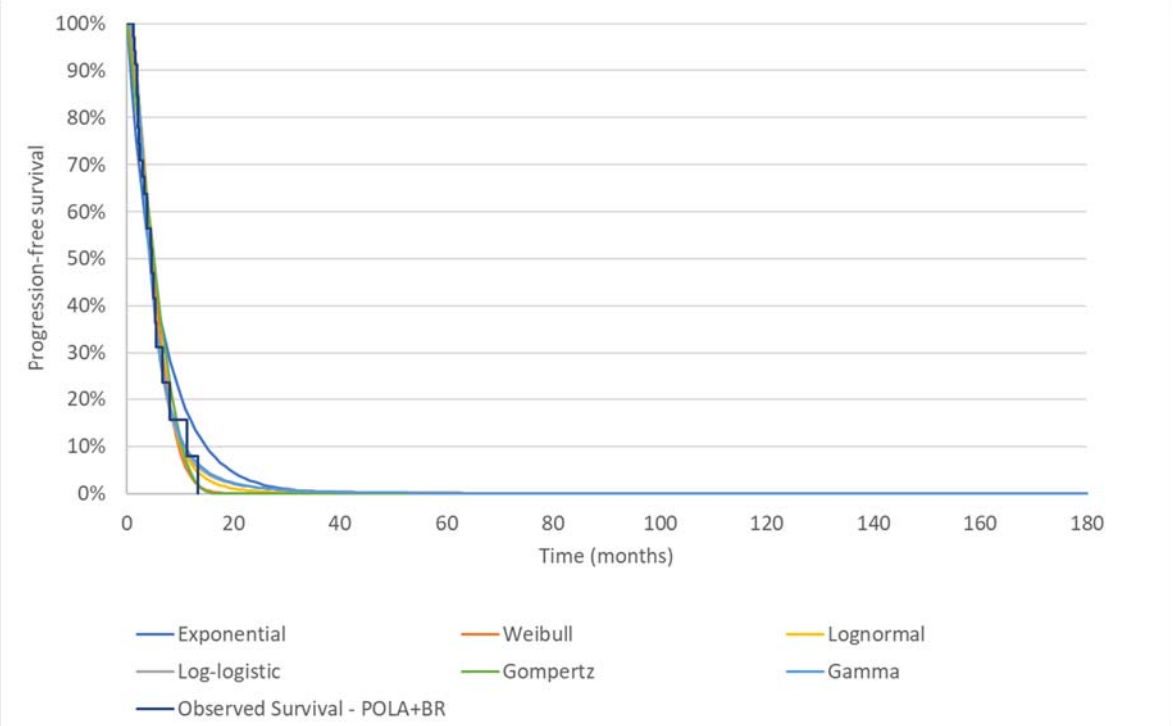
4.2.6.7.1 Pola-BR

Based on the assessment of the log cumulative hazard and the Schoenfeld residuals test plots as presented in Figures 94 and 95, respectively, in Appendix M of the CS, the company concluded that a PH assumption between TAFA+LEN and pola-BR PFS was not appropriate.[48] An overlaid PFS plot of the KM curves for the matched TAFA+LEN patients and the original L-MIND data was presented in Figure 96 in Appendix M of the CS.[48] The company concluded that the curves were substantially different, and, therefore, an "adjustment factor" of 1.13 was estimated between the matched and unmatched TAFA+LEN population and its inverse (0.88) was applied to the unadjusted PFS parametric curves for pola-BR obtained from RE-MIND2 data with the idea of making these curves more comparable to the original L-MIND population.

Based on the AICC/BIC estimates for the unadjusted parametric curves presented in Tables 153 and 154 in Appendix M of the CS, the lognormal distribution resulted in the lowest AICC and BIC values.[48] However, all distributions resulted in AICC values differing in less than 4 points from the lognormal AICC value, with the exception of the Gompertz and exponential distributions (7.71 and 11.09 points, respectively), and all distributions resulted in BIC values differing in less than 10 points from the lognormal BIC value.

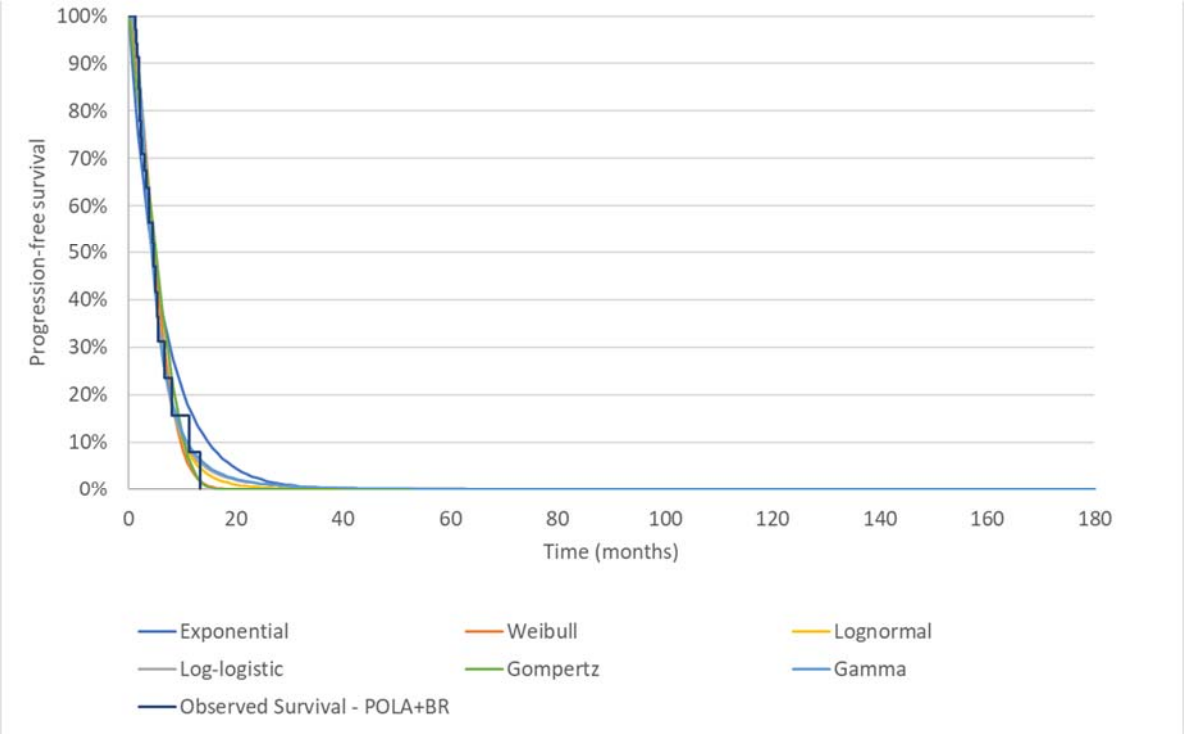
Visual inspection of the PFS *unadjusted* and *adjusted* extrapolations for the pola-BR arm are shown in Figures 4.16 and 4.17, respectively. The interpretation is similar to that of the OS curves, and all distributions resulted in a similar extrapolations and visual fit to the KM curve except the exponential. However, it should be noted that the KM curve for PFS reached 0% at approximately 15 months.

Figure 4.16: Unadjusted PFS extrapolations for pola-BR



Based on Figure 97 in Appendix M of the CS.[48]
CS = company submission; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Figure 4.17: Adjusted PFS extrapolations for pola-BR



Based on Figure 98 in Appendix M of the CS.[48]
CS = company submission; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

The company presented in Tables 4.11 and 4.12 the estimated percentage of PFS patients at two, five, and ten years based on the unadjusted and adjusted PFS curves, respectively. In line with the conclusions from the OS analyses for the pola-BR arm, the three clinical experts interviewed by the company concluded that all the adjusted parametric distributions resulted in "*overly pessimistic*" PFS extrapolations for pola-BR in relation to what should be expected in clinical practice (e.g. persistent remission in some pola-BR patients and improved efficacy against BR alone).[25]

Table 4.11: Expected (unadjusted) PFS per distribution for pola-BR

Distribution	2-year PFS	5-year PFS	10-year PFS
Weibull	0%	0%	0%
Lognormal	1%	0%	0%
Log-logistic	1%	0%	0%
Exponential	2%	0%	0%
Generalised gamma	1%	0%	0%
Gompertz	0%	0%	0%

Based on Table 155 in Appendix M of the CS[48]
CS = company submission; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

Table 4.12: Expected (adjusted) PFS per distribution for pola-BR

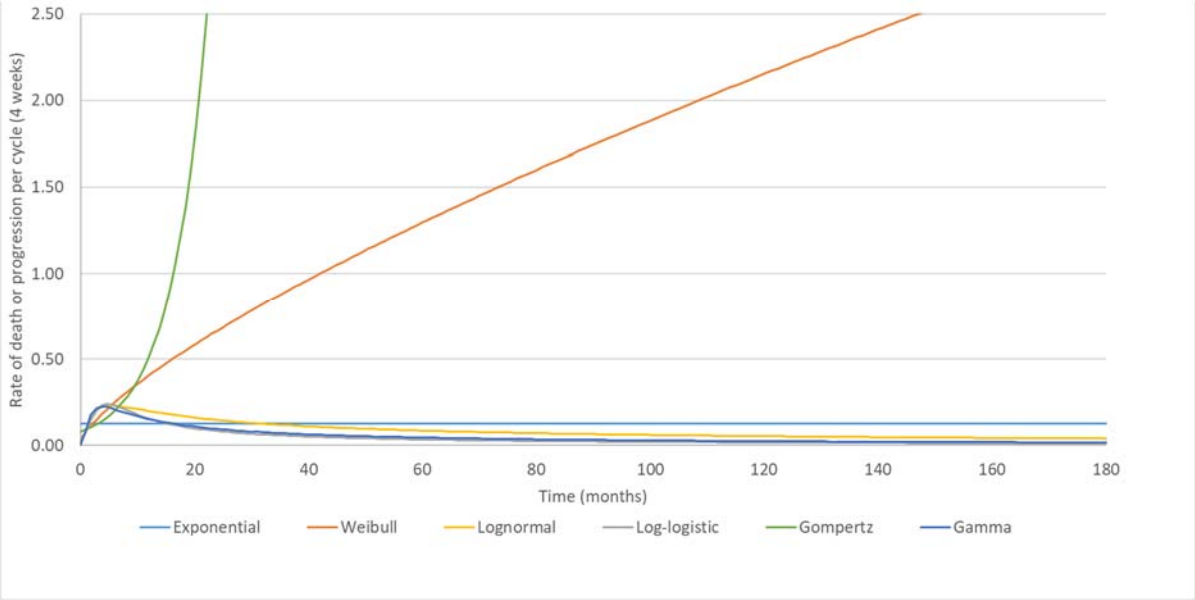
Distribution	2-year PFS	5-year PFS	10-year PFS
Weibull	0%	0%	0%

Distribution	2-year PFS	5-year PFS	10-year PFS
Lognormal	1%	0%	0%
Log-logistic	2%	0%	0%
Exponential	4%	0%	0%
Generalised gamma	2%	0%	0%
Gompertz	0%	0%	0%

Based on Table 156 in Appendix M of the CS[48]
CS = company submission; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

The hazard plots for PFS are shown in Figure 4.18. The clinical experts interviewed by the company indicated that they would expect an increasing then decreasing hazard as the most plausible profile for PFS, and with two of them preferring the lognormal hazard profile.

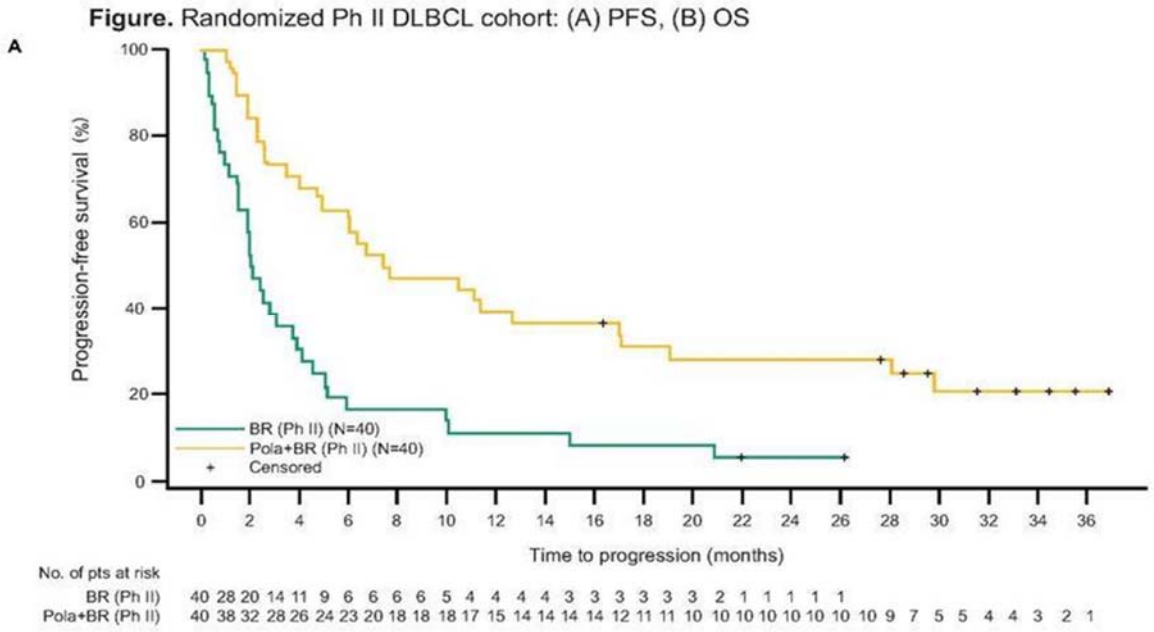
Figure 4.18: PFS smoothed hazard plots for pola-BR



Based on Figure 99 in Appendix M of the CS.[48]
CS = company submission; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab

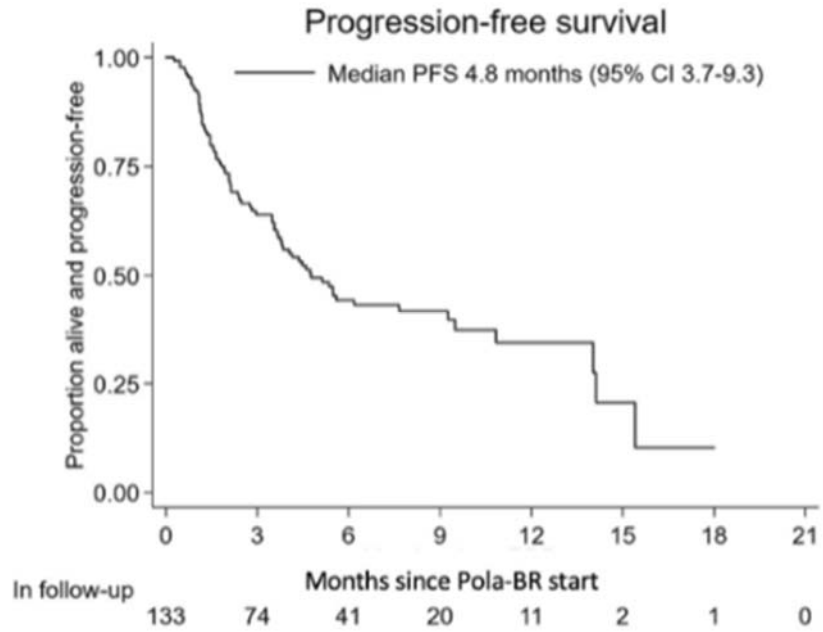
As done with the parametric OS extrapolations, the PFS extrapolations for the pola-BR arm were also compared to available clinical trial data from Sehn 2019 and real-world data from Northend 2021.[49, 50] PFS data from Sehn 2019 and Northend 2021 can be seen in Figures 4.19 and 4.20, respectively. The Sehn 2019 trial data reported a 2-year PFS of approximately 34% for pola-BR patients.[50] The Northend 2021 study reported a 1-year PFS estimate of approximately 28% for pola-BR.[49] This confirms that the parametric extrapolations estimated by the company may have largely underestimated PFS in relation to the data presented in both studies.

Figure 4.19: PFS estimates for pola-BR, Sehn 2019



Based on Figure 100 in Appendix M of the CS.[48] and Sehn et al. 2019[50]
BR = bendamustine + rituximab; CS = company submission; DLBCL = diffuse large B-cell lymphoma; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab

Figure 4.20: PFS estimates for pola-BR, Northend 2021



Based on Figure 101 in Appendix M of the CS.[48] and Northend et al. 2021[49]
CI = confidence interval; CS = company submission; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab

Nevertheless, based on the company's interpretation of the plausibility of the long-term extrapolations in relation to the available external data, the exponential distribution was chosen as the most appropriate candidate to model PFS in the pola-BR arm for the RE-MIND2 data.

ERG comment: The concerns raised by the ERG for the estimation of OS in the pola-BR based on RE-MIND2 data also apply to PFS. Therefore, please refer to Section 4.2.6.4.1 for details. Additionally, the ERG would like to note that the clinical experts indicated that they would expect an increasing then decreasing hazard as the most plausible profile for PFS in the pola-BR arm. However, when assessing PFS in TAFA+LEN, the experts mentioned that they expected an only decreasing. It is unclear to what extent the PFS profile is dependent on the treatment and further clarification should be provided.

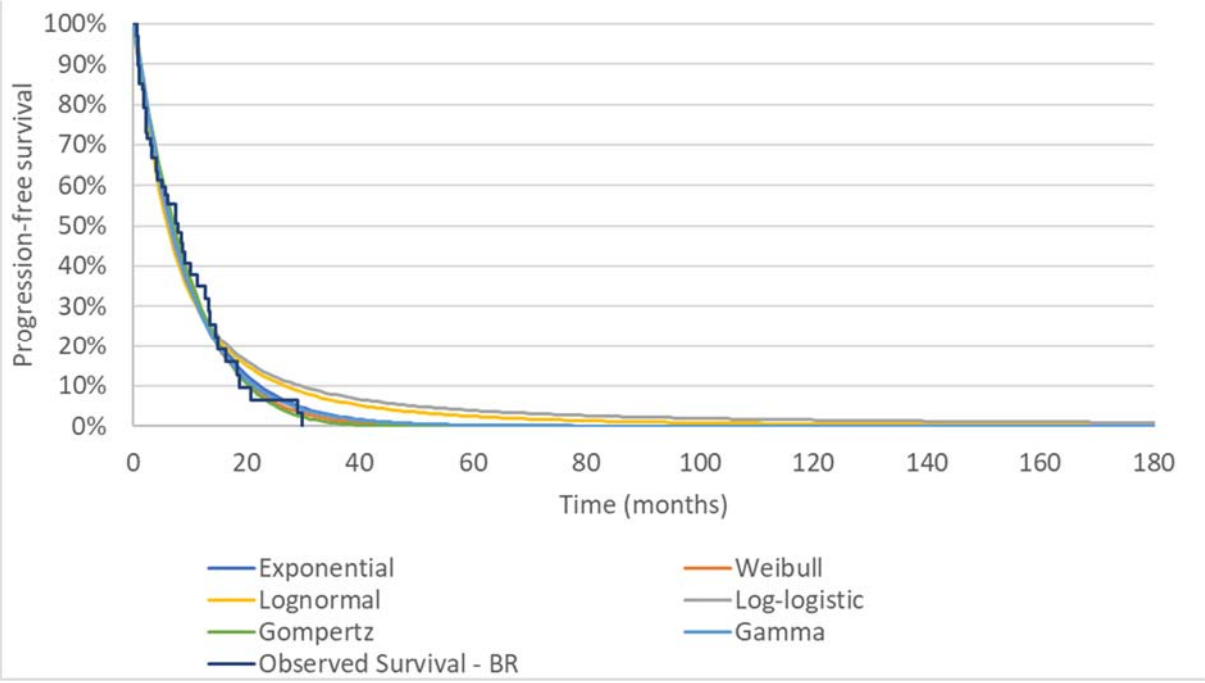
4.2.6.7.2 BR

Based on the assessment of the log cumulative hazard and the Schoenfeld residuals test plots as presented in Figures 80 and 81, respectively, in Appendix M of the CS,[48] the company concluded that a PH assumption between TAFA+LEN and BR PFS was not appropriate. An overlaid PFS plot of the KM curves for the matched TAFA+LEN patients and the original L-MIND data were presented in Figure 82 in Appendix M of the CS.[48] The company concluded that the curves were substantially similar, and, therefore, no "adjustment factor" was estimated.

Based on the AICC/BIC estimates for the unadjusted parametric curves presented in Tables 146 and 147 in Appendix M of the CS, the exponential distribution resulted in the lowest AICC and BIC values.[48] However, all distributions resulted in AICC values differing in less than 4 points from the lognormal AICC value, with the exception of the log-logistic distribution (6.04 points), and all distributions resulted in BIC values differing in less than 10 points from the log-logistic BIC value.

Visual inspection of the PFS *unadjusted* extrapolations for the BR arm are shown in Figure 4.21. All distributions resulted in a similar extrapolations and visual fit to the KM curve. The company considered that towards the final third of the curve, the log-logistic and lognormal parametric distributions seem to overestimate the observed survival, with the other parametric distributions providing a close fit to the tail.

Figure 4.21: Unadjusted PFS extrapolations for BR



Based on Figure 83 in Appendix M of the CS.[48]
CS = company submission; PFS = progression-free survival; BR = bendamustine + rituximab

The company presented in Table 4.13 the estimated percentage of PFS patients at two, five, and ten years based on the unadjusted PFS curves. The three clinical experts interviewed by the company expressed similar preferences. The first expert preferred the generalised Gamma distribution on the expectation that 5- and 10-year PFS would be close to 0%. The second and third experts expected a small proportion of patients to be in PFS at 5 and 10-years, an indicated a similar expectation for R-GemOx. One expert preferred the lognormal distribution and the other expert preferred either the lognormal or loglogistic distribution.

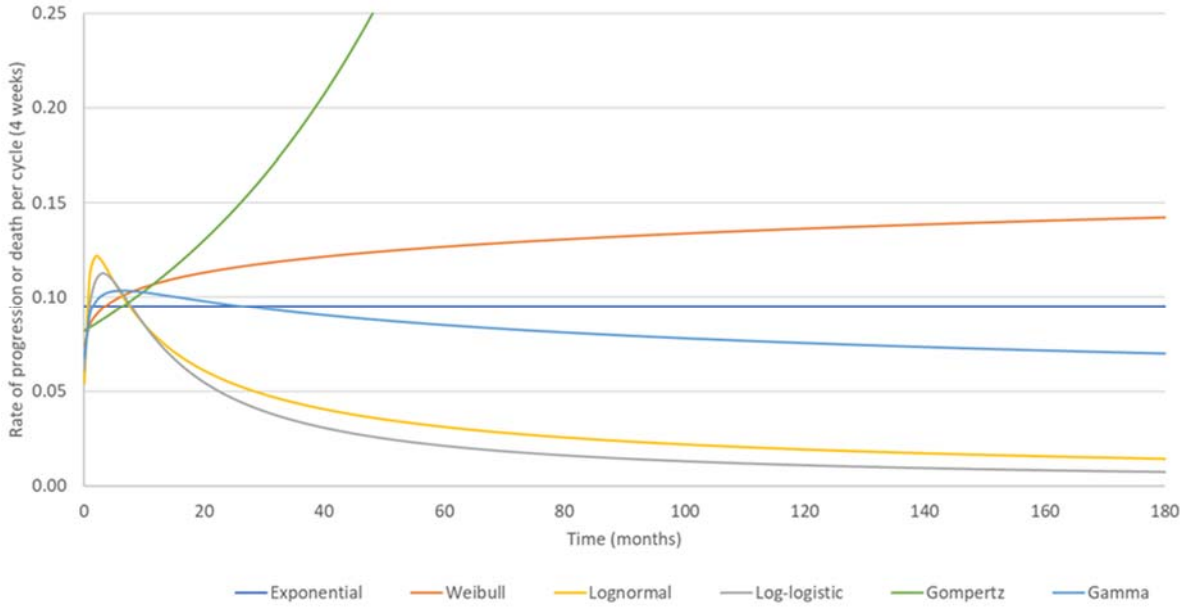
Table 4.13: Expected PFS per distribution for BR

Distribution	2-year PFS	5-year PFS	10-year PFS
Weibull	7%	0%	0%
Lognormal	12%	2%	1%
Log-logistic	13%	4%	1%
Exponential	8%	0%	0%
Generalised gamma	8%	0%	0%
Gompertz	6%	0%	0%

Based on Table 148 in Appendix M of the CS[48]
CS = company submission; BR = bendamustine + rituximab; PFS = progression-free survival

The hazard plots for PFS are shown in Figure 4.24. Two of the clinical experts interviewed by the company preferred a lognormal hazard profile (with one indicating the loglogistic as the next most plausible). The third indicated a general expectation of an increasing then decreasing hazard profile.

Figure 4.22: PFS smoothed hazard plots for BR



Based on Figure 84 in Appendix M of the CS48
BR = bendamustine + rituximab; CS = company submission; PFS = progression-free survival

PFS data from the Sehn 2019 study for the for the BR arm were also shown in Figure 4.19. The Sehn 2019 trial data reported a 2-year PFS of approximately 5% for BR patients, which was below the range estimated by the parametric models (6% to 13%).[50] The company chose lognormal distribution as the most appropriate candidate to model PFS in the BR arm for the RE-MIND2 data. This choice was mostly driven by clinical experts' feedback. The generalised Gamma distribution was explored in

scenario analysis since it provided a closer match to the Sehn 2019 data (6% at 2-years), and it was the preferred distribution (in terms of long-term extrapolations) of one of the clinical experts.[50]

ERG comment: The concerns raised by the ERG for the estimation of OS in the BR based on RE-MIND2 data also apply to PFS. Therefore, please refer to Section 4.2.6.4.2 for details. Also, for BR the clinical experts indicated that they would expect an increasing then decreasing hazard as the most plausible profile for PFS in this arm. As explained above for pola-BR, further clarification should be provided.

4.2.6.7.3 R-GemOx

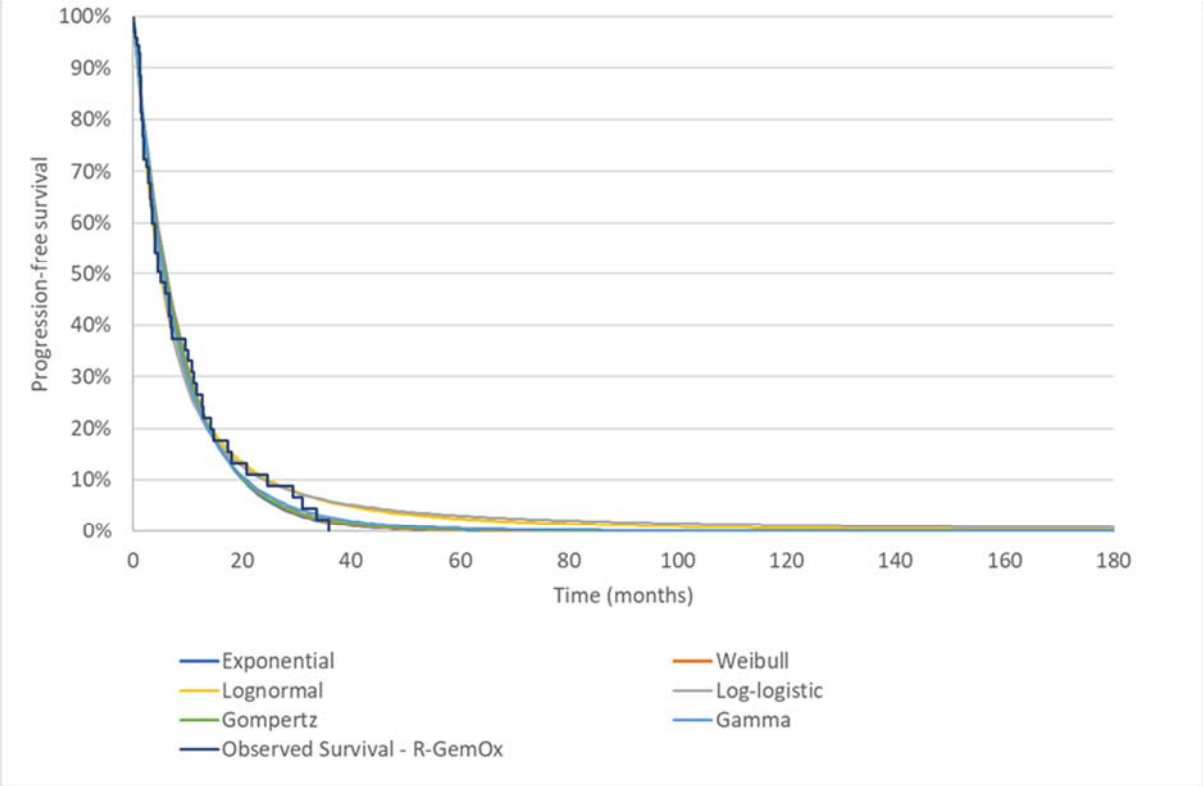
Log cumulative hazard and Schoenfeld residuals test plots are presented in Figures 72 and 73, respectively, in Appendix M of the CS.[48] Based on these, the company concluded that a PH assumption between TAFA+LEN and R-GemOx PFS was not appropriate.

An overlaid PFS plot of the KM curves for the matched TAFA+LEN patients and the original L-MIND data was presented in Figure 74 in Appendix M of the CS.[48] The company concluded that the curves were substantially similar, and, therefore, no "adjustment factor" was estimated.

Based on the AICC/BIC estimates for the unadjusted parametric curves presented in Tables 143 and 144 in Appendix M of the CS,[48] the exponential distribution resulted in the lowest AICC and BIC values. However, all distributions resulted in AICC values differing in less than 4 points from the exponential AICC value, with the exception of the lognormal distribution (4.72 points), and all distributions resulted in BIC values differing in less than 10 points from the log-logistic BIC value.

Visual inspection of the PFS *unadjusted* extrapolations for the R-GemOx arm are shown in Figure 4.23. All distributions resulted in a similar extrapolations and visual fit to the KM curve up to approximately 15 months. After that, the log-logistic and lognormal distributions predicted a higher PFS, and between approximately 15 months and 30 months, these distributions seem to produce a better visual fit to the data. After approximately 30 months the KM curve drops to 0% and the other distributions seem to generate a closer fit to the KM tail.

Figure 4.23: Unadjusted PFS extrapolations for R-GemOx



Based on Figure 75 in Appendix M of the CS.[48]
CS = company submission; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

The company presented in Table 4.14 the estimated percentage of PFS patients at two, five, and ten years based on the R-GemOx unadjusted PFS curves. The three clinical experts interviewed by the company expressed a preference for the lognormal or the log-logistic distribution, based on the expectation that a small proportion of patients would be in PFS at 5 and 10 years (2% to 3% and 1%, respectively).[25]

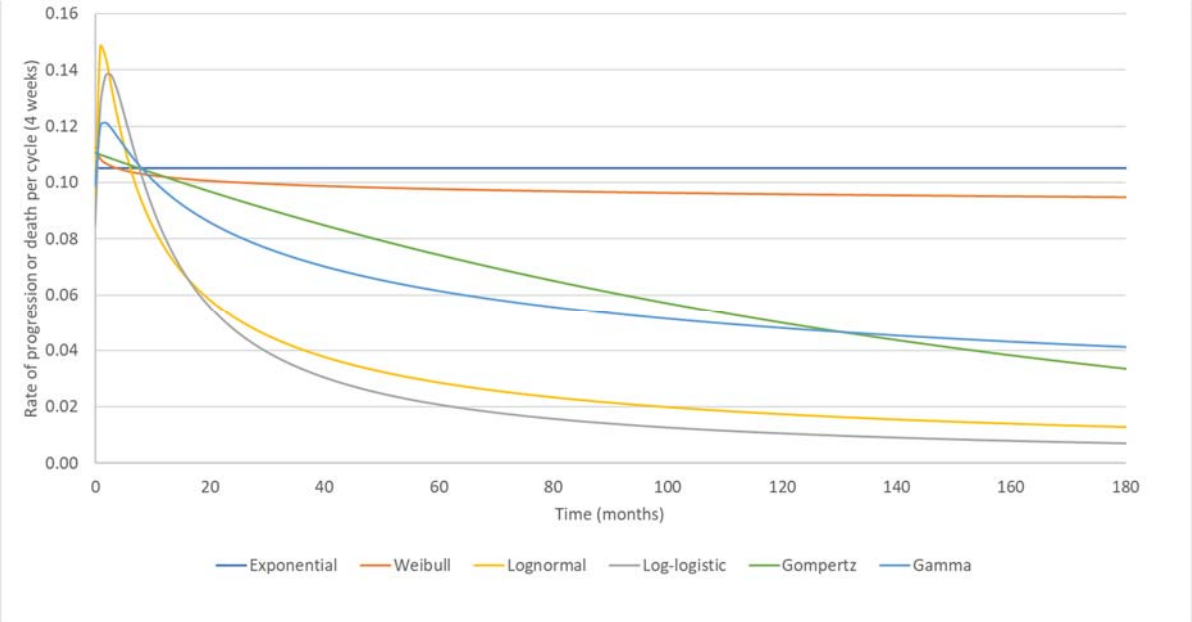
Table 4.14: Expected PFS per distribution for R-GemOx

Distribution	2-year PFS	5-year PFS	10-year PFS
Weibull	7%	0%	0%
Lognormal	11%	2%	1%
Log-logistic	10%	3%	1%
Exponential	6%	0%	0%
Generalised gamma	8%	0%	0%
Gompertz	7%	0%	0%

Based on Table 145 in Appendix M of the CS[48]
CS = company submission; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

The hazard plots for PFS are shown in Figure 4.24. The three clinical experts interviewed by the company expected an increasing then decreasing hazard profile, with preferences varying from the generalised Gamma, lognormal or log-logistic distributions.

Figure 4.24: PFS smoothed hazard plots for R-GemOx



Based on Figure 76 in Appendix M of the CS.[48]
CS = company submission; PFS = progression-free survival; R-GemOx = rituximab + gemcitabine and oxaliplatin

PFS estimates for R-GemOx from Mounier 2013 were also shown in Figure 4.12. The Mounier 2013 data reported a PFS probability of approximately 19% and 13% at two and 5-years, respectively, for R-GemOx patients.[31] The extrapolations estimated by the company seemed to underestimate 2-year PFS (6% to 11%) and 5-year PFS (0% to 3%) compared to Mounier 2013 data. The company chose lognormal distribution as the most appropriate candidate to model PFS in the R-GemOx arm for the RE-MIND2 data. This choice was mostly driven by clinical experts' feedback.

ERG comment: The concerns raised by the ERG for the estimation of OS in the R-GemOx based on RE-MIND2 data also apply to PFS. Therefore, please refer to Section 4.2.6.4.3 for details. Also, the clinical experts indicated that they would expect an increasing then decreasing hazard as the most plausible profile for PFS in the R-GemOx arm. As explained above for pola-BR and BR, further clarification should be provided.

4.2.6.8 Progression free survival: MAIC

MAIC methodology and results are presented in Sections 3.3 and 3.4 this report. The studies included in the MAIC for PFS are summarised in Table 4.15.

Table 4.15: PFS studies identified for the MAIC

Comparator	Study	Data sources
Pola-BR	GO29365[26, 27]	ORR, CRR, PFS-IRCb: Sehn et al. 2020[27] PFS-IRC and DoR: FDA regulatory appraisal[b]
BR	GO29365a[26, 27]	ORR, CRR, PFS-IRCb: Sehn et al. 2020[27] PFS-IRC and DoR: FDA regulatory appraisal[b]

Comparator	Study	Data sources
	Ohmachi et al. 2013[29]	Ohmachi et al. 2013 (no OS or DoR results) [29]
	Vacirca et al. 2014[30]	Vacirca et al. 2014 (no OS results reported) [30]
R-GemOx	Mounier et al. 2013[31]	Mounier et al. 2013 (only median DoR without CI reported)[31]

Based on Table 16 of the CS[1]

[redacted]

[b] The FDA re-analysis of the GO29365 trial explicitly censored PFS records of patients who received a subsequent anti-cancer treatment without a recorded progression events at the time of the last progression assessment available. A similar censoring rules was used in the L-MIND study, and as a result, the PFS reported by the FDA re-analysis appeared more comparable to the L-MIND data than the PFS reported in the Sehn et al. Journal of Clinical Oncology paper. Therefore, the comparative analyses against the data reported in the FDA dossier were used in the base-case analyses. Comparative analyses for PFS-IRC used the Sehn et al. Journal of Clinical Oncology paper as a data source.

BR = bendamustine and rituximab; CI = confidence interval; CRR = complete response rate; CS = company submission; DoR = duration of response; FDA = Food and Drug Administration; IRC = independent radiology/clinical review committee; ORR = objective response rate; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab, gemcitabine, oxaliplatin

The MAIC for BR and R-GemOx also relied on the assumption of a constant HR. For pola-BR, however, the company concluded that assuming PFS PH in between TAFA+LEN and pola-BR was not appropriate, based on log-cumulative PFS hazard plots in Figure 103 in Appendix M of the CS.[48] The interpretation of the plot was the same as the one for OS. Therefore, please refer to Section 4.2.6.5 for details. An overview of the HR's estimated for PFS from the MAIC are summarised in Table 4.16.

Table 4.16: MAIC HR's for PFS

Comparator	HR (vs. TAFA+LEN)	Notes
R-GemOx	1.69	Calculated from MAIC outputs (1/0.59)
BR	2.56	Calculated from MAIC outputs (1/0.39) Pooled estimate using three studies
Pola-BR: 4-month split - first 4 months	0.70	Calculated from MAIC outputs (1/1.42)
Pola-BR: 4-month split - after 4 months	2.56	Calculated from MAIC outputs (1/0.39)
Pola-BR: 11-month split - first 11 months	1.00	Calculated from MAIC outputs (1/1.04)
Pola-BR: 11-month split - after 11 months	4.00	Calculated from MAIC outputs (1/0.25)

Comparator	HR (vs. TAFA+LEN)	Notes
Pola-BR: constant HR	1.14	Calculated from MAIC outputs (1/0.88)
Pola-BR: 3-month split - first 3 months	0.74 (0.33-1.67)	Sensitivity analysis
Pola-BR: 3-month split - after 3 months	2.00 (0.79-5.00)	Sensitivity analysis
Pola-BR: 9-month split - first 9 months	0.92 (0.46-1.82)	Sensitivity analysis
Pola-BR: 9-month split - after 9 months	4.17 (1.18-14.29)	Sensitivity analysis

Based on Table 158 in Appendix M of the CS[48]
BR = bendamustine + rituximab; HR = hazard ratio; CS = company submission; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin

ERG comment: The concerns raised by the ERG for the MAIC estimation of OS also apply to PFS. Therefore, please refer to Section 4.2.6.5 for details.

4.2.6.9 Summary of OS and PFS company base-case assumptions

The data sources and methods selected by the company to model OS and PFS in their base-case analysis are summarised in Table 4.17. The resulting OS and PFS curves are shown in Figures 4.25 and 4.26, respectively.

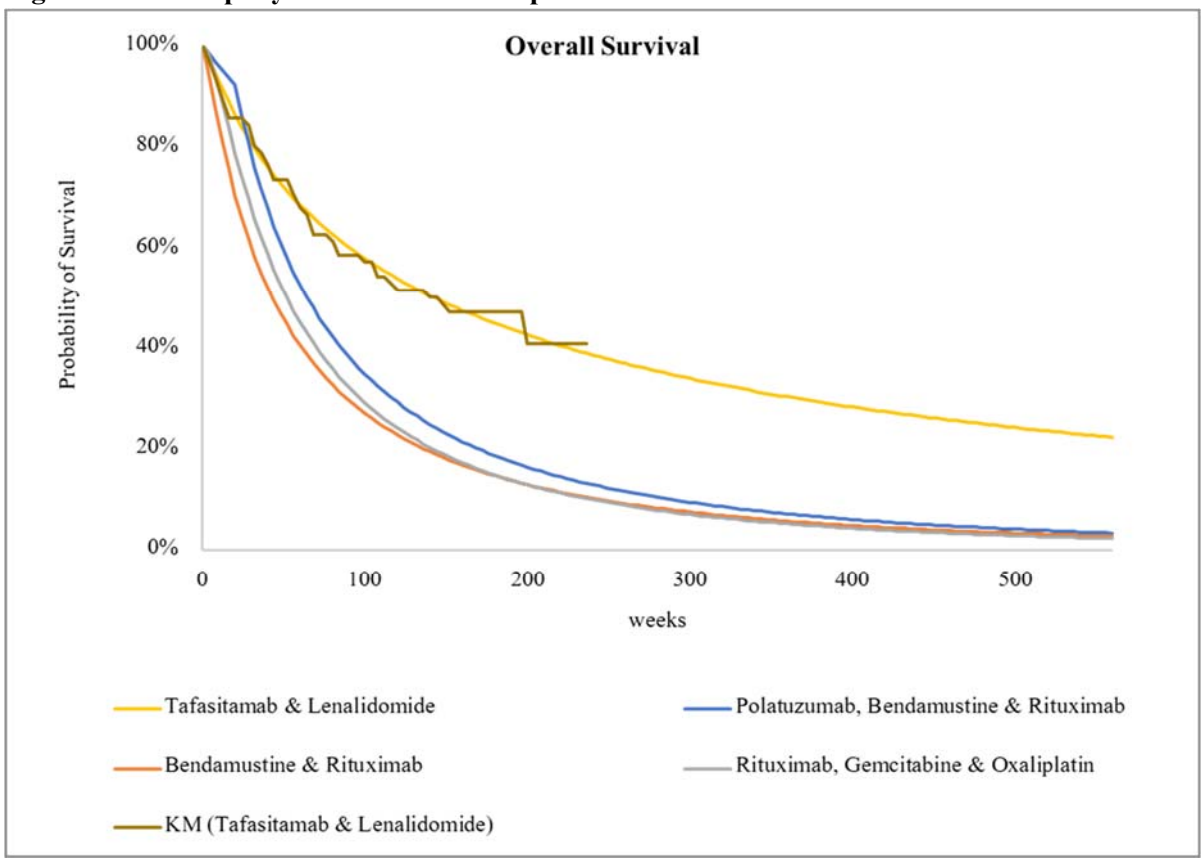
Table 4.17: Company base-case modelling approaches for OS and PFS

Treatment	Data source	Justifications
TAFA+LEN	Parametric extrapolations of L-MIND data	Extrapolation following standard methods.
Pola-BR	MAIC time-varying HRs with 4-month split	MAIC based on clinical expert feedback regarding plausibility of extrapolations from RE-MIND2, as well as lower sample size for RE-MIND2 matched population. Time-varying HRs (apparent violation of PH assumption) with 4-month split.
BR	RE-MIND2 constant HR (OS) and unadjusted parametric fit (PFS)	RE-MIND2 data selected due to larger sample size and indication from UK clinical experts that RE-MIND2 data for BR was plausible in relation to clinical practice. PH assumption plausible for OS. Constant HR (2.392) applied to TAFA+LEN curve to estimate BR OS. For PFS, unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution.
R-GemOx	RE-MIND2 unadjusted parametric fits	RE-MIND2 data selected due to larger sample size and indication from UK clinical experts that RE-

Treatment	Data source	Justifications
		MIND2 data for R-GemOx was plausible in relation to clinical practice. Limitations with MAIC for comparison against R-GemOx. PH assumption not valid for both OS and PFS. Unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution for OS and PFS.

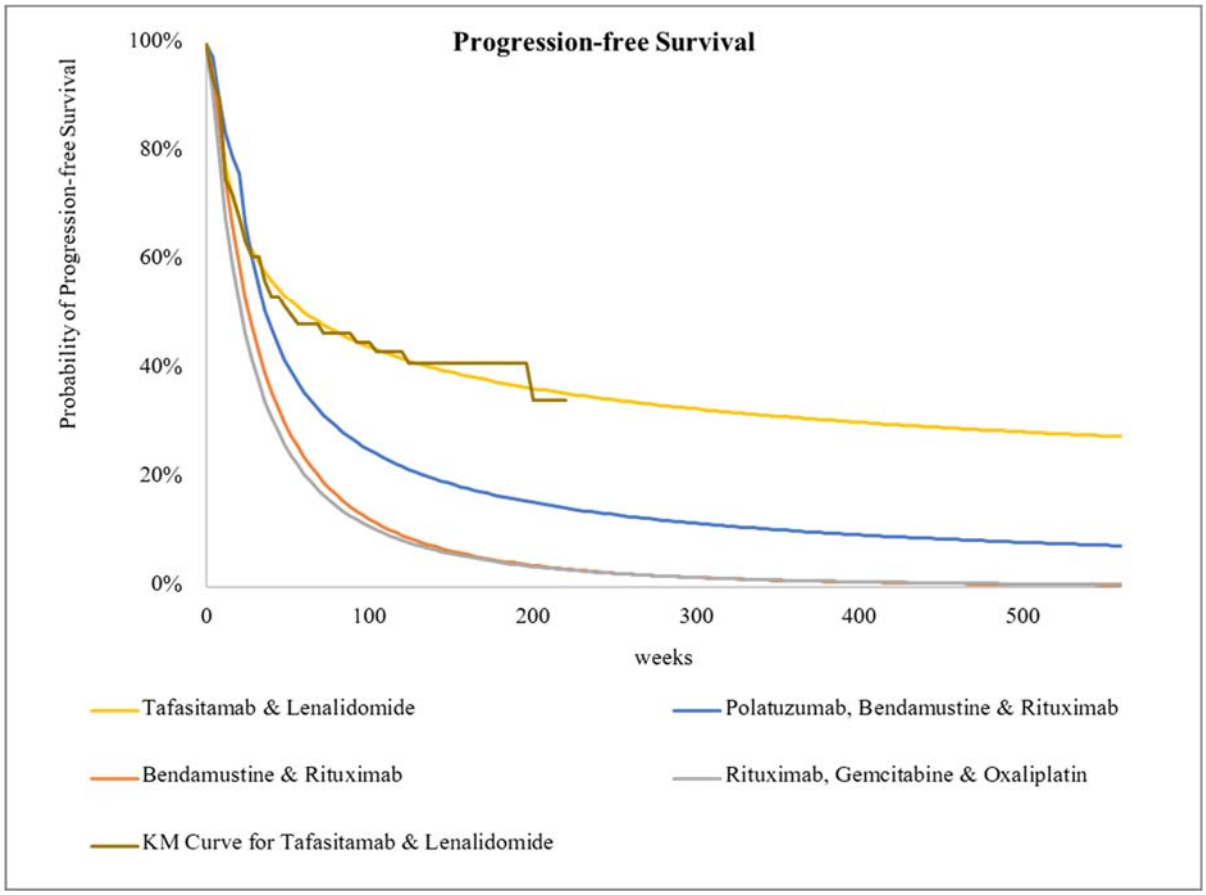
Based on Table 24 of the CS[1]
BR = bendamustine + rituximab; CS = company submission; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

Figure 4.25: Company base-case OS extrapolations



Based on Figure 19 of the CS.[1]
CS = company submission; KM = Kaplan-Meier; OS = overall survival

Figure 4.26: Company base-case PFS extrapolations



Based on Figure 20 of the CS.[1]
CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival

ERG comment: The ERG considers that, in general, the company have used appropriate methods to analyse OS and PFS data by either of the methods selected, i.e. parametric extrapolations of patient-level data or the MAIC. However, several concerns have been raised throughout this Section. In particular, the ERG considers that careful attention should have been paid to assess the plausibility of certain choices made by the company, since some of these seem to lack both face and external validity when compared to clinical experts' expectations and to available (external) data. An overview of the ERG concerns and an assessment of the validity of the company's assumptions on OS and PFS is presented in Tables 4.18 and 4.19.

A MAIC implies adjusting the intervention data to better match the comparator population. Therefore, if there are multiple comparators, each with outcomes estimated from a different data source, then estimating a MAIC for each is likely to lead to a bias in treatment effects, i.e. the outcomes with each comparator relative to the others. On the other hand, estimating the treatment effect of the intervention and comparators from the same pooled data and adjusting the data for all comparators to better match the characteristics of those who received the intervention is liable to lead to greater comparability. This is the case in principle with the analyses performed using RE-MIND2 data. However, as shown in the tables below, the method that provides the better external (clinical) validity for pola-BR is not the use of RE-MIND2: the MAIC is superior. Also, although the PH assumption seems to be invalid, assuming a constant HR (thus, PH) from the MAIC seems to provide the most clinically valid results. By contrast, if the MAIC is selected for R-GemOx, OS results seem to be overestimated. For BR, either the MAIC

or the RE-MIND2 approaches lead to similar results (1.04 vs. 1.13 QALYs, respectively). Therefore, guided largely by clinical validity, for the ERG base-case, our preference for OS would be:

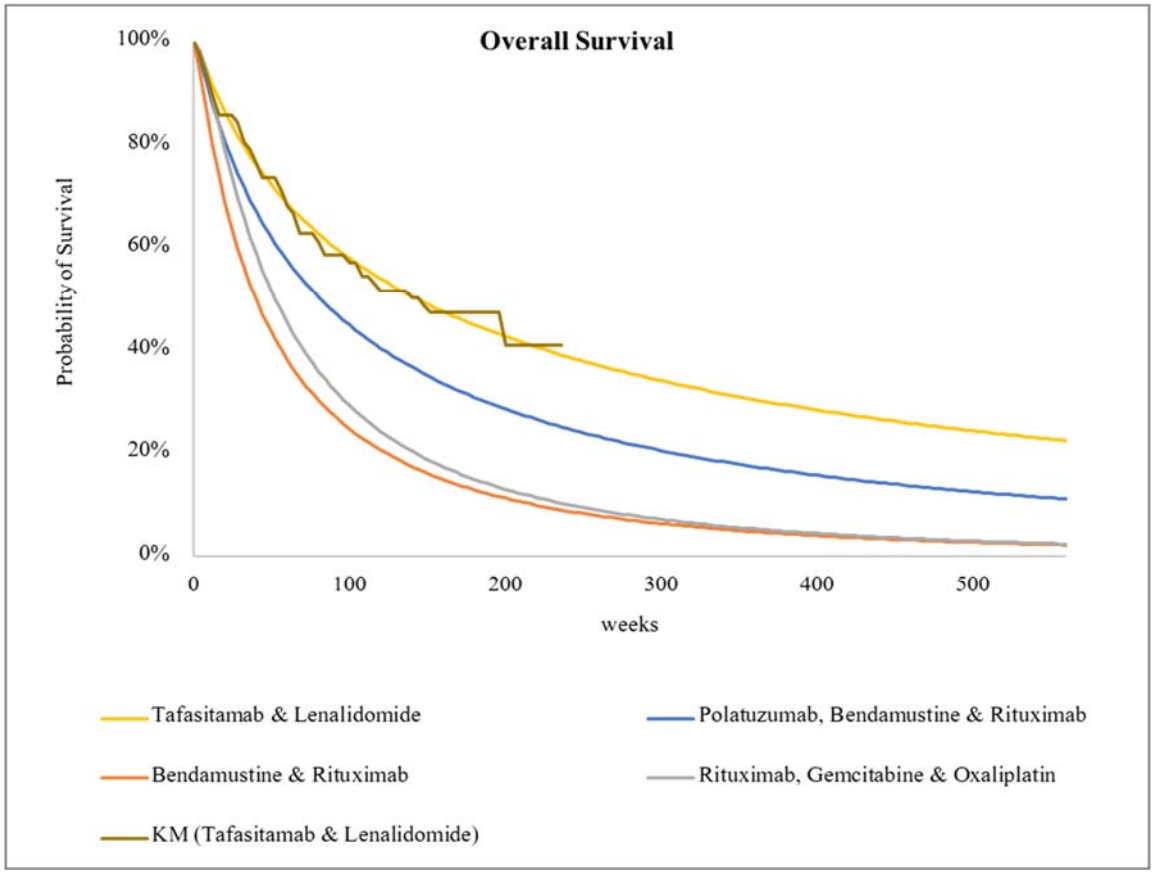
- TAFA+LEN: lognormal based on L-MIND
- Pola-BR: MAIC based on constant HR
- BR: MAIC based on constant HR
- R-GemOx: lognormal based on RE-MIND2

Likewise, the ERG preference for PFS would be:

- TAFA+LEN: lognormal or log-logistic (but the same across all comparators whenever possible) based on L-MIND
- Pola-BR: MAIC based on constant HR
- BR: lognormal or log-logistic based on RE-MIND2. However, this option is not possible in the model, since the same source of data has to be selected for OS and PFS. Therefore, the MAIC based on constant HR was also selected here
- R-GemOx: lognormal or log-logistic based on RE-MIND2

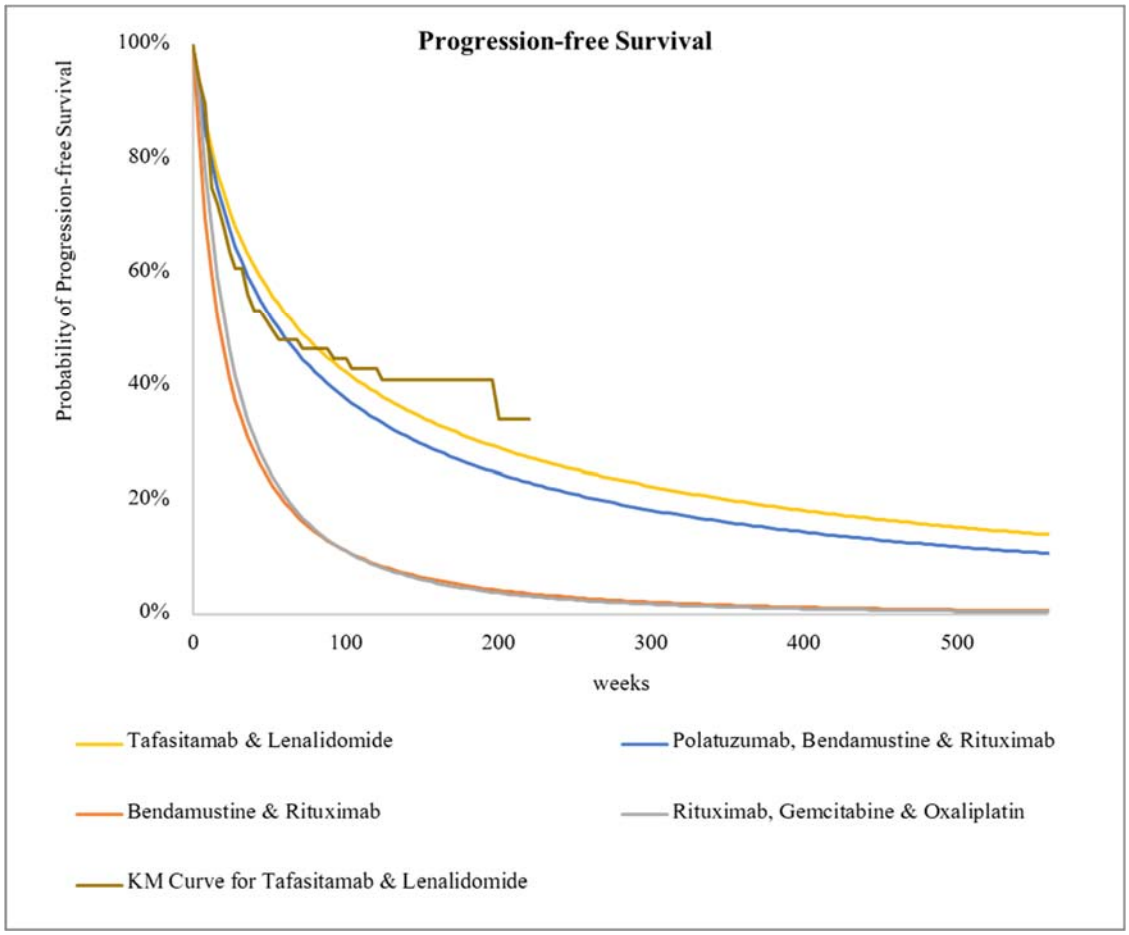
However, it should be emphasised that this ERG "base-case" does not represent a best-case but a least-worse. A number of violations are still present in this ERG "base-case" that cannot be resolved with the current available evidence. The resulting OS and PFS curves in the ERG base-case are shown in Figures 4.27 and 4.28, respectively.

Figure 4.27: ERG base-case OS extrapolations



Sourced from electronic model.
ERG = Evidence Review Group; KM = Kaplan-Meier; OS = overall survival

Figure 4.28: ERG base-case PFS extrapolations



Sourced form electronic model.
ERG = Evidence Review Group; KM = Kaplan-Meier; PFS = progression-free survival

Table 4.18: Comparison and validity of OS predictions

Arm	Approach	2-year OS	5-year OS	10-year OS	ERG comment
TAFA+LEN	L-MIND	56%-61%	29%-40%	9%-34%	Experts provided wide range of expectations. Company base-case (lognormal) towards upper limits (37% at 5-years and 24% at 10-years). Scenario analyses needed. Gompertz seems unrealistically high and can be excluded.
	Clinical experts[25]		<30%-40%	9%-25%	
Pola-BR	RE-MIND2	15%-20%	0%-6%	0%-2%	In general, analyses based on patient-level data (RE-MIND2) are preferred over those based on synthesis of data (MAIC). However, RE-MIND2 analyses based on pola-BR are lacking clinical validity: the survival curves used in the model deviate significantly from those observed in the GO29365 trial (Sehn 2020)[27] and from clinical experts' expectations (as confirmed by the experts consulted by the company, who indicated that predictions based on RE-MIND2 data are overly pessimistic for pola-BR). When these OS/PFS curves are input into the cost effectiveness model, the results in terms of life-years, QALYs, etc. are consequently also not in line with the expectations and/or with previous assessments (e.g. TA649).[42] Therefore, RE-MIND2 analyses for pola-BR should not be considered. Regarding the MAIC, assuming time-varying HRs seems to underestimate OS compared to Sehn data by 3%-4% at year 2 (which can be argued that it is not too much). Assuming a constant HR MAIC seems to overestimate OS compared to Sehn data by ~6% at year 2 (which can be deemed as conservative for TAFA+LEN). However, there are other issues with the long-term extrapolations depending on the type of MAIC assumed. In the company base-case a time-varying HR was assumed for pola-BR and a PH model (constant HR compared to TAFA+LEN) for BR. This choice implies a sort of treatment waning for pola-BR compared to BR, since the OS curves get closer over time, while the TAFA+LEN compared to
	MAIC (time varying HR, 4 months)	33.63%	11.68%	3.91%	
	MAIC (time varying HR, 11 months)	33.97%	9.13%	2.35%	
	MAIC (constant HR)	43.88%	23.19%	12%	
	External data	38% (Sehn 2020*)[27]			
	Clinical experts	Predictions based on RE-MIND2 data are overly pessimistic.[25]			

Arm	Approach	2-year OS	5-year OS	10-year OS	ERG comment
					pola-BR seems to increase and the effect compared to BR stays constant. There is no clear rationale for this assumption, which seems to lead to an underestimation of the effect of pola-BR compared to BR, and possibly compared to TAFA+LEN too. It seems the most plausible results for the pola-BR arm are obtained when a MAIC with a constant HR for OS (compared to TAFA+LEN) is assumed. However, the tests for PH conducted by the company clearly suggest that this assumption is not correct.
BR	RE-MIND2	PH: 26.18% Fit: 23.65%-26.45%	PH: 9.28% Fit: 2.72%-12.79%	PH: 3.18% Fit: 0.07%-9.8%	Analyses based on RE-MIND2 data assumed a PH model in the company's base-case, but no discussion about the validity of the extrapolations was provided. The ERG has concerns regarding this assumption, as mentioned above. Individual curve fitting is also possible in the model. However, some curve choices result in OS BR > OS pola-BR, which seems invalid, since pola-BR has been accepted to be (cost-)effective vs. BR in TA649. Also, some choices result in more than 2 life years for BR, which according to TA649 is not possible (end of life criteria were applied). The MAIC for BR implies a constant HR only, thus a PH model. But it is a different model than the PH model obtained from RE-MIND2. As mentioned above, mixing approaches in treatment arms can result in contradictory model outcomes: PH vs. individual fit, implicit wane of effect is seen for pola-BR. All approaches considered by the company seem to overestimate OS BR compared to Sehn data by 4%-6% at year 2 (which can also be argued that it is not too much). However, the long-term extrapolations may vary from 0%-10%.
	MAIC	23.78%	7.82%	2.48%	
	External data	~20% (Sehn 2020)[27]			
	Clinical experts	Clinical experts did not express concerns regarding the extrapolations for the BR arm.[25]			
R-GemOx	RE-MIND2	27%-29%	4%-10%	0%-4%	

Arm	Approach	2-year OS	5-year OS	10-year OS	ERG comment
	MAIC	36.11%	16.42%	7.27%	Analyses based on RE-MIND2 seem to underestimate OS compared to Mounier data by 7%-9% at year 2, and by 4%-10% at year 5; assuming a constant HR MAIC seems to be more in line with Mounier data.[31] However, if the MAIC estimates are chosen for R-GemOx, then OS R-GemOx is considerably higher than OS BR, and in the long-term OS R-GemOx is also higher than OS pola-BR with time varying HRs, as in the company base-case, which results in R-GemOx being more effective than pola-BR. This seems invalid too.
	External data	36% (Mounier 2013)[31]	14% (Mounier 2013)[31]		
	Clinical experts	Agreed in general with predictions based on RE-MIND2 data.[25]			

Based on economic model.

* The company refers to Sehn 2020,[27] as the source for the OS and PFS plots presented in Appendix M.[48] The ERG was unable to find the plots presented by the company in Sehn 2020 – Figure 2.[27] However, these were found in Sehn 2019.[50] It should be noted that the 2-year predictions in both curves seem to be similar.

BR = bendamustine + rituximab; ERG = Evidence Review Group; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

Table 4.19: Comparison and validity of PFS predictions

Arm	Approach	2-year PFS	5-year PFS	10-year PFS	ERG comment
TAFA+LEN	L-MIND	40%-44%	12%-37%	2%-37%	Experts' expectations were aligned. Gompertz was mentioned as unrealistically high (36.98% at 5 years and 36.83% at 10 years) and can be excluded. Company base-case (generalised Gamma) predicts 33.97% at 5 years and 28.17% at 10 years. This is significantly higher than experts' expectations. Thus, PFS in TAFA+LEN might be (largely) overestimated. Note also that for OS the company selected the lognormal distribution which resulted in OS probability of 37% at 5 years and 24% at 10 years. This results in PFS > OS at 10 years, which is against the general assumption in partitioned survival models that PFS < OS (however, this was capped in the model, and should not be an issue).
	Clinical experts[25]		23%-25%	10%-15%	

Arm	Approach	2-year PFS	5-year PFS	10-year PFS	ERG comment
					The ERG prefers the lognormal or the log-logistic distributions for PFS, which predict ~25% at 5 years and 15% at 10 years. Note that this still represents the upper limits estimated by the experts.
Pola-BR	RE-MIND2	0%-4%	0%	0%	As with OS, RE-MIND2 analyses based on pola-BR are lacking clinical validity and should not be considered. This is supported by the clinical experts interviewed by the company.[25] Regarding the MAIC, assuming time-varying HRs seems to underestimate PFS compared to Sehn data by 14% at year 2. Assuming a constant HR MAIC seems to overestimate PFS compared to Sehn data by ~2.5% at year 2 (which can be seen as conservative for TAFA+LEN). The PFS curve is flat in the tails but this was be capped by OS in the cost effectiveness model. It seems that also for PFS the most plausible results for the pola-BR arm are obtained when a MAIC with a constant HR for OS (compared to TAFA+LEN) is assumed. However, the tests for PH conducted by the company clearly suggest that this assumption is not correct.
	MAIC (time varying HR, 4 months)	19.46%	14.80%	14.64%	
	MAIC (time varying HR, 11 months)	19.84%	12.93%	12.72%	
	MAIC (constant HR)	36.46%	32.29%	32.14%	
	External data	34% (Sehn 2020)[27]			
	Clinical experts	Predictions based on RE-MIND2 data are overly pessimistic, as with OS.[25]			
BR	RE-MIND2	6%-13%	0%-4%	0%-1%	Unlike OS, the PFS analyses based on RE-MIND2 data did not rely on a PH model. Individual curve fitting did not show very large differences in the long-term. The company chose the exponential distribution predicting 8.48% at 2 years, 0.21% at 5 years and 0% at 10 years. However, assuming a constant hazard over time seem unrealistic. The MAIC for BR implies a constant HR only, thus a PH model. Predictions still seem plausible. All approaches considered by the company seem to overestimate PFS BR compared to Sehn data by 1%-8% at year 2, but clinical experts did not express concerns regarding the extrapolations for the BR arm.
	MAIC	10.66%	2.79%	0.76%	
	External data	5% (Sehn 2020)[27]			
	Clinical experts	Close to 0% or a small proportion of patients still in PFS at 5 and 10 years. Same expected for R-GemOx.[25]			
R-GemOx	RE-MIND2	6%-11%	0%-3%	0%-1%	

Arm	Approach	2-year PFS	5-year PFS	10-year PFS	ERG comment
	MAIC	22.77%	9.39%	3.97%	Analyses based on RE-MIND2 seem to underestimate OS compared to Mounier data by 8%-13% at year 2, and by 6%-9% at year 5; assuming a constant HR MAIC seems to be more in line with Mounier data but it would overestimate PFS at 2 years and underestimate it at 5 years.[31] However, as it occurred with OS, if the MAIC estimates are chosen for R-GemOx, then PFS R-GemOx is considerably higher than PFS BR, and in the long-term PFS R-GemOx is also higher than PFS pola-BR with time varying HRs, as in the company base-case, which results in R-GemOx being more effective than pola-BR. This seems invalid too.
	External data	19% (Mounier 2013)[31]	13% (Mounier 2013)[31]		
	Clinical experts	Preference for a small proportion of PFS at 5 and 10 years (lognormal or log-logistic).[25]			
Based on economic model. BR = bendamustine + rituximab; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide					

4.2.6.10 Time to treatment discontinuation (TTD)

TTD data were also included in the CE model. TTD was used to inform drug acquisition and administration cost calculations. The approaches to modelling TTD in the different treatment arms of the model are described below.

4.2.6.10.1 TAFA+LEN (L-MIND)

TTD (and PFS) KM curves for TAFA+LEN observed for the overall L-MIND population are shown in Figure 4.29. TTD was defined post-hoc among patients who received at least one dose of TAFA+LEN as follows: the date of treatment discontinuation or death (whichever occurred first) minus the date of treatment initiation, plus one day. Different treatment schedules were used for lenalidomide and tafasitamab: lenalidomide was given for up to 12 treatment cycles (in the absence of disease progression or unacceptable toxicity) and tafasitamab was given until disease progression or unacceptable toxicity (or other reason for discontinuation) without a fixed maximum treatment duration.

Figure 4.29: TTD KM curves: TAFA+LEN

[redacted]

Based on Figure 108 in Appendix M of the CS[48]
CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival; LEN = lenalidomide; TAFA = tafasitamab; TTD = time-to-treatment discontinuation

Survival analyses for TAFA TTD were conducted using L-MIND data and following the recommendations by TSD14.[44] [redacted].

AICC/BIC estimates for the parametric curves modelling TTD for TAFA were presented in Tables 161 and 162 in Appendix M of the CS.[48] [redacted]

[redacted].

TTD extrapolations for tafasitamab are shown in Figure 4.30. [redacted].

Figure 4.30: TTD TAFA extrapolations

Based on Figure 109 in Appendix M of the CS[48]
CS = company submission; KM = Kaplan-Meier; TAFA = tafasitamab; TTD = time-to-treatment discontinuation

The company presented in Table 4.20 the estimated median and percentage of patients on tafasitamab treatment at two, five, and ten years. [redacted].

Table 4.20: Median TTD and percentage of patients on treatment for tafasitamab

Distribution	Median (months)	Predicted 2-year TTD	Predicted 5-year TTD	Predicted 10-year TTD
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Median (months)	Predicted 2-year TTD	Predicted 5-year TTD	Predicted 10-year TTD
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 163 in Appendix M of the CS[48] CS = company submission; TTD = time to treatment discontinuation or death				

ERG comment: The approach to modelling TTD for tafasitamab and lenalidomide seems appropriate. Given the lack of external data to validate the TTD extrapolations for tafasitamab, [redacted].

4.2.6.10.2 Comparators

The company considered two approaches for modelling TTD in the comparators. The first approach was based on median treatment duration estimates obtained from published clinical trial data or prior NICE TAs, and fitting exponential distributions to the median TTD estimates. The second approach was based on available TTD data from the RE-MIND2 study. When the MAIC is selected as the data source for a comparator, the median treatment duration is considered in the model for TTD. When RE-MIND2 data are selected as the data source for a comparator, TTD is modelled directly assuming KM curves derived from RE-MIND2 data. For their base-case analysis, the company chose TTD estimates to align with the base-case data sources; thus, [redacted].[54] Additional details on both methods are provided in Appendix M to the CS.[48]

ERG comment: The two approaches for modelling TTD in the comparators considered by the company are linked to the efficacy data source selected for each comparator. Thus, when the MAIC is selected, the median treatment duration is considered in the model for TTD, and when RE-MIND2 data are selected, TTD is modelled assuming KM curves derived from RE-MIND2 data. In the company base-case, [redacted]. This implies that in the ERG base-case, [redacted].

4.2.6.11 Other considerations

The company indicated that no evidence of treatment effect waning was observed in the clinical trial data. This assumption seems to be consistent with previous R/R DLBCL appraisals (see, e.g. Table 23 in the CS).[1] Therefore, no additional assumptions were considered regarding treatment effect duration or waning.

Cure assumptions were not included in the base-case analysis, given the feedback obtained from clinical expert feedback and the uncertainty around the validity of cure assumptions (see, e.g. TA649). [54] However, these were explored in scenario analyses. For additional details please refer to Appendix M of the CS.[48]

Patients experiencing death before progression were modelled differently, by assuming a constant ratio of death to progression among PFS events as follows:

$$Pre-progression\ Deaths(t) = [PFS(t-1) - PFS(t)] \times Ratio\ of\ Death\ during\ PFS$$

This was assumed to avoid overestimating the incidence of progression and, therefore, post-progression costs. The proportion of death in the PFS health state, which includes both death and progression events, was estimated at 10% as the ratio of death within the PFS events based on data for tafasitamab and lenalidomide from the L-MIND study. For the other comparators, the same ratio was assumed in the absence of treatment specific data.

Finally, the option of a "prolonged PFS" health state was also included in the model. The rationale for this was to reflect possible reduced resource usage when patients are in the PFS health state for an extended period of time. This assumption only affects monitoring and disease management resource use costs and but not health outcomes. This option was explored as an extension to the cure assumptions in scenario analyses, assuming the same timing (at 2-years or at crossing of PFS and OS) and proportion of patients experiencing reduced resource use costs (78.6% at 2-years or all patients from crossing of PFS and OS curves) as for the cure assumptions.

ERG comment: Given the lack of data to support the several assumptions discussed in this section, the ERG agrees with company's choices and considers that the best approach to assess these uncertainties is by means of scenario analyses.

4.2.7 Adverse events

All Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and higher AEs that occurred in at least 5% of study subjects in the L-MIND study and trials of other treatment alternatives (GO29365 trial for Pola-BR and BR, and NICE TA649 for R-GemOx) were included in the model.[42] The incidence and duration of AEs are not modelled explicitly. Rather, a one-off lumpsum cost and utility decrement is applied at the start of the treatment. To that end, the treatment-specific cumulative incidences of AEs over the trial duration are used as the probability of AEs occurring for each treatment. Table 4.21 shows the probability of AEs occurring for each treatment alternative.

Table 4.21: Incidence of adverse events included in the model (CTCAE ≥ Grade 3, ≥5% incidence)

AE	TAFA+LEN	Pola-BR	BR	R-GemOx
Anaemia	7.4%	28.20%	17.90%	33.00%
Febrile neutropenia	12.3%	10.30%	12.80%	
Hypokalaemia	6.2%	NA	NA	NA
Leukopenia	11.1%	NA	NA	NA
Neutropenia	49.4%	46.20%	33.30%	73.00%
Pneumonia	9.9%	NA	NA	NA
Thrombocytopenia	17.3%	41.00%	23.10%	23.00%
Lymphopenia	NA	12.80%	NA	NA

Based on Table 55 of the CS[1]

AE = adverse event; BR = bendamustine + rituximab; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; LEN = lenalidomide; NA = not applicable; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = Rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

ERG comment: Although the company states that all grade ≥3 AEs that occurred in ≥5% of patients were included for all treatment arms, for pola-BR and BR only the grade ≥3 AEs that occurred in ≥10%

of patients in GO29365 were included based on Sehn et al. 2020.[27] Based on Table 4.16 in the ERG report of NICE TA649 that shows grade ≥3 AEs that occurred in ≥5% of patients in GO29365 at the data cut-off that was used at the time, the following AEs were not taken into account for the current appraisal (incidence between brackets): leukopenia (7.7% in pola-BR, 7.7% in BR), pneumonia (7.7% in pola-BR and 2.6% in BR), hypokalaemia (7.7% in pola-BR and 2.6% in BR) and rash (0% in pola-BR and 7.7% in BR).[42] The ERG notes that, given the relatively low incidences between 5% and 10%, the omission of these AEs in pola-BR and BR is not likely to have a substantial impact on the results. Therefore, the ERG prefers to retain the assumptions on incidences of AEs as per the company's analysis. To address the impact on the CE results of using the same 10% threshold for grade ≥3 AEs across all treatment arms, the ERG performed a scenario analysis where they excluded all AEs with incidence lower than 10%. This resulted in slightly lower ICERs.

4.2.8 Health-related quality of life

4.2.8.1 Identification and selection of utility values

HRQoL data were not collected in the population enrolled in the L-MIND study. The company searched for published sources of health state utility values in treating transplant ineligible relapsed/refractory DLBCL through a SLR and previous R/R DLBCL NICE submissions. The systematic review identified 30 studies which reported HRQoL data in patients with relapsed or refractory disease. Out of these, health utility estimated from only three studies were included.[38-40] Four sources identified were previous NICE appraisals (TA649, TA567, TA559 and TA306).[42, 54-56] All identified sources each provided utility values for the required PFS and PD health states. TA567 and TA559 obtained utility data directly from trials, while TA306 utilised published sources of utility data. TA567 used SF-36 data (mapped to EQ-5D) from 34 patients from the JULIET trial, assessing tisagenlecleucel in DLBCL patients. TA559 used EQ-5D-5L data (mapped to EQ-5D-3L) from 34 patients (87 observations) from the ZUMA-1 trial assessing axicabtagene in mixed histology lymphoma, (including DLBCL). TA649 obtained utility values sourced from NICE TA559. TA306 provided utility values based on several published studies on NHL patients. The company chose to include the base-case utility values estimated from TA559 (CAR-T). Health state utilities from NICE TA567 were also explored in a scenario analysis. Details of all studies and NICE appraisals identified are provided in Table 27 of the CS. Details of the utilities used within the model for patients in PFS or PD are provided in Table 28 of the CS.[1]

In the base-case, the company chose to adopt the TA559 health state utility values obtained from the ZUMA-1 trial data (0.72 for PFS, 0.65 for PD) which were also applied in the NICE R/R DLBCL TA for pola-BR (TA649). This source was chosen as the use of the van Hout mapping algorithm to estimate EQ-5D-3L values from 5L values aligns with the NICE reference case and position statement on the use of the EQ-5D-5L valuation set for England.[41] Upon consultation with three UK clinical experts, the TA559 utility values were indicated as reasonable by two, while one of the two experts also noted that the PD patient population receiving TAFA+LEN may be older than those receiving CAR-T, thus they might have lower health utility values. Therefore, even though the company considered the utility data derived from the patient population of the ZUMA-1 receiving CAR-T, it may not be generalisable to patients from the L-MIND study population due to age differences. Cure assumptions were not included in the base-case analysis, but cure assumption-related scenario analyses were conducted. Base-case analysis also included quality of life loss from subsequent CAR-T therapy identified as lower utility estimated for the first 2 months of therapy compared to chemotherapy. A one-off disutility of 0.05 for CAR-T treatment was applied that was identified as the difference in utility values between chemoimmunotherapy and tisagenlecleucel for the first 2 months of therapy.[57]

The company conducted one scenario analysis using health state utilities from NICE TA567 (0.83 for PFS, 0.71 for PD).[54] Another cure assumption-related scenario analysis was also performed in which assumption of equivalent quality of life to progression-free patients and assumption of equivalent quality of life to the general population were explored.

The utilities were adjusted for age and sex. In the base-case analysis, a multiplicative adjustment approach was applied in which a multiplication factor was derived between the health state utility and the age and sex-matched general population utility under the assumption that there may be an overlap in disease symptoms or patient related outcomes with other age-related conditions.

For the base-case analysis, the general population regression model from Chang-Douglass 2020 was applied as it includes a larger dataset that includes Health Survey for England (HSE) datasets for 2008, 2010-2012, 2014 and 2017.[58]

ERG comment: Given that HRQoL data was not collected in the L-MIND trial, the ERG consider that the company conducted a thorough search for relevant health state utility values. The TA559 utility values utilised in the base-case were obtained from the safety population of the single arm ZUMA-1 trial. The exact approach was adopted in the previous polatuzumab NICE submission. The ERG considers this approach appropriate. For further details, please refer to the polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma NICE submission.[42]

4.2.8.2 Adverse event disutilities

As HRQoL data were not available from the L-MIND trial, the company applied a one-off QALY loss to each treatment. Disutilities and AE durations were sourced from several sources including previous NICE appraisals as shown in Table 4.22. Disutilities were weighted by the probability of the AE occurring for each treatment.

Table 4.22: Adverse event disutility values and durations used in the model

AE	Disutility	Duration (days)	Source
Anaemia	0.25	16.00	NICE TA649[42]
Febrile neutropenia	0.15	7.10	NICE TA649, NICE TA306[42, 55]
Hypokalaemia	0.09	72.00	Assumed same as leukopenia
B cell aplasia	0.37	72.00	Assumption – maximum of reported durations GO29365[51]
Blood creatinine decreased	0.09	72.00	Assumed same as leukopenia
Decreased appetite	0.37	72.00	NICE TA649[42]
Confusional state	0.37	72.00	Assumption – maximum of reported durations GO29365[51]
Encephalopathy	0.37	72.00	Assumed same as leukoencephalopathy
Cytopenia	0.19	72.00	Sarkar et al. 2019[59]
Fatigue	0.13	31.50	Walter et al. 2019[60]
Leukopenia	0.09	14.00	NICE TA649, NICE TA306[42, 55]
Lower respiratory tract infection	0.20	72.00	NICE TA649[42]

AE	Disutility	Duration (days)	Source
Neutropenia	0.09	15.10	NICE TA649, NICE TA306[42, 55]
Nausea	0.05	6.00	Zhu et al. 2018[61]
Tremor	0.22	72.00	Li et al. 2019[62]
Vomiting	0.05	2.300	NICE TA649[42]
Decreased white blood cell count	0.09	72.00	Holleman et al. 2020[63]
Abdominal pain	0.07	17.00	NICE STA ID414[64]
Dyspnoea	0.26	12.70	Holleman et al. 2020[63]
Pneumonia	0.20	14.90	NICE TA649, NICE TA306[42, 55]
Thrombocytopenia	0.11	23.20	NICE TA649, NICE TA306[42, 55]
Lymphopenia	0.09	34.00	Bullement et al. 2019, NICE TA306[55, 65]
Diarrhoea	0.10	72.00	NICE TA649[42]

Based on Table 29 and the electronic model in the CS[1]

AE = adverse event; CS = company submission; NICE = National Institute for Health and Care Excellence; TA = technology appraisal

ERG comment: A one-off disutility for CAR-T therapy was included for all patients receiving CAR-T as subsequent therapy for any treatment arm. An option for application of another set of one-off disutilities for allogenic or autologous stem cell transplant (SCT) was also present in the model. The rationale for application of these disutilities is based on the possibility that some patients may subsequently become eligible for SCT (autologous or allogeneic) following discontinuation of treatment with TAFA+LEN or other comparators. Since the company reported that the proportion of patients receiving SCT as subsequent therapy is very low, the company assumed that no patient in the included patient population would receive SCT as a subsequent treatment. Inclusion of these disutilities is therefore an option and would have a negligible impact on the results of the base-case model.

The sources used to identify disutilities associated with the included AEs appear appropriate. For a selection of included AEs, the company assume the maximum of reported durations in the GO29365 trial.[39] The model states that this assumption is used where no duration was recorded in the trial. The maximum duration seen for an AE in the GO29365 trial was 72 days for diarrhoea, with an assumed associated disutility of 0.01. This assumed AE duration of 72 days was used for 15 of the included AEs: B-cell aplasia, decreased blood creatinine, confusional state, decreased appetite, diarrhoea, encephalopathy, cytopenia, hypokalaemia, lower respiratory tract infection, tremor, decreased white blood cell count, infection, hypercalcaemia, raised LDH and hypophosphatemia. The company states that this assumption was used in TA649. Four of these 14 AEs are also assumed to have the maximum disutility of AEs seen in TA306 of 0.37.[55] Again, the company states that this assumption was used in the polatuzumab NICE submission. In addition, asthenia also had the assumed maximum utility for an AE of 0.37, with duration of 35.30 days. The assumption of maximum disutilities in combination with maximum duration for these AEs may overweight the importance of these events. However, AE disutilities and durations are expected to have a minor impact on the ICER and, therefore, this is unlikely to have a substantial effect on the results.

4.2.8.3 HRQoL data used in the cost effectiveness analysis

The utility values as used by the company for the PFS and PD health states, and the disutility due to CAR-T in their base-case and scenario analyses are summarised in Table 4.23.

Table 4.23: Health state utility values

	Utility values (SE)		Source
	Base-case	Scenario	
PFS	0.72 (0.03)	0.83 (0.03)	Base-case: NICE TA559[56] Scenario: NICE TA567[27, 66]
PD	0.65 (0.06)	0.71 (0.06)	
Disutility: CAR-T (One-Off)	0.0083 (0.0008)	0.0083 (0.0008)	Lin 2019[57] 0.05 disutility for CAR-T therapy relative to chemoimmunotherapy applied for a 2-month duration
Based on Table 28 and information provided in the CS[1] CS = company submission; PD = Progressed disease; PFS = Progression free disease; SE = Standard error			

Cure assumptions were not included in the company's base-case analysis. However, assumption of equivalent quality of life to progression-free patients and assumption of equivalent quality of life to the general population were both explored in cure assumption-related scenario analyses.

To adjust for age and sex, a multiplication factor was applied to the general population utility curve derived for the modelled population sex characteristics and age over time in order to generate a utility curve by age for each health state. Reference population characteristics used to generate the disutility multiplier vs. the general population for the progression-free and progressed disease health states were based on the ZUMA-1 trial (median age of 58 years, 67% male), with reference population characteristics for the utility scenario analysis based on the JULIET trial (median age of 56 years, 64.5% male).[67, 68] General population utility was modelled according to published UK regression models from Ara and Brazier 2010 and Chang-Douglass et al. 2020.[58, 69] Both studies provide general population regression models derived from HSE data, with Chang-Douglass et al. 2020 updating the Ara and Brazier regression model to include additional HSE datasets for 2008, 2010-2012, 2014 and 2017. For the base-case analysis, the general population regression model from Chang-Douglass 2020 was applied given the larger sample size of HSE data included in the analysis, and due to the availability of uncertainty data around the regression model coefficients (which were not provided in the Ara and Brazier 2010 study).

The disutilities due to AEs as used by the company are provided in Table 4.24 below. These were applied as a one-off QALY lumpsum at the start of the model.

Table 4.24: Adverse event disutilities

Adverse event	Disutility	Duration (days)	Source
Anaemia	0.25	16.00	NICE TA649[42]
Febrile neutropenia	0.15	7.10	NICE TA649[42] and NICE TA306[55]
Hypokalaemia	0.09	72.00	Assumed same as leukopenia
Leukopenia	0.09	14.00	NICE TA649[42] and NICE TA306[55]
Neutropenia	0.09	15.10	NICE TA649[42] and NICE TA306[55]

Adverse event	Disutility	Duration (days)	Source
Pneumonia	0.20	14.90	NICE TA649[42] and NICE TA306[55]
Thrombocytopenia	0.11	23.20	NICE TA649[42] and NICE TA306[55]
Lymphopenia	0.09	34.00	Bullement et al. 2019[65] and NICE TA306[55]
Based on Table 29 in the CS[1] CS = company submission; PD = Progressed disease; PFS = Progression free disease; SE = Standard error			

4.2.9 Resources and costs

The following cost categories were included in the analysis: drug acquisition costs for the intervention and comparator, drug administration costs, radiotherapy costs, concomitant medication costs, subsequent treatment costs, monitoring costs, disease management costs, costs for the treatment of AEs, and end-of-life costs.

4.2.9.1 Drug acquisition costs

The drug acquisition costs for tafasitamab at list price are £705 per vial of powder containing 200 mg of tafasitamab concentrate for solution for infusion. A Patient Access Scheme (PAS) discount has been approved which equates to a fixed price discount of [redacted]% with a PAS price of £[redacted] per vial. Tafasitamab is administered by IV infusion at a dose of 12 mg/ kg. For the first three treatment cycles tafasitamab is administered weekly on days 1, 8, 15 and 22 of each 28-day treatment cycles, with an additional loading dose administered on day 4 of the first treatment cycle. After the first three treatment cycles, tafasitamab is administered on days 1 and 15 (i.e. bi-weekly) of each 28-day treatment cycle. Treatment with tafasitamab is continued until disease progression or unacceptable toxicity. It was assumed that all patients who have not discontinued treatment by the end of the induction phase (i.e. the first 12 treatment cycles) continue to receive tafasitamab during the maintenance phase (i.e. from treatment cycle 13 onwards). A median dose intensity of [redacted] was assumed for tafasitamab based on L-MIND.[23]

The drug acquisition costs for lenalidomide at list price are £4,368 per pack of 21 hard capsules containing 25 mg lenalidomide per capsule. Other dose formulations that result in a higher price per mg are available in the model, but these are not used for the analysis. [redacted] With this assumed price reduction, lenalidomide costs £[redacted] per pack of 21 capsules of 25 mg. Lenalidomide is administered orally at a dose of 25 mg per day on days 1 to 21 of each 28-day treatment cycle, up to a maximum of 12 treatment cycles. A median dose intensity of [redacted] was assumed for lenalidomide based on L-MIND,[22] which was calculated as a weighted average from median dose intensities of [redacted] for treatment cycles 1 to 8 and [redacted] for treatment cycles 9 to 12.

The following comparator regimens were included in the model: polatuzumab vedotin with bendamustine and rituximab (pola-BR); bendamustine and rituximab (BR); and rituximab, gemcitabine and oxaliplatin (R-GemOx). For these drugs the drug acquisition costs were sourced from either the British National Formulary (BNF, October 2021) or the electronic Market Information Tool (eMIT,

September 2021).[70, 71] For drugs that have multiple dose formulations available, the price that resulted in the lowest cost per mg was used in the model. These are summarised in Table 4.25.

Table 4.25: Drug acquisition costs for comparator regimens as used in the model

Drug	Dosage (pack size)	List price per pack	Source
Polatuzumab	30 mg (1)	£2,370	eMIT[71]
Bendamustine	100 mg (5)	£76.49	eMIT[71]
Rituximab	100 mg (1)	£157.17	eMIT[71]
Gemcitabine	1,000 mg (1)	£10.20	eMIT[71]
Oxaliplatin	100 mg (1)	£12.52	eMIT[71]
Based on the electronic model. eMIT = electronic market information tool			

For pola-BR treatment consists of six 3-weekly treatment cycles, during which polatuzumab and rituximab are administered once per treatment cycle and bendamustine is administered twice per treatment cycle.

For BR treatment consists of six 3-weekly treatment cycles, during which rituximab is administered once per treatment cycle and bendamustine is administered twice per treatment cycle.

For R-GemOx treatment consists an induction phase of four 2-weekly treatment cycles, during which all components of the regimen are administered once per treatment cycle, followed by a maintenance phase of two 2-weekly treatment cycles, in line with UK guidelines that recommend a maximum of up to six treatment cycles for R-GemOx, during which all components of the regimen are administered once per treatment cycle. It was assumed that 78% of the patients who remained on treatment with R-GemOx during the induction phase continued to receive treatment during the maintenance phase, based on Mounier et al. 2013.[31]

The assumptions for dosage, cost per dose, and dose intensities for the intervention and comparators during the induction and maintenance phases are listed in Tables 30 and 31 of the CS.[1] Note that these are based on the list price of tafasitamab and the price of lenalidomide with the assumed [redacted]% reduction. The cost per dose based on the PAS price of tafasitamab is £[redacted] and the cost per dose for lenalidomide at list price is £[redacted]. An overview of the treatment schedules during the induction and maintenance phases for the intervention and comparators are listed in Tables 32 and 33 of the CS, respectively.[1] Dose intensities for pola-BR and BR were sourced from NICE TA649.[42] The company initially assumed 100% dose intensities for the components of R-GemOx (as indicated in Table 30 of the CS), which at the request of the ERG during clarification were corrected to 91.6% for rituximab, 93.3% for gemcitabine and 92.5% for oxaliplatin based on Mounier et al. 2013.[31]

To calculate drug dosage based on body weight for tafasitamab and polatuzumab, a mean weight of [redacted] kg was assumed based on L-MIND.[72] To calculate drug dosage based on body surface area (BSA) for bendamustine, rituximab, gemcitabine and oxaliplatin, a mean BSA of [redacted] m^2 was calculated based on a mean weight of [redacted] kg and mean height of [redacted] cm in L-MIND.[72] The company modelled a normal distribution around the mean weight and BSA to calculate a weighted average cost per dose based on the proportions of patients requiring different numbers of vials.

No vial sharing was assumed in the base-case, with vial sharing assumed for all treatments administered by IV infusion in scenario analyses.

ERG comment: The ERG prefers to use current drug prices in the CEA and therefore has used the list price of lenalidomide instead of assuming a reduced price in anticipation of there being a generic version available in the future. The ERG preferred base-case analysis further is based on the PAS price for tafasitamab and list prices (i.e. excluding discounts) for all other drugs. The results of analyses based on the lowest nationally available prices (i.e. including confidential PAS discounts) for all drugs are presented in a confidential appendix to the ERG report.

4.2.9.2 Drug administration costs

For treatments that are administered by IV infusion, administration costs were included based on unit costs for outpatient attendance for chemotherapy infusion (i.e. currency code SB13Z for the first attendance and SB15Z for subsequent attendances) that were sourced from the NHS Reference costs 2019/2020.[73]

4.2.9.3 Concomitant medication costs

In L-MIND, all patients received co-medications prior to tafasitamab infusion for the first three infusions. In the absence of infusion related reactions and at the discretion of the investigator, co-medications were not mandated for subsequent infusions.[74] Otherwise, co-medications were continued for subsequent infusions. For the company base-case analysis, it was assumed that all patients in the intervention arm received co-medications during the first 4-week treatment cycle and none thereafter. For the comparator arms it was assumed that all patients received co-medications during the entire fixed duration treatment period. For pola-BR and BR the included co-medications were based on NICE TA649,[42] and for R-GemOx these were based on El Gnaoui et al. 2007.[75] Details regarding the dosing, administration and costs of co-medications are provided in Table 35 and Table 36 of the CS.[1] Although in L-MIND patients received methylprednisone in doses that varied between 80 and 120 mg, a fixed dose of 100 mg was assumed for the intervention arm. Co-medications that are administered by IV infusion at the same frequency were assumed to be administered simultaneously. The total co-medication costs for each treatment arm are shown in Table 4.26.

Table 4.26: Total co-medication costs per model cycle

Treatment	Co-medication Cost per Model Cycle (Induction)	Co-medication Cost per Model Cycle (Maintenance)
TAFA+LEN	£1,019.94[a]	£509.97[b]
Pola-BR	£2.62	-
BR	£2.62	-
R-GemOx	£508.71	-

Based on Table 37 of the CS[1]

[a] Only applied in first model cycle in company's base-case analysis; [b] Not used in company's base-case analysis
BR = bendamustine and rituximab; CS = company submission; LEN = lenalidomide; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

4.2.9.4 Subsequent treatment costs

The analysis included the costs of subsequent treatments that patients received after progression. The proportions of patients receiving different subsequent treatments are based on the full analysis set for RE-MIND2 and listed in Table 38 of the CS.[1] The total costs for each subsequent treatment, including administration costs for treatments administered by IV infusion, as used for the CE results as reported in the original CS are included in Table 39 of the CS (with the exception of radiotherapy costs, which

are shown in Table 34 of the CS).[1] These were based on the assumption that all subsequent treatment are provided for their maximum duration. In response to a request by the ERG during the clarification phase to justify the plausibility of that assumption, the company updated the durations of subsequent treatments to reflect their median durations from available studies. These treatment durations, and their corresponding sources and assumptions made, are provided in Table 25 of the response to request for clarification.[4] A 2% threshold was applied for inclusion of subsequent treatments from RE-MIND2 among any treatment arm, with the exception of CAR-T. In response to a request by the ERG during the clarification phase, the company included the option to assume the same proportions of patients receiving each subsequent treatment for each treatment arm in the model, based on the 'systemic therapies pooled cohort' in RE-MIND2.[4] These proportions are provided in Table 4.27. The total costs for subsequent treatments, based on the treatment arm-specific proportions of patients receiving each subsequent treatment and based on the median durations, as specified by the company, in each treatment arm are shown in Table 4.28.

Table 4.27: Proportions of patients that received subsequent treatments based on the 'systemic therapies pooled cohort' in RE-MIND2.

Subsequent treatment	Proportion
Rituximab, Gemcitabine & Oxaliplatin	5.3%
Lenalidomide & Rituximab	2.6%
Pixantrone	2.6%
Bendamustine, Polatuzumab & Rituximab	3.9%
Bendamustine & Rituximab	3.9%
Rituximab	2.6%
Cyclophosphamide, Etoposide, Prednisone & Procarbazine	2.6%
Based on the updated model provided alongside the response to request for clarification[4]	

Table 4.28: Total subsequent treatment costs

Treatments	Total cost
TAFA+LEN	£3,286.87
Pola-BR	£17,114.20
BR	£13,647.69
R-GemOx	£15,650.41
Based on the updated model provided alongside the response to request for clarification[4] BR = bendamustine and rituximab; LEN = lenalidomide; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab.	

ERG comment: The ERG noted substantial differences in the proportions of patients in each arm receiving specific subsequent treatments and therefore asked the company to justify whether the included treatments are reflective of clinical practice in the UK, including the differences in the proportions of patients receiving them. In addition to a detailed explanation that confirms the relevance of each included treatment regimen to UK clinical practice, the company indicated that the variation across the regimens used in clinical practice is a consequence of a lack of a standard-of-care treatment for patients with R/R DLBCL who are ineligible for transplant, including limited guidance from NICE in guideline NG52 and the NICE clinical pathway for DLBCL.[76-79]

Due to the variation across the regimens used in clinical practice and its underlying reasons, the ERG considers that there is substantial uncertainty regarding the assumed proportions of patients receiving

subsequent treatments specific to each treatment arm. At the same time, the ERG considers that indeed some subsequent treatments may be less likely to be provided depending on the prior treatment received. For example, patients who progressed on treatment with R-GemOx are less likely to receive R-GemOx again as subsequent treatment. Therefore, the ERG retains the same treatment-arm specific proportions of patients receiving subsequent treatments as in the company base-case for the ERG preferred base-case and performed a scenario analysis using the same proportions for each treatment arm based on the systemic therapies pooled cohort' in RE-MIND2. During the clarification phase, the ERG requested the company to check, and amend where needed, for all subsequent treatments that assumptions for the maximum number of cycles (i.e. as in the original model) are in line with UK clinical practice. For example, a maximum number of 7 cycles was assumed for R-GemOx whereas UK guidelines recommend a maximum of 6 cycles. In response to this request the company referred to their response in which they updated the model to assume median durations from available studies. However, for R-GemOx this resulted in not 7 but 7.5 cycles assumed. This was adjusted by the ERG to the maximum recommended number of 6 cycles in the UK for the ERG preferred base-case analysis. Similarly, the ERG noted that for some treatments the median durations that were assumed in the updated company model were longer than the maximum durations assumed in the original company model. The ERG considers it inconsistent to assume median durations that are longer than maximum durations and therefore prefers to use the minimal number of the two for the ERG preferred base-case analysis. Still, it is uncertain whether the assumed minima of maximum and median durations of subsequent treatments are in line with clinical practice in the UK. The durations of subsequent treatments as assumed in the original company base-case, the updated company base-case and the ERG preferred base-case are shown in Table 4.29.

Another important consideration is that the company included CAR-T as a subsequent treatment. However, CAR-T is only recommended in the Cancer Drug Fund (CDF) and therefore, in line with NICE's position statement on the consideration of products that are recommended in the CDF as comparators or in the treatment sequence, in the appraisal of a new cancer product,[80] the ERG preferred not to include CAR-T as subsequent treatment in the ERG preferred base-case analysis and performed a scenario analysis where CAR-T is included. The exclusion of CAR-T had a substantial impact on the total costs for subsequent treatments, which are shown in Table 4.30 alongside the option to model the proportions of patients that received each subsequent treatment based on the 'systemic therapies pooled cohort' in RE-MIND2 and including the abovementioned changes for assuming the minima of maximum and median durations of subsequent treatments and adjustment of the number of cycles of R-GemOx. Importantly, the total cost based on the 'systemic therapies pooled cohort' in RE-MIND2 applies to all treatment arms in the model when this option is selected.

Table 4.29: Assumptions on durations of subsequent treatments

Treatments	Original company model (maximum durations)	Updated company model (median durations)	ERG preferred model (minima of maximum and median durations)
Rituximab, Gemcitabine & Oxaliplatin			
Rituximab	7	7.5	6
Gemcitabine	7	7.5	6
Oxaliplatin	7	7.5	6

Treatments	Original company model (maximum durations)	Updated company model (median durations)	ERG preferred model (minima of maximum and median durations)
Lenalidomide & Rituximab			
Lenalidomide	8	4	4
Rituximab	4	4	4
Pixantrone			
Pixantrone	4	2	2
Lenalidomide			
Lenalidomide	4	4	4
Polatuzumab, Bendamustine & Rituximab			
Bendamustine	3	4.64	3
Polatuzumab	3	4.64	3
Rituximab	3	4.64	3
Bendamustine & Rituximab			
Bendamustine	3	2.03	2.03
Rituximab	3	2.03	2.03
Rituximab			
Rituximab	4	2.03	2.03
Carboplatin, Etoposide, Ifosfamide & Rituximab			
Carboplatin	3	3	3
Etoposide	3	3	3
Ifosfamide	3	3	3
Rituximab	3	3	3
Cyclophosphamide, Etoposide, Prednisolone & Procarbazine			
Cyclophosphamide	3	3	3
Etoposide	3	3	3
Prednisolone	3	3	3
Procarbazine	3	3	3
Cyclophosphamide, Doxorubicin hydrochloride & Rituximab			
Cyclophosphamide	6	3	3
Doxorubicin hydrochloride	6	3	3
Rituximab	6	3	3
Rituximab, Dexamethasone, Cytarabine & Oxaliplatin			
Rituximab	8	3	3
Dexamethasone	8	3	3
Cytarabine	8	3	3
Oxaliplatin	8	3	3

Treatments	Original company model (maximum durations)	Updated company model (median durations)	ERG preferred model (minima of maximum and median durations)
Rituximab, Dexamethasone, Cytarabine & Cisplatin			
Rituximab	3	3	3
Dexamethasone	3	3	3
Cytarabine	3	3	3
Cisplatin	3	3	3
CAR-T			
CAR-T	1	1	1
Cyclophosphamide & Fludarabine phosphate			
Cyclophosphamide	6	6	6
Fludarabine phosphate	6	6	6
Methotrexate			
Methotrexate	1	1	1
Gemcitabine & Oxaliplatin			
Gemcitabine	7	5	5
Oxaliplatin	7	5	5
Radiotherapy			
Radiotherapy	1	1	1

Source: The original company model provided alongside the CS,[1] and the updated model provided alongside the response to request for clarification[4]
CAR-T = chimeric antigen receptor T-cell therapy; CS = company submission; ERG = evidence review group

Table 4.30: Total subsequent treatment costs without CAR-T

Treatments	Total cost (without CAR-T)	Total cost (with CAR-T)
TAFA+LEN	£2,856.82	£2,856.82
Pola-BR	£2,304.31	£16,699.25
BR	£1,668.54	£13,311.70
R-GemOx	£2,828.13	£14,762.36
Systemic therapies pooled	£2,843.98[a]	

Based on the updated model provided alongside the response to request for clarification[4]
Note: Assuming the minima of maximum and median durations and 6 cycles of R-GemOx and including proportions based on the 'systemic therapies pooled cohort' in RE-MIND2
[a] CAR-T is not included when using the option based on the 'systemic therapies pooled cohort.
BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell therapy; LEN = lenalidomide; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab.

4.2.9.5 Monitoring and disease management costs

4.2.9.5.1 Monitoring costs

The analysis included costs for treatment and disease progression monitoring up to the point of progression. For the intervention arm, the types and frequencies of healthcare resource use and laboratory tests were based on L-MIND. For pola-BR and BR these were based on NICE TA649,[42] and for R-GemOx these were based on NICE TA567.[54] Since levels of resource use may depend on the time spent in PFS, the frequencies of resource use related to disease monitoring were separated according to whether patients where in PFS for ≤2 years (i.e. referred to as 'without prolonged PFS') or >2 years (i.e. referred to as 'prolonged PFS'). The unit costs of monitoring tests are provided in Table 41 of the CS (i.e. with additional details regarding the source used, such as the currency codes for NHS Reference costs, for all unit costs in the CS provided in response to clarification question C15),[4] the frequencies of resource use for patients who are in PFS for ≤2 years are provided in Table 42 of the CS, and the frequencies of resource use for patients who are in PFS for >2 years are provided in Table 45 of the CS by year of prolonged PFS status.[1] Due to a lack of data specific to R/R DLBCL patients, the latter are based on DLBCL guidelines.[76] The total per-cycle monitoring costs for PFS patients without prolonged PFS are provided in Table 4.31, and the total per-cycle monitoring cost for PFS patients with prolonged PFS are provided in Table 4.32 by year of prolonged PFS status.

Table 4.31: Total per-cycle monitoring costs for PFS patients without prolonged PFS

Treatments	Total cost
TAFA+LEN	£111.55
Pola-BR	£137.08
BR	£137.08
R-GemOx	£6.83

Based on Table 44 of the CS[1]
BR = bendamustine and rituximab; CS = company submission; LEN = lenalidomide; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab.

Table 4.32: Total per-cycle monitoring costs for PFS patients with prolonged PFS

Year	Cost per cycle
Year 1 of prolonged PFS	£31.49
Year 2 of prolonged PFS	£15.64
Year 3+ of prolonged PFS	-

Based on Table 46 of the CS[1]
CS = company submission; PFS = progression-free survival

Additional one-off monitoring costs were included for the intervention arm and for R-GemOx to account for use of resources that are used for a limited period of time and therefore are not applicable for the whole duration of PFS. For the intervention arm, this one-off cost amounted to £1,359.59 and included B, T and NK cell flow cytometry up to model cycle 8, electrocardiograms (ECGs) up to model cycle 12 and positron emission tomography (PET) computerised tomography (CT) only once at model cycle 12. The frequencies at which these resourced were assumed to be used were not further specified. For R-GemOx, a one-off monitoring cost of £452.22 was sourced from NICE TA567 that pertained to additional resource use (i.e. with no further specification) during months 1 through 5.[54]

4.2.9.5.2 Disease management costs

The analysis included costs for disease management. For the intervention arm, the types and frequencies of healthcare resource use were based on L-MIND. For pola-BR and BR these were based on NICE TA649,[42] and for R-GemOx these were based on NICE TA567.[54] Since levels of resource use may depend on progression status as well as the time spent in PFS, the frequencies of resource use related to disease monitoring were separated according to whether patients where in PFS for ≤2 years (i.e. referred to as 'without prolonged PFS'), >2 years (i.e. referred to as 'prolonged PFS') or in progressed disease. The unit costs of disease management resources are provided in Table 47 of the CS (i.e. with additional details regarding the source used, such as the currency codes for NHS Reference costs, for all unit costs in the CS provided in response to clarification question C15),[4] the frequencies of resource use for patients who are in PFS for ≤2 years as assumed in the original company model are provided in Table 48 of the CS, the frequencies of resource use for patients who are in PFS for >2 years are provided in Table 50 of the CS by year of prolonged PFS status, and the frequencies of resource use for patients with progressed disease are in Table 52 of the CS.[1] Due to a lack of data specific to R/R DLBCL patients, the frequencies of resource use for patients who are in PFS for >2 years are, similar to monitoring costs, based on DLBCL guidelines.[76] In response to the ERG's request during the clarification phase to compare the approach to modelling costs and resource use in this appraisal and in TA649, the company indicated that they had overestimated the disease management costs for pola-BR and BR due to the fact that while different resource use frequencies for the on and off treatment period were applied in TA649, in the model used for the CS, only the on-treatment frequencies were applied for pola-BR and BR in the PFS health state regardless of treatment status. The updated model therefore assumed different estimates of resource use frequencies for disease management depending on whether patients without prolonged PFS were on or off treatment with pola-BR and BR. These updated frequencies are provided in Table 27 and Table 28 of the response to request for clarification.[4] The total per-cycle disease management costs for patients without prolonged PFS are provided in Table 4.33 for each treatment arm, the total per-cycle disease management costs for patients with prolonged PFS are provided in Table 4.34 by year of prolonged PFS status, and the total per-cycle disease management costs for patients with progressed disease are provided in Table 4.35.

Table 4.33: Total per-cycle disease management costs for PFS patients without prolonged PFS

Treatments	Total cost	
	On treatment	Off treatment
TAFA+LEN	£311.49	
Pola-BR	£1,973.21	£754.40
BR	£1,973.21	£754.40
R-GemOx	£80.08	

Based on the updated model provided alongside the response to request for clarification[4]
BR = bendamustine and rituximab; LEN = lenalidomide; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

Table 4.34: Total per-cycle disease management costs for PFS patients with prolonged PFS

Year	Cost per cycle
Year 3	£66.73
Year 4	£33.37
Year 5	£33.37

Year	Cost per cycle
Year 6	£16.68
Year 7+	£16.68
Based on Table 51 of the CS[1] CS = company submission; PFS = progression-free survival	

Table 4.35: Total per-cycle disease management costs for patients with progressed disease

Treatments	Total cost
TAFA+LEN	£1,571.25
Pola-BR	£1,571.25
BR	£1,571.25
R-GemOx	£3,550.65
Based on Table 53 of the CS[1] CS = company submission; PFS = progression-free survival BR = bendamustine and rituximab; LEN = lenalidomide; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab.	

Additional one-off costs were included for patients in progressed disease based on the costs for the use of a palliative care team sourced from NICE TA649 and for patients who died based on the terminal care costs in NICE TA567.[42, 54] These costs were £473.10 and £2,712.38, as shown in Table 54 of the CS, respectively.[1]

ERG comment: The ERG scrutinised the sources that were used to inform the frequencies of health care resource use for each treatment arm in the model, which were the following:

- For tafasitamab + lenalidomide these were sourced from L-MIND for PFS and from TA649 for progressed disease (PD);[42]
- For pola-BR and BR these were sourced from TA649 (polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma), which in turn were sourced from TA306 (pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma), where it was based on clinical expert opinion;[42, 55]
- For R-GemOx these were sourced from TA567, which in turn were sourced from Appendix A in NICE NG52 which in turn were based on McNamara et al. 2011[81] and assumptions for PFS from Muszbek et al. 2016[82] where it was based on clinical expert opinion for PD.[54, 79]

The different sources that were used raised concerns with the ERG regarding the consistency of the assumptions on health care resource use between the treatment arms of the model. During the clarification phase, the company provided justification for the consistency by noting that the inputs were sourced from the relevant previous NICE appraisals and that differences could be explained by differences in treatment stopping rules and toxicity profiles. The company also explained that the monitoring resource use was assumed to be specific for each treatment arm and that limited data was available to inform resource use specifically for UK patients with R/R DLBCL (i.e. hence, the resource use inputs were sourced from previous NICE appraisals). Although the ERG requested the company during the clarification phase to include the options to assume the same resource use across treatments based on the different sources that were used for each treatment arm, the company denied this request and indicated that they did not believe this to be appropriate due to lack of data for the intervention arm and differences in treatment stopping rules and toxicity profiles. The ERG agrees to use the same monitoring and disease management costs as per the company base-case for patients in PFS. However,

the ERG prefers the assumption that in PD the costs of disease management are the same for all treatment arms. Therefore, instead of using a different value (of £3,550.65) for R-GemOx the ERG assumed the same cost (of £1,571.25) for all treatment arms. In addition, the ERG performed a scenario analysis where the costs of patients in PFS for ≤2 years was assumed the same for all treatment arms based on the costs as used by the company for TAFA+LEN of £311.49.

The ERG is uncertain whether it is appropriate to assume one-off costs for palliative care both upon progression and upon death. However, the ERG preferred not to make changes for this aspect since these costs have a negligible impact on the results.

4.2.9.6 Adverse event costs

An overview of the incidences of the included AEs is provided in Table 55 of the CS and the corresponding unit costs for their treatment are provided in Table 56 of the CS (i.e. with additional details regarding the source used, such as the currency codes for NHS Reference costs, for all unit costs in the CS provided in response to clarification question C15).[1, 4] The total costs for the treatment of AEs are shown in Table 4.36. These were applied as one-off lumpsum costs at the start of the model.

Table 4.36: Total costs for the treatment of adverse events

Treatments	Total AE cost
TAFA+LEN	£1,974.06
Pola-BR	£2,339.46
BR	£1,487.16
R-GemOx	£2,152.53

Based on Table 57 of the CS[1]
AE = adverse event; BR = bendamustine and rituximab; CS = company submission; LEN = lenalidomide; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine and oxaliplatin; TAFA = tafasitamab

5 COST EFFECTIVENESS RESULTS

The company provided a corrected version of the model (with a list of the changes made) alongside their response to the ERG's clarification questions. As mentioned in Section 4.2.9.1, a PAS for tafasitamab was approved by the Patient Access Scheme Liaison Unit (PASLU) after the ERG received the main CS. Furthermore, as mentioned also in Section 4.2.9.1, the company assumed [redacted]. Thus, all results shown in the remaining of this chapter are based on the revised version of the model submitted in response to the ERG's clarification questions, tafasitamab PAS price and the (confidential) discount price for lenalidomide assumed by the company.

5.1 Company's cost effectiveness results

Table 5.1 shows the deterministic CE results of the updated company's base-case analysis (i.e. as provided alongside their response to request for clarification and including the PAS discount for tafasitamab). All results are discounted. Given that there are three comparators included in the analyses, results are reported in a full incremental way. Pairwise ICERs of TAFA+LEN vs. each of the comparators are also reported for completeness. Results indicated that [redacted].

The disaggregated discounted QALYs and costs are shown in Tables 5.2 and 5.3, respectively.

Table 5.1: Company base-case deterministic cost effectiveness results (tafasitamab PAS price, assumed discount price for lenalidomide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.76	1.13					[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]				[redacted]
Pola-BR	[redacted]	2.20	1.45	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	3.32	[redacted]	[redacted]	

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.
* All pairwise ICERs are calculated vs. TAFA+LEN
BR = bendamustine + rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

Table 5.2: Disaggregated QALYs results

Technologies	Progression-free	Post-progression	AE disutility	Total
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 2 of CS Appendix J[83]
AE = adverse event; BR = bendamustine and rituximab; CS = company submission; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALYs = quality-adjusted life years; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

Table 5.3: Disaggregated cost results (£)

Technologies	Acquisition	Administration	Co-medication	Monitoring	AEs	Disease management	Subsequent treatment	Total
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Acquisition	Administration	Co-medication	Monitoring	AEs	Disease management	Subsequent treatment	Total
R-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.
AEs = adverse events; BR = bendamustine and rituximab; CS = company submission; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

Overall, the new technology is modelled to affect QALYs by:

- Increasing the progression-free and reducing the post-progression health state occupancy.
- The decrease in utility due to AEs associated to the new technology is minor.

Overall, the technology is modelled to affect costs by:

- Its higher unit price compared to current treatments.
- Increasing administration and monitoring costs.
- Decreasing costs associated to disease management and subsequent treatments.

ERG comment: Following the ERG comments in Section 4.2.6.9 of this report, the ERG conducted a quick validity check of the company's base-case results. In TA649 pola-BR was deemed as a cost-effective alternative compared to BR.[42] With the results obtained by the company in Table 5.1, the ICER for the comparison pola-BR vs. BR was [redacted].

5.2 Company's sensitivity and scenario analyses

5.2.1 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 1,000 iterations. The input parameters and the probability distributions used in the PSA can be found in Appendix L of the CS.[84] The main distributional assumptions for the model parameters highlighted by the company are described below:

- Beta distributions were assumed for input parameters restricted to the interval 0 to 1 (such as proportions and utility values).
- Gamma distributions were assumed for cost parameters and for resource use frequencies.
- HRs were modelled assuming log-normal distributions.
- Multivariate normal distributions were assumed for time-to-event-related parameters (OS, PFS, etc.) and for the coefficients of the general population utility regression equation (applying Cholesky decompositions to covariance matrices).
- Normal distributions were assumed for all other input parameters.
- Standard errors were used where available. Otherwise, a deviation of ±20% from the mean was assumed.

The average PSA results are summarised in Table 5.4. [redacted].

Table 5.4: Company base-case probabilistic cost effectiveness results (tafasitamab PAS price, assumed discount price for lenalidomide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.85	1.18					[redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
R-GemOx	[redacted]	1.85	1.18	[redacted]				[redacted]
Pola-BR	[redacted]	2.47	1.59	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.09	[redacted]	[redacted]	3.24	[redacted]	[redacted]	

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab

* All pairwise ICERs are calculated vs. TAFA+LEN

BR = bendamustine and rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; NR = not reported; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

The company also plotted the PSA outcomes on a CE-plane. This was done for the three comparators separately. The CE-plane for the comparison vs. BR, the only comparator that was not (extendedly) dominated, can be seen in Figure 5.1. It can be seen that [redacted]. From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and plot in Figure 5.2. The CEAC plot indicates that [redacted]. At the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that TAFA+LEN is a cost-effective alternative to the other comparators was [redacted].

Figure 5.1: Probabilistic sensitivity analysis cost effectiveness plane (PAS price for tafasitamab and assumed discount price for lenalidomide): TAFA+LEN vs. BR

[redacted]

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.

ICER = incremental cost effectiveness ratio; PAS = patient access scheme; QALY = quality-adjusted life year

Figure 5.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve (PAS price for tafasitamab and assumed discount price for lenalidomide)

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.
PAS = patient access scheme.

5.2.2 Deterministic sensitivity analysis

The company also conducted deterministic sensitivity analyses (DSAs) comparing TAFA+LEN against the three relevant comparators separately. Key parameters were individually varied at lower and upper bounds of values based on CIs where available. Otherwise, the upper and lower bounds for the DSA were calculated as ±20% deviation from the mean value. For details, please refer to Appendix L of the CS.[84]

The results of the DSAs were presented by the company in the form of tornado diagrams. The tornado diagram for the comparison vs. BR, the only comparator that was not (extendedly) dominated, can be seen in Figure 5.3. In general,

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Figure 5.3: DSA tornado diagram for TAFA+LEN vs. BR (PAS price for tafasitamab and assumed discount price for lenalidomide)

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.
2L+ = second line and later; DSA = deterministic sensitivity analysis; HR = hazard ratio; ICER = incremental cost effectiveness ratio; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year; Tx Disc = treatment discontinuation

5.2.3 Scenario analysis

The company conducted several scenario analyses to assess the robustness of the model results to changes in modelling assumptions. A summary of these scenarios is provided in Table 5.5. These included exploring alternative long-term extrapolations and data source for survival curves, testing the impact of cure assumptions, changing utilities, assuming vial sharing, considering shorter model time horizons or lower discount rates. Note that the company only presented pairwise ICERs for TAFA+LEN vs. the three comparators separately. Results in the form of full incremental analysis were not reported. Therefore, it is unknown whether in any of these scenarios some of the technologies were (extendedly) dominated or not.

Several scenarios resulted in increased ICERs compared to the base-case. Assuming a 5-year time horizon led to an ICER increase ranging from [redacted]% to [redacted]% depending on the comparator. When a 10-year time horizon was assumed the increase in the ICER ranged from [redacted]% to [redacted]%. Assuming a Weibull distribution for modelling OS in the TAFA+LEN arm resulted in an ICER increase between [redacted]% and [redacted]%. When a log-normal distribution was assumed to model PFS in the TAFA+LEN arm the ICER increased by [redacted]% to [redacted]%. MAIC assumptions had a large impact on the ICER. For example, assuming a MAIC with constant HRs for pola-BR increased the ICER vs. pola-BR by [redacted]% and applying MAIC HRs and median TTD data for R-GemOx increased the ICER vs. R-GemOx by [redacted]%. Other scenarios resulted in decreased ICERs compared to the base-case. Other assumptions resulting in a decrease in the ICER compared to the base-case were using RE-MIND2 data for pola-BR ([redacted]% decrease in ICER), assuming health state utility values from NICE TA567 (decrease in ICER ranging from [redacted]% to [redacted]%) and assuming vial-sharing for all IV therapies (decrease in ICER

ranging from [redacted]% to [redacted]%). In conclusion, the modelling assumptions explored by the company that had the greatest effect on the ICER were related to:

- Alternative MAIC assumptions.
- Alternative OS/PFS extrapolations.
- Using RE-MIND2 data for the pola-BR arm.
- Alternative utility values (TA567).[42]
- Assuming vial-sharing for all IV therapies.
- Model time horizon.

Table 5.5: Summary of company scenario analyses*

Scenario	Description	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
Base-Case	See Chapter 4 of this report	[redacted]	[redacted]	[redacted]
1	5-year time horizon	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	[redacted]	[redacted]
3	1.5% discount rate for costs and outcomes	[redacted]	[redacted]	[redacted]
4	TAFA+LEN OS: generalised Gamma	[redacted]	[redacted]	[redacted]
5	TAFA+LEN OS: Weibull	[redacted]	[redacted]	[redacted]
6	TAFA+LEN PFS: log-normal	[redacted]	[redacted]	[redacted]
7	Pola-BR: MAIC HRs with 11-month split for OS and PFS	[redacted]	[redacted]	[redacted]
8	Pola-BR: constant MAIC HRs for OS and PFS	[redacted]	[redacted]	[redacted]
9	Pola-BR: RE-MIND2 data (generalised Gamma for OS, exponential for PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
10	BR PFS: generalised Gamma	[redacted]	[redacted]	[redacted]
11	R-GemOx OS: Gompertz	[redacted]	[redacted]	[redacted]
12	R-GemOx PFS: generalised Gamma	[redacted]	[redacted]	[redacted]
13	MAIC HRs for OS/PFS and median TTD durations for BR and R-GemOx	[redacted]	[redacted]	[redacted]
22	Utility of 0.83 for PFS and 0.71 for PD (NICE TA567)	[redacted]	[redacted]	[redacted]
23	Vial sharing for all IV administered treatments	[redacted]	[redacted]	[redacted]

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.

* The ERG was unable to replicate scenarios 14-21 with the PAS price assumed for tafasitamab as presented by the company in the original CS.[1] Thus, conclusions from these scenarios have not been presented above. It should be noted that these scenarios were related to "cure" assumptions. While these have a substantial impact on the results, "cure" assumptions were deemed uncertain and/or unlikely by the company and the clinical experts they consulted.

BR = bendamustine and rituximab; ICER = incremental cost effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PFS = progression-free survival; pola-BR = polatuzumab vedotin

Scenario	Description	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
with bendamustine and rituximab; QALY = quality-adjusted life year; R=GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide; TTD = time to treatment discontinuation				

5.3 Model validation and face validity check

Validation efforts conducted on the economic model were shortly discussed in the validation section of the CS (B.3.9).[1] Most of the validation efforts discussed in the CS referred to those conducted on parametric survival extrapolations for L-MIND and RE-MIND2 data with three UK clinical experts.[25] The experts also provided feedback on other modelling features such as the comparators included in the analyses, cure assumptions, subsequent treatment usage and utility values. In response to clarification questions C22 and C23,[4] additional validation details were provided by the company.

ERG comment: The main concerns of the ERG regarding validation were extensively discussed in this report and summarised in Section 4.2.6.9. The ERG considered that there are issues with the validity of the OS/PFS extrapolations, especially (but not exclusively) for the pola-BR arm, which in turn resulted in CE results very different to those obtained for example in TA649,[42] as illustrated in Section 5.1. The root of the problems causing these issues should be carefully re-investigated by the company and, if possible, corrected.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

6.1.1 Explanation of the ERG adjustments

The changes that the ERG made (to the model received with the response to the clarification letter) can be subdivided into the following three categories (according to Kaltenthaler et al. 2016):[85]

- Fixing errors (correcting the model where the company's electronic model is unequivocally wrong).
- Fixing violations (correcting the model where the ERG considers that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred).

After the proposed changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the CE results.

6.1.1.1 Fixing errors

No errors were corrected by the ERG in the model provided in response to the clarification letter.

6.1.1.2 Fixing violations

- Lenalidomide list price was assumed for the CEAs. It is incorrect to assume a [redacted].

6.1.1.3 Matters of judgement

The ERG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- Survival modelling: as explained in Section 4.2.6, the ERG had several concerns regarding the lack of both face and external validity of the company's assumptions on OS and PFS. These concerns are still present in the ERG base-case but it is expected that, with the following choices, some of them will be at least mitigated:
    - OS for pola-BR: assuming MAIC based on constant HR (the company chose a MAIC with a time-varying HR).
    - OS for BR: assuming MAIC based on constant HR (the company chose a PH model based on RE-MIND2 data).
    - PFS for TAFA+LEN: assuming a lognormal distribution based on L-MIND data (the company chose a generalised Gamma distribution).
    - PFS for pola-BR: assuming MAIC based on constant HR (the company chose a MAIC with a time varying HR).
    - PFS for BR: assuming a MAIC based on constant HR (the company chose a lognormal fit based on RE-MIND2 data).
- Resource use and costs:
    - Excluding CAR-T as subsequent treatment.
    - Assuming 6 cycles duration for R-GemOx as subsequent treatment.
    - Assuming the minimum between the maximal and median durations reported by the company (to correct for potential inconsistencies) for all other subsequent treatments.
    - Applying the same disease management costs (£1,571.25) in PD for all treatment arms.

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 6.1.

Table 6.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Survival model OS	TAFA+LEN: lognormal based on L-MIND. Pola-BR: MAIC with time-varying HR. BR: PH model based on RE-MIND2 data R-GemOx: lognormal based on RE-MIND2.	TAFA+LEN: lognormal based on L-MIND. Pola-BR: MAIC with constant HR. BR: MAIC with constant HR. R-GemOx: lognormal based on RE-MIND2.	To minimise the impact of OS/PFS assumptions on the validity of the results (Section 4.2.6.9).
Survival model PFS	TAFA+LEN: generalised Gamma based on L-MIND. Pola-BR: MAIC with time-varying HR. BR: lognormal based on RE-MIND2. R-GemOx: lognormal based on RE-MIND2.	TAFA+LEN: lognormal based on L-MIND. Pola-BR: MAIC with constant HR. BR: MAIC with constant HR. R-GemOx: lognormal based on RE-MIND2.	To minimise the impact of OS/PFS assumptions on the validity of the results (Section 4.2.6.9).
Lenalidomide price	Discounted price	List price	Incorrect to assume a [redacted] (Section 4.2.9.1).
CAR-T as subsequent treatment	Included	Excluded	To be in line with NICE's position statement on CDF drugs (Section 4.2.9.4).
R-GemOx cycle duration as subsequent treatment	7.5	6	The maximum recommended number in UK guidelines is 6 (Section 4.2.9.4).
Cycle duration for other subsequent treatments	Median durations from available trials	Minimum between the maximal and median durations reported by the company	To correct for logical inconsistencies when median durations exceed maximal durations (Section 4.2.9.4).

Base-case preferred assumptions	Company	ERG	Justification for change
Management costs in PD health state	Different cost of £3,550.65 assumed for R-GemOx	Same cost of £1,571.25 for all treatment arms	Unclear rationale to assume different costs for R-GemOx (Section 4.2.9.5).

CS = company submission; BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell therapy; CDF = Cancer Drug Funds; ERG = Evidence Review Group; HR = hazard ratio; LEN = lenalidomide; MAIC = matched-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressed disease; PFS = progression-free survival; PH = proportional hazards; pola-BR = polatuzumab with bendamustine and rituximab; R-GemOx = Rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab; UK = United Kingdom

6.1.2 Additional scenarios conducted by the ERG

The ERG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the CE analyses. These uncertainties were related to the survival modelling (in terms of choice of parametric distributions and other modelling assumptions), the criteria to include AEs in the model, the sources of utility data and cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. A description of scenario analyses conducted by the ERG is provided below.

OS is expected to have a major impact on the model results, not only in terms of changes in the ICER, but also regarding the clinical validity of the results, as explained in Section 4.2.6.9 of this report. Therefore, it was felt important to explore OS assumptions in a detailed way. A summary of the OS-related scenarios conducted by the ERG is presented in Table 6.2.

Table 6.2: ERG OS scenarios

Scenarios OS	ERG preferred assumption	Change	ERG comment
TAFA+LEN	Lognormal (L-MIND)	Exponential	Based on survival analyses results, preference for log-logistic and generalised Gamma. Other distributions tested for completeness.
		Weibull	
		Log-logistic	
		Gompertz	
		Generalised Gamma	
Pola-BR	MAIC constant HR	MAIC time-varying HR (4 months)	All choices seem to result in implausible extrapolations for pola-BR. Choosing RE-MIND2 as data source implies for both OS and PFS in the model (constant HR for OS and PFS).
		MAIC time-varying HR (11 months)	
		RE-MIND2 constant HR (most optimistic)	
BR	MAIC constant HR	Exponential (RE-MIND2)	Exponential and Weibull seem implausible compared to R-GemOx. Log-logistic and lognormal (preferred if RE-MIND2 data is chosen) seem plausible. Gompertz and generalised Gamma seem implausible (high tails). A constant HR seems plausible (except that PH assumption is inappropriate).
		Weibull (RE-MIND2)	
		Lognormal (RE-MIND2)	
		Log-logistic (RE-MIND2)	
		Gompertz (RE-MIND2)	
		Generalised Gamma (RE-MIND2)	
		Constant HR (RE-MIND2)	
R-GemOx	RE-MIND2 lognormal	Exponential (RE-MIND2)	Based on survival analyses results, preference for log-logistic and Gompertz.
		Weibull (RE-MIND2)	

Scenarios OS	ERG preferred assumption	Change	ERG comment
		Log-logistic (RE-MIND2)	Generalised Gamma seems high. A constant HR seems high compared to BR and PH assumption inappropriate Other distributions tested for completeness.
		Gompertz (RE-MIND2)	
		Generalised Gamma (RE-MIND2)	
		Constant HR (RE-MIND2)	
BR = bendamustine and rituximab; ERG = Evidence Review Group; HR = hazard ratio; LEN = lenalidomide; MAIC = matched-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PH = proportional hazards; pola-BR = polatuzumab with bendamustine and rituximab; R-GemOx = Rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab			

PFS is expected to have less impact on the model results than OS. However, in terms of clinical validity it is still possible to make inappropriate choices, as explained in Section 4.2.6.9 of this report. Also note that when the data source is changed (MAIC or RE-MIND2), in the model this is selected for both PFS and OS. Therefore, the impact of the change in PFS cannot be isolated. A summary of the PFS-related scenarios conducted by the ERG is presented in Table 6.3.

Table 6.3: ERG PFS scenarios

Scenarios PFS	ERG preferred assumption	Change	ERG comment
TAFA+LEN	Lognormal (L-MIND)	Exponential	Based on survival analyses results, preference for log-logistic and generalised Gamma. Changing TAFA+LEN curve also changes pola-BR since it is based on a constant HR in ERG base-case. Other curves for TAFA+LEN and pola-BR seem highly implausible.
		Weibull	
		Log-logistic	
		Gompertz	
		Generalised Gamma	
Pola-BR	MAIC constant HR	MAIC time-varying HR (4 months)	Curves for pola-BR seem implausible.
		MAIC time-varying HR (11 months)	
BR	MAIC constant HR	No scenarios	The only option is constant HR for the MAIC. If we select RE-MIND2 data, OS is changed too.
R-GemOx	RE-MIND2 lognormal	Exponential (RE-MIND2)	All curves seem to be Similar, except the for the constant HR curve, which gives better PFS than BR over time.
		Weibull (RE-MIND2)	
		Log-logistic (RE-MIND2)	

Scenarios PFS	ERG preferred assumption	Change	ERG comment
		Gompertz (RE-MIND2)	
		Generalised Gamma (RE-MIND2)	
		Constant HR (RE-MIND2)	
BR = bendamustine and rituximab; ERG = Evidence Review Group; HR = hazard ratio; LEN = lenalidomide; MAIC = matched-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PH = proportional hazards; pola-BR = polatuzumab with bendamustine and rituximab; R-GemOx = Rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab			

TTD alternative assumptions for TAFA and LEN separately and TAFA+LEN combined were explored by the ERG. A summary of the TTD-related scenarios conducted by the ERG is presented in Table 6.4.

Table 6.4: ERG TTD scenarios

Scenarios TTD	ERG preferred assumption	Change	ERG comment
TAFA	Lognormal (L-MIND)	Exponential	The log-logistic and the generalised Gamma cues are similar to the lognormal. Exponential, Weibull and Gompertz seem implausible (overestimate TTD). Modelling directly from the KM curve seems implausible too since treatment stops abruptly at week 236.
		Weibull	
		Log-logistic	
		Gompertz	
		Generalised Gamma	
		TAFA KM	
LEN	KM (L-MIND)	Exponential	All curves show an extremely por fit to the KM curve. Only the exponential distribution was selected for scenario analysis (closest fit to KM).
		Weibull	
		Lognormal	
		Log-logistic	
		Gompertz	
		Generalised Gamma	
TAFA+LEN	Lognormal (L-MIND) + KM (L-MIND)	Treat until progression (both)	Seems implausible since lenalidomide is given for maximum of 12 treatment cycles.
		Treat until progression only TAFA	Plausible since TAFA is administered until disease progression.
BR = bendamustine and rituximab; ERG = Evidence Review Group; KM = Kaplan-Meier; LEN = lenalidomide; pola-BR = polatuzumab with bendamustine and rituximab; R-GemOx = Rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab; TTD = Time to treatment discontinuation			

Other assumptions explored by the ERG included the following:

- Using a 10% threshold for including AEs instead of the 5% assumed by the company.

- Utilising different sources of utility values identified by the company, including those values from TA567,[54] TA306[55] and TA176 final appraisal document (FAD),[86] as done by the ERG in TA649.[87]
- The sensitivity of the results to alternative assumptions regarding differences in the proportions of patients receiving specific subsequent treatments (i.e. instead of assuming the treatment arm-specific durations from RE-MIND2 and excluding CAR-T) was assessed by:
    - Including CAR-T as subsequent treatment.
    - Assuming no differences in the proportions of patients receiving specific subsequent treatments by using the same proportions based on the 'systemic therapies pooled cohort in RE-MIND2' for all treatment arms (NB. CAR-T is not included in this scenario).
- The sensitivity of the results to alternative assumptions regarding the durations of specific subsequent treatments (i.e. instead of assuming the minimal of maximal and median durations) was assessed by:
    - Assuming maximum treatment durations (as per original company base-case).
    - Assuming median treatment durations (as per company base-case after clarification).
- The sensitivity of the results to alternative assumptions regarding the disease management costs for patients who were in PFS ≤2 years (i.e. instead of assuming resource use based on L-MIND for TAFA+LEN, based on TA649 for Pola-BR and BR, and based on TA567 for R-GemOx) was assessed by:
    - Using the same disease management costs as TAFA+LEN (£311.49) for all comparators.
- Assuming vial sharing in the cost calculations for all treatments included in the model for which vial sharing is possible (i.e. tafasitamab, polatuzumab, bendamustine, rituximab, gemcitabine, oxaliplatin, cytarabine, cisplatin and pixantrone).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.2.1 Results of the ERG preferred base-case scenario

Table 6.5 shows the deterministic CE results of the ERG preferred base-case analysis. All results are discounted.

[redacted]

Table 6.5: ERG preferred base-case deterministic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.60	1.02	[redacted]				[redacted]
R-GemOx	[redacted]	1.82	1.16					[redacted]
Pola-BR	[redacted]	3.36	2.20	[redacted]	1.53	1.04	[redacted]	[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	1.73	[redacted]	[redacted]	

Based on the ERG preferred base-case model and including the PAS discount for tafasitamab.
* All pairwise ICERs are calculated vs. TAFA+LEN

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR = bendamustine + rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab								

The disaggregated discounted QALYs and costs are shown in Tables 6.6 and 6.7, respectively.

Table 6.6: Disaggregated QALYs results, ERG preferred base-case

Technologies	Progression-free	Post-progression	AE disutility	Total
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]	[redacted]	[redacted]
Based on the ERG preferred base-case model and including the PAS discount for tafasitamab. AE = adverse event; BR = bendamustine and rituximab; ERG = Evidence Review Group; LEN = lenalidomide; PAS = Patient Access Scheme; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALYs = quality-adjusted life years; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab				

Table 6.7: Disaggregated cost results (£), ERG preferred base-case

Technologies	Acquisition	Administration	Co-medication	Monitoring	AEs	Disease management	Subsequent treatment	Total
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the ERG preferred base-case model and including the PAS discount for tafasitamab.
AEs = adverse events; BR = bendamustine and rituximab; ERG = Evidence Review Group; LEN = lenalidomide; PAS = Patient Access Scheme; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

6.2.1.2 ERG preferred probabilistic base-case cost effectiveness results

The average PSA results of the ERG preferred base-case are summarised in Table 6.8. These are broadly in line with the deterministic ones shown in Table 6.5, [redacted].

Table 6.8: ERG preferred base-case probabilistic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
R-GemOx	[redacted]	1.85	1.18					[redacted]
BR	[redacted]	1.86	1.18	[redacted]				[redacted]
Pola-BR	[redacted]	3.55	2.29	[redacted]	1.69	1.11	[redacted]	[redacted]
TAFA+LEN	[redacted]	5.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

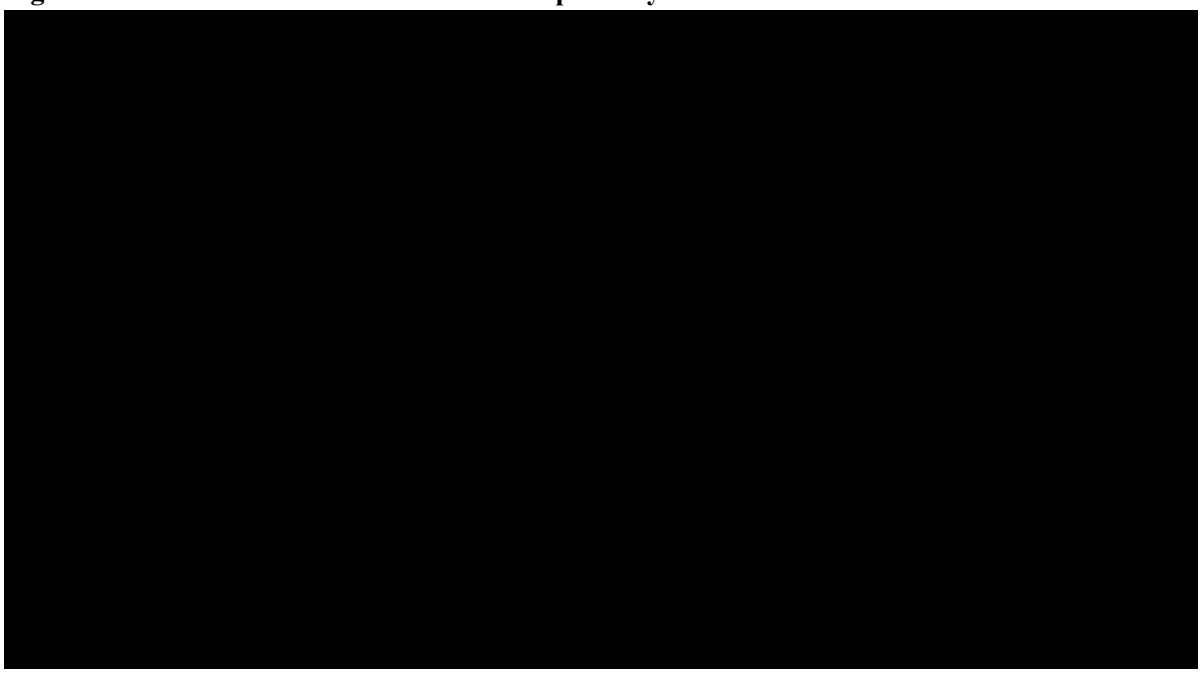
Based on the ERG preferred base-case model and including the PAS discount for tafasitamab.
* All pairwise ICERs are calculated vs. TAFA+LEN
BR = bendamustine and rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; NR = not reported; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

The CE-plane for the comparison TAFA+LEN vs. pola-BR can be seen in Figure 6.1. This plot shows that [redacted]. The plot of the PSA outcomes on the CE-plane for the comparisons vs. BR and R-GemOx were similar to that in Figure 6.1 but are not shown in this report (they can be found in the company's electronic model). From the PSA results, a CEAC was also calculated and plot in Figure 6.2. The CEAC indicated that [redacted]. At the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that TAFA+LEN is a cost-effective alternative to the other comparators was [redacted].

Figure 6.1: ERG PSA cost effectiveness plane: TAFA+LEN vs. Pola-BR

Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; LEN = lenalidomide; PAS = patient access scheme; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; TAFA = tafasitamab

Figure 6.2: ERG PSA cost effectiveness acceptability curve



Based on the updated model provided alongside the response to request for clarification,[4] and including the PAS discount for tafasitamab.
ERG = Evidence Review Group; PAS = patient access scheme; PSA = probabilistic sensitivity analysis

6.2.2 Results of the ERG additional exploratory scenario analyses

The results of the additional scenario analyses conducted by the ERG are provided in Table 6.9. With the idea of synthetising these results as much as possible, results in the form of full incremental analysis were not reported. Therefore, only pairwise ICERs for TAFA+LEN vs. the three comparators separately and total costs and QALYs per treatment are included in Table 6.9.

The ICER was reasonably stable for alternative choices of TAFA+LEN OS extrapolations, with the exception of the Weibull and exponential distributions. Note that changing the OS distribution for TAFA+LEN implied also a change in OS for pola-BR and BR, since for these treatments, PH models (with respect to TAFA+LEN) were assumed. Note also that, as explained in Table 6.2, not all scenarios are seen as equally plausible by the ERG. The two most plausible alternative parametric model extrapolations for OS (the log-logistic and generalised Gamma) resulted in ICERs close to the ERG base-case. Results based on the alternative OS assumptions for pola-BR explored by the ERG (time-varying MAIC and constant HR based on RE-MIND2 data) showed large differences with respect to the ERG base-case. QALYs for the pola-BR arm varied from 1.16 to 1.47, values below what is expected from for example TA649.[42] Modelling OS in the BR arm based on RE-MIND2 data resulted in ICERs, compared to TAFA+LEN, ranging from £[redacted] to £[redacted] per QALY gained. Results for R-GemOx were in general robust to changes in R-GemOx-specific OS assumptions. Most of the PFS extrapolations for TAFA+LEN and pola-BR seem highly implausible but overall, PFS assumptions do not seem to affect the ICER as much as OS. TTD assumptions for TAFA and LEN separately, or TAFA+LEN combined, can have a substantial impact on the ICERs given that total costs for the TAFA+LEN arm may vary between [redacted], when TAFA TTD is modelled according to the observed KM curves in L-MIND (even though this scenario is likely to be implausible), and to [redacted], when both TAFA and LEN are assumed to be administered until progression. The latter can also be seen as a non-realistic scenario since LEN is limited to a maximum of 12 treatment cycles. However, a scenario in which only TAFA is assumed to be administered until progression can be deemed as realistic. In that scenario, total costs for the TAFA+LEN arm were [redacted], and the ICERs for the comparison TAFA+LEN to pola-BR, BR and R-GemOx were £[redacted], £[redacted] and £[redacted], respectively; thus, substantially higher than in the ERG base-case. The remaining scenarios had a moderate impact on the ICERs. From these, those that had the largest impact on the ICERs were assuming utility values as in TA567 (decreased all ICERs by approximately £[redacted]), including CAR-T as subsequent therapy (decreased the ICER for the comparison vs. pola-BR by approximately £[redacted]) and assuming disease management costs for all arms equal to those in TAFA+LEN (increased the ICER for the comparison vs. pola-BR by approximately £[redacted]).

Table 6.9: ERG scenario analyses results

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
ERG base-case	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: TAFA+LEN											
Exponential	[redacted]	[redacted]	[redacted]	1.71	[redacted]	[redacted]	0.99	[redacted]	[redacted]	1.16	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	1.88	[redacted]	[redacted]	0.97	[redacted]	[redacted]	1.16	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	2.14	[redacted]	[redacted]	1.00	[redacted]	[redacted]	1.16	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	2.63	[redacted]	[redacted]	1.23	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	2.36	[redacted]	[redacted]	1.07	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: pola-BR											
MAIC time-varying HR (4 months)	[redacted]	[redacted]	[redacted]	1.47	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
MAIC time-varying HR (11 months)	[redacted]	[redacted]	[redacted]	1.36	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
RE-MIND2 constant HR	[redacted]	[redacted]	[redacted]	1.16	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: BR											
Exponential (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	0.88	[redacted]	[redacted]	1.16	[redacted]
Weibull (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	0.93	[redacted]	[redacted]	1.16	[redacted]
Lognormal (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.11	[redacted]	[redacted]	1.16	[redacted]
Log-logistic (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.16	[redacted]	[redacted]	1.16	[redacted]

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
Gompertz (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.47	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.36	[redacted]	[redacted]	1.16	[redacted]
Constant HR (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.13	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: R-GemOx											
Exponential (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.01	[redacted]
Weibull (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.00	[redacted]
Log-logistic (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.20	[redacted]
Gompertz (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.10	[redacted]
Generalised Gamma (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.20	[redacted]
Constant HR (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.30	[redacted]
Alternative PFS: TAFA+LEN											
Exponential	[redacted]	[redacted]	[redacted]	2.14	[redacted]	[redacted]	1.03	[redacted]	[redacted]	1.16	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	2.18	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	2.21	[redacted]	[redacted]	1.04	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	2.21	[redacted]	[redacted]	1.04	[redacted]	[redacted]	1.16	[redacted]

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
Alternative PFS: pola-BR											
MAIC time-varying HR (4 months)	[redacted]	[redacted]	[redacted]	2.10	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
MAIC time-varying HR (11 months)	[redacted]	[redacted]	[redacted]	2.09	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative PFS: R-GemOx											
Exponential (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Weibull (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Log-logistic (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.17	[redacted]
Gompertz (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Constant HR (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.17	[redacted]
Alternative TTD: TAFA+LEN											
Exponential (TAFA only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Weibull (TAFA only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Log-logistic (TAFA only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
Gompertz (TAFA only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma (TAFA only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
TAFA KM	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Exponential (LEN only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Treat until progression (TAFA+LEN)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Treat until progression (TAFA only)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Adverse events											
Inclusion 10% cut-off	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative utility inputs											
TA567 (PFS=0.83 PD=0.71)	[redacted]	[redacted]	[redacted]	2.51	[redacted]	[redacted]	1.14	[redacted]	[redacted]	1.30	[redacted]
TA306 (PFS=0.81 PD=0.60)	[redacted]	[redacted]	[redacted]	2.44	[redacted]	[redacted]	1.06	[redacted]	[redacted]	1.19	[redacted]
TA176 FAD (PFS=0.76 PD=0.68)	[redacted]	[redacted]	[redacted]	2.32	[redacted]	[redacted]	1.08	[redacted]	[redacted]	1.22	[redacted]
Alternative resource use and costs assumptions											
CAR-T included as subseq. treatment	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
Pooled proportions (subseq. treatments)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Max. durations	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Median durations	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Disease management costs as TAFA+LEN	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Vial sharing (all treatments)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]

Based on the updated model provided alongside the response to request for clarification.[4]

CS = company submission; BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell therapy; ERG = Evidence Review Group; FAD = Final Appraisal Determination; HR = hazard ratio; ICER = incremental cost effectiveness ratio; KM =Kaplan-Meier; LEN = lenalidomide; MAIC = matching-adjusted indirect comparison; OS = overall survival; PD = progressed disease, PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine, oxaliplatin; TA = Technology Appraisal; TAFA = tafasitamab; TTD = time to treatment discontinuation

6.3 ERG preferred assumptions

Table 6.10 shows the step-by-step changes made by the ERG to the company base-case and one-by-one impact of each change on the results. The changes with the largest impact on the results were the assuming a constant HR from the MAIC to extrapolate OS in the pola-BR arm, assuming a lognormal distribution (based on L-MIND data) to extrapolate PFS in the TAFA+LEN arm, using lenalidomide list price in the CE calculations, excluding CAR-T as subsequent treatment, and assuming the same disease management costs after progression for all treatments.

Table 6.10: Incremental impact of ERG preferred assumptions (one-by-one)

Preferred assumption	ICER vs. Pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
1. Original company BC	[redacted]	[redacted]	[redacted]
2. Post-clarification company BC	[redacted]	[redacted]	[redacted]
3. Post-clarification company BC + PAS discount for TAFA	[redacted]	[redacted]	[redacted]
3 + OS for pola-BR based on MAIC with constant HR	[redacted]	[redacted]	[redacted]
3 + PFS for TAFA+LEN using lognormal based on L-MIND	[redacted]	[redacted]	[redacted]
3 + PFS for Pola-BR based on MAIC with constant HR	[redacted]	[redacted]	[redacted]
3 + OS for BR based on MAIC with constant HR[a]	[redacted]	[redacted]	[redacted]
3 + PFS for BR based on MAIC with constant HR			
3 + Exclude CAR-T as subsequent treatment	[redacted]	[redacted]	[redacted]
3 + 6 cycles of R-GemOx as subsequent treatment	[redacted]	[redacted]	[redacted]
3 + Minimum between maximal and median durations for all other subsequent treatments	[redacted]	[redacted]	[redacted]
3 + Same disease management costs in PD for all treatments	[redacted]	[redacted]	[redacted]
3 + List price for lenalidomide	[redacted]	[redacted]	[redacted]

[a] This change is included in '3 + PFS for BR based on MAIC with constant HR' since these changes cannot be applied in isolation.

BC = base-case; BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell therapy; ERG = evidence review group; HR = hazard ratio; ICER = incremental cost effectiveness ratio; LEN = lenalidomide; MAIC = matching-adjusted indirect comparison; OS = overall survival; PD = progressed disease; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

6.4 Conclusions of the cost effectiveness section

To assess the CE of tafasitamab in combination with lenalidomide for the treatment of patients with DLBCL who are ineligible to receive SCT, the company developed a partitioned survival model that consist of three health states: progression-free, progressed disease and death. For the intervention arm, transitions between health states were determined by PFS and OS survival curves calculated from L-MIND trial data. The proportion of patients that are on treatment, while in progression-free, was informed by L-MIND TTD data. The comparators included in the model were polatuzumab vedotin in combination with bendamustine and rituximab, bendamustine in combination with rituximab, and rituximab in combination with gemcitabine and oxaliplatin. Data for the comparators were sourced from the RE-MIND2 study and a MAIC using published data from various studies. The model has a cycle length of four weeks and includes a half-cycle correction. The economic analyses were conducted from the perspective of the NHS and PSS, with a time horizon of 45 years that is considered as a lifetime horizon, and costs and QALYs were discounted at 3.5% per annum.

The population in the final scope by NICE was defined as *"adults with relapsed or refractory diffuse large B-cell lymphoma and who are not eligible for have autologous stem-cell transplantation"*, in line with the conditional marketing authorisation by the EMA for the use of tafasitamab and the population enrolled in the L-MIND study that was used to inform the model.[2] As detailed in Section 3.2.1, the study population reflects the patient population in which the indication for treatment is being sought.

Survival analyses for the TAFA+LEN arm, were conducted using L-MIND data and following TSD14 recommendations.[44] In the absence of head-to-head data to compare the (clinical) effectiveness of TAFA+LEN against any of the three comparators included in the CEAs, the company relied on two indirect treatment comparisons to estimate PFS and OS in the comparator arms of the model: a 1:1 NN matching with external (synthetic) control arms, using RE-MIND2 data,[22] and a MAIC against published clinical studies (summarised in Tables 4.9 and 4.16) of key comparators.[23] The ERG considers that, in general, the company have used appropriate methods to analyse OS and PFS data by either of the methods selected. However, several concerns were identified throughout this report and the ERG considers that careful attention should have been paid to assess the plausibility of certain choices made by the company, since some of these seem to lack both face and external validity when compared to clinical experts' expectations and to available (external) data. These concerns affect all treatment arms to some extent but seem to be more serious for the pola-BR arm.

AEs were included in the model based on data from L-MIND study and trials of other treatment alternatives. A one-off lumpsum cost and utility decrement was applied at the start of the model.

Given that HRQoL data were not collected in the L-MIND trial, the company utilised in their base-case utility values obtained from the safety population of the single arm ZUMA-1 trial from TA559,[56] the exact approach adopted in TA649.[42] The ERG considers this approach appropriate but explored other options to source utility values in scenario analyses.

The economic analyses included drug acquisition costs for the intervention and comparators, drug administration costs, concomitant medication costs, subsequent treatment costs, monitoring costs, disease management costs, costs for the treatment of AEs, and end-of-life costs. Drug acquisition costs for tafasitamab were based on the recently approved PAS discount. For lenalidomide, the company [redacted], but the ERG preferred to use the current list price. Drug acquisition costs of all other treatments, including the comparators and subsequent treatments, were based on their list price prices. The costs of subsequent treatments were included using data from RE-MIND2 on the proportions of

patients receiving different treatments after receiving prior treatments corresponding to the different treatment arms in the model. In line with NICE's position statement on the consideration of products that are recommended in the CDF (i.e. CAR-T is only recommended in the CDF) as comparators or in the treatment sequence, the ERG preferred analysis excludes CAR-T as subsequent treatment. Monitoring and disease management costs, except for patients who were in PFS for >2 years, were included based on L-MIND for the intervention, for pola-BR and BR these were based on NICE TA649, and for R-GemOx these were based on NICE TA567. For patients who are in PFS for >2 years, monitoring and disease management costs were based on DLBCL guidelines. The analysis also included costs for the treatment of adverse events and palliative care.

Results of the company's base-case analysis (including the PAS discount for tafasitamab) indicated that [redacted]. Given the concerns raised regarding the validity of the results for the pola-BR arm, a quick validity check of the company's base-case results was conducted. In TA649 pola-BR was deemed as a cost-effective alternative compared to BR.[42] With the results obtained by the company the ICER for the comparison pola-BR vs. BR was £[redacted]. The average PSA results were in line with the deterministic ones, but in the PSA [redacted]. The CEAC plot indicated that [redacted]. At the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that TAFA+LEN is a cost-effective alternative to the other comparators was [redacted]. The company conducted scenario analyses to assess the robustness of the model results to changes in modelling assumptions. The modelling assumptions explored by the company that had the greatest effect on the ICER were related to alternative MAIC assumptions, alternative OS/PFS extrapolations, using RE-MIND2 data for the pola-BR arm, alternative utility values (TA567),[42] and assuming vial-sharing for all IV therapies.

The ERG defined a new preferred base-case by selecting different OS (for pola-BR and BR) and PFS (for TAFA+LEN, pola-BR and BR) parametric distributions, as explained in Section 4.2.6 of this report, and by changing resource use/costs assumptions such as using lenalidomide list price, excluding CAR-T as subsequent treatment, assuming 6 cycles duration for R-GemOx as subsequent treatment, changing the treatment durations reported by the company (to correct for potential inconsistencies) for all other subsequent treatments and applying the same disease management costs in PD for all treatment arms. However, it should be emphasised that this ERG "base-case" does not represent a best-case but a least-worse. A number of violations are still present in this ERG "base-case" that cannot be resolved with the current available evidence. The results of the ERG's base-case analysis indicated that [redacted]. The ICER of pola-BR compared to R-GemOx was £[redacted] per QALY gained, and the ICER of TAFA+LEN compared to pola-BR was £[redacted] per QALY gained. A quick validity check of the ERG's base-case results for the comparison pola-BR vs. BR indicated that the ICER was [redacted]. The average PSA results of the ERG preferred base-case were broadly in line with the deterministic ones, [redacted]. The CEAC indicated that

[redacted]. At the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that TAFA+LEN is a cost-effective alternative to the other comparators was [redacted]. The scenario analyses conducted by the ERG indicated that the ICER was reasonably stable for alternative choices of TAFA+LEN OS extrapolations. However, not all scenarios were deemed as equally plausible by the ERG. The two most plausible alternative parametric model extrapolations for OS (the log-logistic and generalised Gamma) resulted in ICERs close to the ERG base-case. Results based on the alternative OS assumptions for pola-BR showed large differences with respect to the ERG base-case with QALYs varying from 1.16 to 1.47, values below what is expected from for example TA649.[42] Most of the PFS extrapolations for TAFA+LEN and pola-BR seem highly implausible but overall, PFS assumptions do not seem to affect the ICER as much as OS. TTD assumptions for TAFA and LEN separately, or TAFA+LEN combined, can have a substantial impact on the total costs for the TAFA+LEN arm. A scenario in which only TAFA is assumed to be administered until disease progression can be deemed as realistic. In that scenario, total costs for the TAFA+LEN arm were [redacted], and the ICERs for the comparison TAFA+LEN to pola-BR, BR and R-GemOx were £[redacted], £[redacted] and £[redacted], respectively. The remaining scenarios had a moderate impact on the ICERs. From these, those that had the largest impact on the ICERs were assuming utility values as in TA567 (decreased all ICERs by approximately £[redacted]), including CAR-T as subsequent therapy (decreased the ICER for the comparison vs. pola-BR by approximately £[redacted]) and assuming disease management costs for all arms equal to those in TAFA+LEN (increased the ICER for the comparison vs. pola-BR by approximately £[redacted]).

7 END-OF-LIFE

The statements underpinning the company's claim that the combination treatment of tafasitamab plus lenalidomide meets the NICE end-of-life criteria are summarised in Table 7.1 below.

Table 7.1: End-of-life criteria

Criterion	Data available	Reference in CS
The treatment is indicated for patients with a short life expectancy, normally less than 24 months.	Patients with R/R DLBCL have a life expectancy of 3 to 9 months, are limited to palliative care, and therefore represent an important unmet need.[88-90]	Section B.1.3.5, page 25[1]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	The K-M estimate for median OS for patients on TAFA+LEN was 33.5 months (95% CI: 18.3 months–not reached); FAS.[66, 91] In the SCHOLAR-1 study median overall survival was 6.3 months in patients who are refractory to 1L therapy.[92] In the model, TAFA+LEN was associated with undiscounted life year gains which were 3.97 vs. Pola-BR, 4.48[a] vs. BR and 4.41 vs. R-GemOx	Section B.2.6.4, page 50[1] Figure 9 of the CS[1] Figure 7-6 of the CSR[91]
Based on Table 21 of the CS[1] [a]Refers to company's base-case model. Section B.3.6.1 shows the estimate for BR as 4.46[1] 1L = first line; BR = bendamustine and rituximab; CI = confidence interval; CS = company submission; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; FAS = full analysis set; KM = Kaplan-Meier; LEN = lenalidomide; NHS = National Health Service; OS = overall survival; Pola-BR = polatuzumab vedotin in combination with bendamustine and rituximab; R-GemOx = rituximab, gemcitabine and oxaliplatin; R/R = relapsed/refractory; TAFA = tafasitamab		

ERG comment: Whilst the statements summarised in Table 7.1 appear to support the company's claim of meeting the NICE end-of-life criteria, the ERG noted some issues with the supporting evidence.

Of the three references cited in support of the statement *"patients with R/R DLBCL have a life expectancy of 3 to 9 months, are limited to palliative care, and therefore represent an important unmet need"* one reported a brief (non-systematic) literature review and did not provide primary supporting data but cited another study in this respect.[88] The second study discussed very small numbers of patients, mainly focusing on the period of clinical management following autologous bone marrow or stem cell transplantation.[89] The third study reported a median OS of 0.75 years in patients with refractory DLBCL who had received salvage chemotherapy however, some also received ASCT.[90] The cited studies seem to have limited relevance to the population described in the CS.

The ERG notes that life expectancy estimates for BR and R-GemOx are likely to be below the 24 months threshold as suggested by the company's base-case analysis, 1.76 and 1.82 LYG respectively (Section B.3.6.1, Table 58 of the CS).[1] The estimates from the ERG's base-case analysis were similar to those from the CS, being 1.6 and 1.82 LYG for BR and R-GemOx respectively (Section 6.2.1 and Table 6.5 above). However, a difference was noted between estimates from the company's and ERG's base-case analyses for pola-BR: 2.20 vs. 3.36 LYG respectively.

Whereas the company's 2.20 LYG estimate could be regarded as borderline, the ERG's estimate is clearly above the 24 months threshold for life expectancy. The ERG's estimate for pola-BR is in line with that summarised in TA649.[42]

A journal article reporting long-term outcomes from the L-MIND study was cited in support of the second above-tabulated statement *"The K-M estimate for median OS for patients on TAFA+LEN was 33.5 months (95% CI: 18.3 months–NR)"*.[66] The median OS estimate appeared in the abstract, main text and tabulation of the paper but the relevant Kaplan-Meier plot was not visible despite being signposted. In order to assist the committee, the ERG has added a reference to the CSR report which shows the relevant Kaplan-Meier plot and has also highlighted the location of this information in both the CS[1] and the CSR.[91]

The ERG questions the relevance of the SCHOLAR-1 study in supporting the statement about the median OS of patients who are refractory to first-line therapy.[92] SCHOLAR-1 pools data from two phase II RCTs together with two observational studies. The population under consideration was patients with refractory DLBCL some of whom were awaiting ASCT. As well as the limited relevance of the population, the pooling approach used was questionable because of differences in study design/risk of bias and the variation in treatment regimens across the included studies.

The above issues taken together leave the ERG uncertain about the strength and relevance of evidence selected to underpin the company's claim in relation to meeting the NICE end-of-life criteria. It is possible that the company could obtain more relevant evidence through targeted literature searches or alternatively could seek statistics on life expectancy from relevant populations from UK-based registries of cancer patients. The ERG has highlighted this as a key issue.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

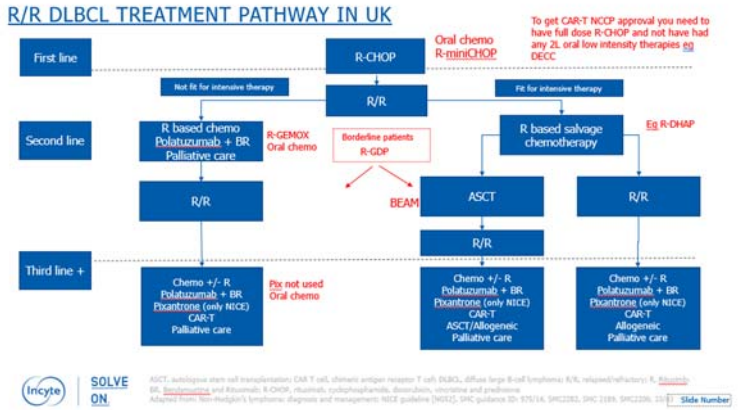
You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 28 February** 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.

Issue 1 Appropriateness of conclusions leading to comparator selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 2.3, page 26, the ERG stated that: "…the company referred to three virtual interviews that were held on Microsoft Teams in September 2021 with UK clinical experts to seek advice on the relevant comparators for the population with transplant-ineligible R/R DLBCL in the UK stating that *"neither R-Gem, R-DECC or R-P-Mit-CEBO were referred to by the UK Experts during the interviews as being used in UK clinical practice for the population who would be eligible for TAFA+LEN. These variations of chemoimmunotherapy are therefore not considered to be relevant comparators for TAFA+LEN in England/the UK… pixantrone is available for use in the 3L and 4L treatment settings; however, the experts all advised that pixantrone is*	We would ask that the order of the wording is updated to provide more context for the answer provided. Add the bolded text as below: "…the company referred to three virtual interviews that were held on Microsoft Teams in September 2021 with UK clinical experts to seek advice on the relevant comparators for the population with transplant-ineligible R/R DLBCL in the UK, stating that ***"the three experts all advised that POLA+BR, R-GemOx and BR would be the most relevant comparators for the UK for TAFA+LEN in transplant-ineligible R/R DLBCL"*** **and that** *"neither R-Gem, R-DECC or R-P-Mit-CEBO were referred to by the UK Experts during the interviews as being used in UK clinical practice for the population who would be eligible for TAFA+LEN. These variations of chemoimmunotherapy are*	As noted in the clarification responses, the conclusions regarding comparators were based on clear guidance from three UK Clinical Experts in response to questions posed after presentation of either a list of the comparators (POLA-BR, R-GemOx, BR) or a figure of the DLBCL treatment pathway (below), similar to figure 1 of the CS.  Providing additional text as suggested would provide further context for the choice of comparators. Further details of the answers provided by the experts are available in the minutes of the interviews shared on 7 December 2021. For further clarity in advance of technical engagement, we would like to note the questions asked during the interviews and highlight some additional sections of the minutes of the meeting. All discussion is related to the population with R/R DLBCL who	Not a factual inaccuracy

rarely used in the UK and is not a relevant comparator… furthermore, given the use of POLA+BR and chemoimmunotherapy for R/R DLBCL in patients ineligible for transplant, best supportive care/palliative care was not considered a suitable option".[4] In discussing how the selected comparators aligned with current UK clinical practice, the company explained that *"the three experts all advised that POLA+BR, R-GemOx and BR would be the most relevant comparators for the UK for TAFA+LEN in transplant-ineligible R/R DLBCL".*[4]	*therefore not considered to be relevant comparators for TAFA+LEN in England/the UK… pixantrone is available for use in the 3L and 4L treatment settings; however, the experts all advised that pixantrone is rarely used in the UK and is not a relevant comparator… furthermore, given the use of POLA+BR and chemoimmunotherapy for R/R DLBCL in patients ineligible for transplant, best supportive care/palliative care was not considered a suitable option".* Remove the following text: "In discussing how the selected comparators aligned with current UK clinical practice, the company explained that *"the three experts all advised that POLA+BR, R-GemOx and BR would be the most relevant comparators for the UK for TAFA+LEN in transplant-ineligible R/R DLBCL"*	are not eligible for autologous stem-cell transplant unless otherwise stated. <u>*Questions asked regarding comparators:*</u> 1. Are R-GemOx, Pola-BR and BR the most relevant model comparators for tafasitamab and lenalidomide for a 2L+ R/R DLBCL population? 2. In your experience, how often are these treatments used in UK clinical practice? Would you consider any of these comparators to be the standard of care (SoC) for R/R DLBCL? 3. Are there any other comparators you think should be considered for the model? <u>*Answers regarding question 3:*</u> • Expert 1 noted that while R-GDP might be used in patients at the "borderline" of fitness for more intensive therapies, this patient population is small, and including R-GDP in the model would add unnecessary complication. • Expert 2 did not think there are any other relevant comparators. Although many other palliative chemotherapy regimens are used, they are probably not relevant for the TAFA+LEN population • Expert 3 noted that additional treatments such as DECC/oral combinations may be used at later therapy lines, but would not be valid comparators for the population at 2L and beyond (2L+)	

Issue 2 Clinical SLR Search Strategy and Data Extraction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Data extraction Section 3.1.3, Page 33. "ERG comment: Extraction of study level details and baseline data by a single reviewer followed by independent checking by a second reviewer is acceptable. However, dual, independent data extraction with a pre-specified approach for achieving consensus is the recommended practice for extracting outcome data in order to minimise errors in estimates of effect. The ERG considers that the outcome data and resulting estimates may be at risk of inaccuracies in light of the process employed by the company." This statement is contradictory, as it says the methods used are acceptable but also considers the outcome data and results estimates may be at risk of inaccuracies.	We ask the ERG to remove or soften/re-order the wording **"**The ERG considers that the outcome data and resulting estimates may be at risk of inaccuracies in light of the process employed by the company**."** "ERG comment: Extraction of study level details and baseline data by a single reviewer followed by independent checking by a second reviewer is acceptable. **However, this method of data extraction may risk inaccuracies.** Dual, independent data extraction with a pre-specified approach for achieving consensus is the recommended practice for extracting outcome data in order to minimise errors in estimates of effect.	While dual, independent data extraction is the recommended practice for extracting outcome data in order to minimise errors in estimates of effect, extraction by a single reviewer followed by independent checking by a second reviewer is a commonly used method for SLRs, and the ERG notes in the first sentence of this paragraph that the method is acceptable.	Not a factual inaccuracy

Issue 3 Generalisability to clinical practice in England and Wales

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In section 3.2.1, page 43 the following text from the clarification letter is cited followed by a comment from the ERG regarding generalisability to routine clinical practice in England and Wales. "In response to the request for the clarification, the company noted that *"the Baseline tumour assessment in the observational cohort study indicated 85% of the population had refractory disease.*[REF 13] *In L-MIND, 44% of patients were refractory to their last prior therapy,*[13] *indicating a lower proportion of patients with refractory disease for L-MIND than in the observational cohort study"*. However, the company stated that *"this is in alignment with clinical expert feedback regarding the population in routine clinical practice"*.[4] The ERG wanted to note this as a potential limitation of the generalisability to clinical practice in England and Wales."	We ask that this paragraph is removed, or at a minimum provide the following additional context from the clarification responses: **Clinical experts advised that *"the L-MIND population is largely comparable to the UK population with R/R DLBCL and ineligible for SCT.*[8] *The exception is that there was a lower proportion of patients with primary refractory disease in L-MIND compared with routine clinical practice, indicating an overall lower-risk population in L-MIND.*[8]*"*** ***"it is important to note that the observational cohort study and L-MIND are not directly comparable: pixantrone is reimbursed for third- or fourth-line treatment only in the UK, as reflected in the observational study population.*[5,13] *By contrast, 50% of the L-MIND population were treated in the second-line setting.*[12] *Therefore some differences in the patient and disease characteristics are expected (e.g., a higher proportion of patients with high-risk factors for worse outcomes may be expected in the 3L+ vs 2L+ setting)."*** ***"It is difficult to compare the proportion of patients with refractory disease between studies, due to differing definitions and limited baseline characteristics data***	The currently-included text requires additional context. We acknowledge that the wording "*"this is in alignment with clinical expert feedback regarding the population in routine clinical practice"* provided in clarification may have caused confusion, as the clinical experts were referring to the population in the 2L+ setting, where there is a slightly higher proportion of patients with refractory disease vs. L-MIND. In the 3L+ setting as in the Eyre et al. retrospective observational study, more patients with high-risk factors such as refractory disease would be expected. This was not clear in the excerpt cited from the clarification responses. Omitting the paragraph would remove this confusion. Alternatively, providing further context as included in the clarification responses would provide a more accurate/relevant discussion regarding the generalisability of L-MIND to the population treated in UK clinical practice.	Not a factual inaccuracy. We made our assessment in light of the available information at the time of drafting the report.

This quote is misleading without further context, as L-MIND and the observational cohort study are not directly comparable and clinical expert feedback was in respect of the 2L+ population with R/R DLBCL, not the 3L+ population in the Eyre et al. retrospective, observational cohort study.	***available in the observational cohort study…"***		

Issue 4 Clinical efficacy and safety clarifications and corrections

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Text included in error Section 3.2, page 35 "A third study, a retrospective, observational cohort, reported data on patients treated with lenalidomide monotherapy (the RE-MIND study), see Section 3.3." This wording about the RE-MIND study appears to be included in error	Remove the sentence.	We suggest deleting the wording about the RE-MIND study here at it was an indirect comparison rather than a prospective clinical trial and is not mentioned in Section 3.3.	Not a factual inaccuracy. The text was not included in error and the signposting to Section 3.3 is correct.
Clarify data cut-offs used in analyses In Section 3.2.1.1.2, page 44, the following statement is included. "PFS was observed in 42 participants and the Kaplan-Meier estimate for median PFS was 11.6 months (95% CI 6.3 to 45.7) with a median follow-up of	Update wording to clarify data cut-off points: "PFS was observed in 42 participants and the Kaplan-Meier estimate for median PFS was 11.6 months (95% CI 6.3 to 45.7) with a median follow-up of 33.9 months (95% CI 26.5 to 35.4) **at the October 2020 data cut off**. Post-hoc analyses **at the November 2018 data cut off** suggested a continued PFS benefit of tafasitamab monotherapy following discontinuation of lenalidomide (median PFS 12.7 months, 95% CI 2.3, upper CI not reached).	Adding the data cut off used for pre-planned and post-hoc analyses will add clarity to the paragraph.	Not a factual inaccuracy

33.9 months (95% CI 26.5 to 35.4). Post-hoc analyses suggested a continued PFS benefit of tafasitamab monotherapy following discontinuation of lenalidomide (median PFS 12.7 months, 95% CI 2.3, upper CI not reached)." This refers to analyses at two different data cut-off points, which can be clarified.			
<u>Table heading</u> Table 3.7 heading, page 44. "Primary efficacy outcomes for L-MIND study." These data are for the October 2020 data cutoff, so suggest this is clarified in the heading.	Update table heading: "**Best objective response and objective response rates for the L-MIND study (October 2020 data cut off).**"		Not a factual inaccuracy. Of note, the data cut-off is mentioned in the text above the Table.
<u>Data transcription errors</u> Table 3.8, page 45.	Updates to table as follows: • Median OS should be changed to median DoR in two rows • The lower CI of median DoR for patients with a CR should be 43.9 (not 45.7).	Updates to data points.	Changed accordingly. Estimate for median DoR (complete response) now entered as 'not reached' in

There are two data errors in the DoR estimates for patients with a complete response and two errors in the row headers (OS is written instead of DoR). Track changes are provided in the next column for ease.	• The lower CI for DoR among patients with a CR at 24 months should be 64.9 (not 65.9) 		accordance with information on pages 47-48 of the CS.
<u>In Section 3.2.1.2, page 48, the ERG makes the following comment:</u> "ERG comment: Of the 45 participants who discontinued both tafasitamab and lenalidomide during cycles 1 to 12, 32 of these did so due to progressive disease (Figure 5 of the CS). An additional four participants discontinued tafasitamab	Remove the second paragraph regarding table 11.	The first paragraph of this statement refers to best ORR, the best response at any point during the trial prior to the October 2020 data cut off. Among the study participants, 13 had progressive disease as their best response, whereas all other participants had a best response of stable disease or better. However, a further 23 participants went on to experience PD following an initial response to TAFA+LEN. Added to the	Not a factual inaccuracy

monotherapy after cycle 12 prior to data cut-off due to progressive disease. Therefore, of the 80 patients within the intention-to-treat (ITT) population (patients who received at least one dose of tafasitamab), almost half (36/80) of these discontinued due to progressive disease by the point of data cut-off. Table 11 of the CS provides alternative information regarding best ORR as of data cut-off, and states that of the 80 participants within the ITT cohort, 13 of these had progressive disease (32 had complete response, 14 had partial response and 13 had stable disease)." This statement is confusing patients who experienced progressive disease as their best objective response with all		13 participants with a PD as best response reaches the total of 36/80 patients who experienced PD at some point during the trial. Per the treat to progression protocol of TAFA+LEN followed by tafasitamab monotherapy, they then discontinued the study treatment.	

patients who experienced progressive disease during the trial.			
<u>Serious adverse events</u> Section 3.2.1.2, Page 49 "The ERG notes that, although comprehensive details were provided regarding all AEs experienced during the follow-up of the L-MIND study, limited details were provided regarding serious adverse events (SAEs). Specifically, Table 17 in the CS lists 85 different AEs, many of which had only a single occurrence (i.e. <2% of patients), whereas SAEs were reported narratively and were limited to those that occurred in two or more patients (i.e. >2%). As 41 patients experienced one or more SAEs, it is concerning that more	Update text on page 49 "The ERG notes that, although comprehensive details were provided regarding all AEs experienced during the follow-up of the L-MIND study, limited details were provided regarding serious adverse events (SAEs). Specifically, Table 17 in the CS lists 85 different AEs, many of which had only a single occurrence (i.e. <2% of patients), whereas SAEs were reported narratively and were limited to those that occurred in two or more patients (i.e. >2%). As 41 patients experienced one or more SAEs, **additional details of the SAEs in the study should be provided**."	We are happy to share additional safety data for L-MIND (and MOR208C201) per the CSR already provided. Details of the SAEs will be provided during technical engagement.	Not a factual inaccuracy

<table>
<tr><td>details of these events were not provided.”</td><td></td><td></td><td></td></tr>
<tr><td><u>MOR208C201 study details</u>

Section 3.2.2. Page 49.

“The CS stated that the model utilised within the MOR208C201 study is based on the L-MIND study of the TAFA+LEN combination in adult patients with R/R DLBCL who are not eligible for transplant”</td><td>Delete text.</td><td>This appears to be an error. MOR208C201 was a single-arm clinical trial, there was no model used in the study.</td><td>Changed accordingly.</td></tr>
<tr><td><u>Data transcription error</u>

Table 3.11, page 50.

In the table “primary efficacy outcomes for MOR208C201 study”, there is an error in the n number for “no response assessment”. This should be n=10/35 (28.6%) and not n=19/35 as</td><td>Update the “no response assessment” row of the table according to the track changes below.

<table><tr><th>Outcome, n (%)</th><th>DLBCL cohort (N=35)</th></tr><tr><td>Complete response</td><td>2 (5.7)</td></tr><tr><td>Partial response</td><td>7 (20)</td></tr><tr><td>Objective response rate [95% CI]</td><td>9 (25.7) [12.5 to 43.3]</td></tr><tr><td>Stable disease</td><td>5 (14.3)</td></tr><tr><td>Disease control rate [95% CI]</td><td>14 (40.0) [23.9 to 57.9]</td></tr><tr><td>Progressive disease</td><td>11 (31.4)</td></tr><tr><td>Not estimable</td><td>0</td></tr><tr><td>No response assessment</td><td><s>19</s> 10 (28.6)</td></tr><tr><td colspan="2">Based on Table 12 of the CS
CI = confidence interval; CS = company submission</td></tr></table></td><td>Update data transcription error.</td><td>Changed accordingly.</td></tr>
</table>

currently stated.			
<u>Description of safety outcomes for MOR208C201</u> Section 3.2.2.2, page 50. The ERG makes the following statement: "As detailed in Table 3.12, the most frequently reported AEs of any grade within the DLBCL cohort were neutropenia and peripheral oedema, both of which occurred in 6/35 participants (17%). Other frequently occurring adverse events included dyspnoea (5/35, 14%) and thrombocytopenia, infusion-related reactions, upper respiratory tract infections and headaches, each of which occurred in 4/35 participants (11%). SAEs occurred in two of the DLBCL patients,	Update text to clarify. "As detailed in **Jurczak et al.,** the most frequently reported AEs of any grade within the DLBCL cohort were neutropenia and peripheral oedema, both of which occurred in 6/35 participants (17%). Other frequently occurring adverse events included dyspnoea (5/35, 14%) and thrombocytopenia, infusion-related reactions, upper respiratory tract infections and headaches, each of which occurred in 4/35 participants (11%). SAEs occurred in two of the DLBCL patients, both of which had a suspected relationship to tafasitamab; one case of febrile neutropenia and one of genital herpes. **AEs of grade 3 or higher occurring in the DLBCL cohort of MOR208C201 are detailed in Table 3.1.2**"	Updating the wording will clarify the content being described and the source of the content.	Not a factual inaccuracy

both of which had a suspected relationship to tafasitamab; one case of febrile neutropenia and one of genital herpes." However, this relates to information in the Jurczak et al. publication and note in table 3.11.			

Issue 5 Description of the MAIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 3.13, page 55 is entitled OS studies identified for the MAIC. However, not all studies identified report OS.	We suggest removing the studies that do not report OS (Vacirca et al. and Ohmachi et al.) from the table to avoid confusion.	This could potentially cause confusion regarding study inclusion in the MAIC for different endpoints.	Table caption changed to 'Studies identified for the MAIC'
Section 3.3.2.1, page 56. In Section 3.3.2.1 regarding the BR studies, it is stated: "It should be noted that results for OS, based on the pooled estimate, could not be located in any of the documents provided by the company." This is due to OS results not being available from the	We ask that this text is rephrased for clarity: It should be noted that OS outcomes were only available in the GO29365 study for BR, therefore no pooled estimate is available for this outcome.	Updating the text would clarify which outcomes are available for the BR studies.	Not a factual inaccuracy

Ohmachi et al. and Vacirca et al. studies.			

Issue 6 Critique of the ITCs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 3.3.1, page 52. One of the two additional factors used in RE-MIND2 sensitivity analyses is incorrectly stated as 'early response (yes vs. no)'	Update the bullet points: "Two additional factors were used in sensitivity analyses, namely: • ECOG (0 to 1 vs. ≥2) • **History of early relapse (yes vs. no) and history of primary progressive disease (yes vs. no)** ***[replaces 'history of primary refractoriness as an adjustment factor']"***	Correction of methodology details for sensitivity analyses.	Changed accordingly.
Section 3.4, page 57. "The company chose to focus only on comparisons of R-GemOx and BR using RE-MIND2 as opposed to pixantrone, CAR-T therapy, and pola-BR, although analyses for the latter two therapies were conducted and a short summary provided.1 The ERG appreciates that CAR-T was not included in the NICE scope, but pola-BR was and the company also stated that clinical	We ask that the wording is updated to include the bold text: "The company chose to focus only on comparisons of R-GemOx and BR using RE-MIND2 as opposed to pixantrone, CAR-T therapy, and pola-BR, although analyses for the latter two therapies were conducted and a short summary provided. The ERG appreciates that CAR-T was not included in the NICE scope, but pola-BR was and the company also stated that clinical experts considered it to be relevant. **Results from the POLA-BR results were provided with the responses to the ERG's clarification questions."**	As noted later in the ERG report, results for the POLA-BR comparison in REMIND2 were provided during clarification. Additional RE-MIND2 results can be provided during technical engagement.	Not a factual inaccuracy

experts considered it to be relevant." This wording does not acknowledge that POLA-BR RE-MIND2 results were provided during clarification.			
In Section 3.4 page 57, the following statement is included: "This population mismatch is compounded when there are multiple comparators each with outcomes estimated from a different data source. This means that to estimate the treatment effect of the intervention versus each comparator, the intervention data are adjusted differently for each comparator. This is therefore likely to lead to a bias in treatment effects between comparators. On the other hand, estimating the treatment effect of the intervention and comparators from the same pooled IPD and adjusting the data for all comparators to better match the characteristics of those who received the intervention is liable to lead to greater comparability. This implies that in principle the ERG prefers RE-MIND2 to the MAICs."	We would propose the following revision: "This population mismatch is compounded when there are multiple comparators each with outcomes estimated from a different data source. This means that to estimate the treatment effect of the intervention versus each comparator, the intervention data are adjusted differently for each comparator. **The use of the shared effect modifier assumption allows to transfer the relative efficacy estimates of TAFA + LEN vs. comparator estimated in a comparator-like population back to the L-MIND population. However, this assumption is difficult to test in practice. As the RE-MIND2 analyses results estimated from the L-MIND ITT population don't need to make this assumption** in principle the ERG prefers RE-MIND2 to the MAICs."	The criticism around this point provided by the ERG is fair, and the point mentioned here is specifically covered in the NICE TSD 18, however the text surrounding it lacks accuracy. The issue can be summarised as the following: in an MAIC changes are made to the efficacy population of the intervention trial through the use of statistical weights to render it comparable to the comparator population. Relative efficacy estimates versus a comparator are therefore estimated in a "comparator-like" population and not in the original intervention population from the trial. The use the shared effect modifier assumption, which states that the effect modifiers of all treatments are the same, and that the change in treatment effect caused by each effect modifier is the same for all treatments in the comparisons, allows to transfer	Not a factual inaccuracy. However, the text has been amended to improve clarity: "This is therefore likely to lead to a bias in **implied** treatment effects between comparators."

		the relative efficacy estimates from the comparator-like population to the original efficacy population. The sentence “This is therefore likely to lead to a bias in treatment effects between comparators” is inaccurate as no treatment effect between comparators are being estimated, but each time the treatment effect between TAFA + LEN and a comparator. Uncertainty in the estimates would be introduced, if the shared-effect modifier assumption does not hold, in the fact that the treatment effect between TAFA + LEN and a comparator would differ between the population in which it is estimated and what it would have been in the intervention efficacy population. Unless the ERG provides some evidence that the shared-effect modifier assumption is likely not to hold we would challenge the likeliness of whether bias is introduced, the direction of which being in addition unclear, and would suggest the following wording. We however understand the preference in principle for the RE-MIND2 study estimates.	

In Section 3.4 page 58, the following statement is included: Also, the only mention of the propensity score in the CS or the appendices was in relation to matching, but the ERG did note that a statistical report of a post-hoc analysis (also mentioned in the clarification letter response) did mention the application of IPW, but only for comparisons with pola-BR, CAR-T and rituximab and lenalidomide (R2)”	We propose that this paragraph be removed from the ERG report.	The result of the RE-MIND2 primary analyses included sensitivity analyses using overlap weights based on the propensity score, that were presented as part of the RE-MIND2 CSR shared with the ERG, IPTW analyses had not been pre-specified and were only used in post-hoc analyses vs pola-BR, R2 and CAR-T, hence this statement is incorrect and should be removed. The statement presented here also contradicts two statements from the ERG presented on p59: “The statistical report for the post-hoc analysis also mentioned that “overlap weights” could be used to mitigate the problem of extreme weights: although not referred to in TSD 17, these are essentially the propensity scores themselves as opposed to the inverse of them and so are more tightly bounded (0 to 1).” “The only results using overlap weights were those versus BR and R-GemOx, which were presented for OS in the QuEENS checklist provided with the clarification letter and also in a CSR for RE-MIND2”	Not a factual inaccuracy. As is standard practice in technology appraisals, by CS the ERG is referring to Document B. As the company agrees, the analyses using overlap weights were not mentioned in either the CS or the appendices. The ERG needs to show how difficult it was to find important information and to signpost readers to the various sources.

In Section 3.4 page 58, the following statement is included: "In fact, when matching as opposed to IPW was used, the baseline characteristics of the TAFA+LEN cohort varied depending on which comparator was being matched (BR, R-GemOx, pola-BR, CAR-T or R2), which suggests difference estimates of the ATE. As explained in TSD 17, the estimation of the ATE might be the ideal, assuming that there are patients who received the comparator who might be the sort of patients who would receive the intervention in clinical practice and vice versa. However, although the characteristics of the comparator and intervention cohorts might be different, the estimation of the ATE still requires sufficient overlap in characteristics between intervention and comparator patients to ensure that the probability of receiving the other treatment is not zero. The additional problem is that, as explained above in relation to a MAIC, matching that involves selecting intervention patients to better match comparator ones necessarily changes the resulting	We would ask to have the text revised to the following: "In fact, when matching as opposed to IPW was used, the baseline characteristics of the TAFA+LEN cohort varied depending on which comparator was being matched (BR, R-GemOx, pola-BR, CAR-T or R2). **This was caused by the impossibility of finding comparator patients in the observational cohorts for all patients enrolled in the L-MIND study. It should be noted however, that most patients enrolled in the efficacy population of L-MIND were found with comparator patients receiving BR and R-GemOx (respectively 75 and 74 L-MIND patients retained out of 80). Therefore, the effect estimated in these comparisons would be close to the ATT.** **In the comparison against POLA + BR, CAR-T or R2 the deviation between the L-MIND matched populations, which differed each time, and the efficacy population from L-MIND are substantial. As explained above in relation to a MAIC, matching that involves selecting intervention patients to better match comparator ones necessarily changes the resulting cohort characteristics and an assumption must be made to transfer the relative efficacy estimate from that subpopulation to the efficacy population. Overall uncertainty of the results increases with the number of comparators as it has to be used several times.** This does not happen when estimating the ATT because only the comparator cohorts are adjusted in order to better match the	We would like the ERG to clarify this statement as the propensity score matching used in these analyses does not allow to estimate ATE but ATT, as full matching was not employed. We would also like to mention that the characteristics of the L-MIND populations matched to BR and to R-GemOx are very close to the efficacy population of the efficacy population for L-MIND (respectively 75 and 74 of the 80 patients that contributed to the L-MIND efficacy analyses were included in the matching sets in these comparisons). Thus, the estimates obtained in these comparisons are expected to be very similar to the one that would have been obtained in the L-MIND efficacy population. It can be noted that out of the 81 patients enrolled in the L-MIND population only 76 were considered in the RE-MIND 2 analyses: 2 patients were not included for not meeting the eligibility criteria, and 3 because of a follow-up of less than 6 months. For the comparison against POLA + BR, BR and R-GemOx the point raised by the ERG is	Not a factual inaccuracy. However, the text has been amended to improve clarity: "…which suggests different estimates of the ATE. Also, although the differences in baseline characteristics were small, and sample size only varied by 1, the fact that an "adjustment factor" was considered if the KM plots suggested that the original and matched TAFA+LEN patients were different in terms of OS or PFS, indicates a more substantial difference between the matched and unmatched TAFA + LEN data. It is therefore unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Although not explicitly stated, if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the *average treatment effect on those treated with the comparator*."

cohort characteristics so that if there are several comparators then there can be a bias in treatment effect between comparators. This does not happen when estimating the ATT because only the comparator cohorts are adjusted in order to better match the intervention cohort characteristics. Therefore, given the need to compare to several comparators, the ERG in principle would prefer a method of adjusting for confounding that estimates the ATT."	intervention cohort characteristics. Therefore, given the need to compare to several comparators, the ERG in principle would prefer a method of adjusting for confounding that estimates the ATT."	correct as these comparisons don't allow to estimate average treatment effect on the TAFA + LEN treated population as numerous treated patients are not included in the comparisons due to lack of matchable comparator patients which entails a deviation from the efficacy population of L-MIND. As detailed in the ERG's discussion some patients who received the intervention could not be found with a match in the comparator populations .Thus the effect estimated in these analyses are not the ATE, as, as the ERG notes "ATE still requires sufficient overlap in characteristics between intervention and comparator patients to ensure that the probability of receiving the other treatment is not zero". In this situation the effect estimated would be the average treatment effect on treated patients for whom an untreated comparator could be found and not the ATE. As for the discussion provided above on the MAIC results using an assumption akin to the shared effect modifier assumption would allow to transfer these estimates back to the L-MIND population.	

		We agree with the committee however that estimations of effect using the entire L-MIND population through ATT would be preferable in principle.	
In Section 3.4 page 58-59, the following statement is included: The company were also asked to explain why they did not consider RA. In response to the request for clarification, the company stated that "regression analyses were not considered because of the observed differences in the L-MIND and observational cohorts that could have led to quasi separation of the data in the estimation of the models, particularly in the analyses against POLA+BR, and concerns over the possibility of finding good models to fit the outcomes of interest (PFS and OS)". It is unclear to the ERG what is meant by this as "quasi separation" suggests that there was very little overlap between intervention and comparator patients such that one or more characteristics might predict treatment almost perfectly, i.e. propensity score = 1 or 0.	We would ask to have the text revised to the following: "The company were also asked to explain why they did not consider RA. In response to the request for clarification, **and follow-up discussion the company stated that they believe the number of covariates that should be included in an RA is high compared with the available sample size and number of events observed. In particular similar sets of covariates would have been included in the RA as in the matching or weighting, amounting to 7 to 10 covariates (including treatment effect). This is whilst the total sample size would only include the 80 patients from the L-MIND study to whom would be added comparator patients (e.g. for POLA + BR, 36 eligible patients with complete profiles). In addition, it is important to consider that the regression models that would be considered in these analyses would consider time-to-event outcomes and thus estimation of the coefficient in these models is powered by the number of events observed, whose occurrence are in addition likely to be correlated with certain characteristics. As not all patients that would be included in the comparison would have experience an event, the estimation of the regression coefficients would have been likely to be subject to**	We agree with the ERG that the expression "quasi separation" may have cause confusion. Indeed, RA was not considered for two reasons: The number of covariates that we believe that should be included in an RA is high compared with the available sample size. The same sets as used in the propensity score matching or weighting would have been used, which amounts to 7 to 10 covariates (including treatment) that should be included in the regression model, whilst the total sample size would only include the 80 patients from the L-MIND study to whom would be added comparator patients (e.g. for POLA + BR, 36 patients). In addition, it is important to consider that the regression models that would be considered in these analyses would consider time-to-event outcomes. Estimation of the coefficient in these models is powered by the number of events observed, whose occurrence are in addition	Not a factual inaccuracy. We look forward to the company exploring the feasibility of RA during technical engagement.

However, this would have also affected the validity of IPW.	**unidentifiability and convergence issues. Furthermore, in an RA approach, the population of inference would no longer be the L-MIND population, but instead a hybrid population between the L-MIND and observational study populations. As the PSM and IPW approaches match populations to the extent possible on all the covariates available, and retain the L-MIND population as the population of inference, were considered, in principle, preferable approaches.**	likely to be correlated with certain characteristics. As not all patients that would be included in the comparison would have experience an event, the estimation of the regression coefficients is likely to be subject to unidentifiability and convergence issues. The comparison made by the committee with the IPW does not appear appropriate to the company as the RA models would be used to estimate OS and PFS and not the probability of receiving the intervention as IPW does. Therefore, we would ask for it to be removed. Furthermore, in an RA approach, the population of inference would no longer be the L-MIND population, but instead a hybrid population between the L-MIND and RE-MIND-2 study populations. As the PSM and IPW approaches match populations to the extent possible on all the covariates available, and retain the L-MIND population as the population of inference, were considered preferable approaches. Feasibility of conducting RA could be explored as part of the technical engagement.	

In Section 3.4 page 59, the following statement is included: "Inferring from all documents provided by the company and the clarification letter response, it appears that matching using the propensity score based on nine covariates to estimate the ATE was used in the base-case for comparison with the following comparators using RE-MIND2: R-GemOx (Section 3.3.1.2) BR (Section 3.3.1.1) Pola-BR (Section 3.3.1.3) R2 CAR-T"	We would ask the text to be revised to the following: "Inferring from all documents provided by the company and the clarification letter response, it appears that matching using the propensity score based on nine covariates to estimate the **ATT** was used in the base-case for comparison with the following comparators using RE-MIND2: R-GemOx (Section 3.3.1.2) BR (Section 3.3.1.1) **Matching using the propensity score based on nine covariates to estimate the average effect of treatment in those treated individuals for whom untreated matches could be found was used in the base-case for comparison with the following comparators using RE-MIND2:** **Pola-BR (Section 3.3.1.3)** **R2** **CAR-T"**	As discussed in the above, we would disagree with the ERG that the propensity score matching would allow to estimate the ATE. In general, propensity score matching allows to estimate the ATT, unless full matching is used, which was not the case in these analyses. In addition, as some of the L-MND patients could not be found a suitable match receiving one of the comparator treatments (i.e. probability of receiving the comparator is 0 or close to 0 for some patients), the ATE cannot be estimated. As discussed previously we believe that it can be assumed that the ATT are being estimated in the comparisons of TAFA + LEN and BR/R-GemOx given that almost the entire L-MIND population is retained in the propensity score matching. In the post-hoc analyses, due to slow accrual of Pola + BR, R2 and CART-T patients in the study reversed matching was performed using the comparator cohort (i.e. POLA + BR, R2 and CAR-T) as the basis to which TAFA + LEN patients were matched. This led to a departure from the L-MIND efficacy	Not a factual inaccuracy. However, the text has been amended to improve clarity: "…it appears that matching using the propensity score based on nine covariates was used in the base-case for comparison with the following comparators using RE-MIND2: It is unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Although not explicitly stated, if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the *average treatment effect on those treated with the comparator*."

		population, as noted by the ERG, and thus the estimand changed from ATT to the average effect of treatment in those treated individuals for whom untreated matches could be found.	
In Section 3.6 page 61, the following statement is included: Inferring from all documents provided by the company and the clarification letter response, it appears that matching using the propensity score based on nine covariates to estimate the ATE was used in the base-case for comparison with the following in-scope comparators using RE-MIND2: R-GemOx, BR and pola-BR. IPW to estimate the ATT appeared to be only used for pola-BR. IPW to estimate the ATT appeared to be only used for pola-BR. Overlap weights to estimate the ATE appeared to be only used for R-GemOx and BR.	We would ask the text to be revised to the following "Inferring from all documents provided by the company and the clarification letter response, it appears that matching using the propensity score based on nine covariates to estimate the **ATT** was used in the base-case for comparison with the following in-scope comparators using RE-MIND2: R-GemOx, BR. **In addition, matching using the propensity score based on nine covariates to estimate the average treatment effect on treated patients for whom a comparator untreated patients could be found was used in the base-case for comparison on the following in-scope comparator: pola-BR**. IPW to estimate the ATT appeared to be only used for pola-BR. Overlap weights to estimate the ATE appeared to be used for R-GemOx, BR and Pola + BR."	The justification for this change is provided in the previous comments. Comparative efficacy analyses of TAFA + LEN v. POLA + BR using overlap weights were also conducted and can be shared.	Not a factual inaccuracy. However, the text has been amended to improve clarity: "…it appears that matching using the propensity score based on nine covariates was used in the base-case for comparison with the following in-scope comparators using RE-MIND2: R-GemOx, BR and pola-BR. It is unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Although not explicitly stated, if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the *average treatment effect on those treated with the comparator*."
In Section 3.6 page 61, the following statement is included: "By contrast, if the MAIC is selected for R-GemOx, OS	We would ask the text to be revised to the following "By contrast, if the MAIC is selected for R-GemOx, OS results seem to be overestimated. It should be	The company acknowledged in the MAIC report the high uncertainty around the results obtained in the comparison against R-GemOx as important	Not a factual inaccuracy

results seem to be overestimated"	noted however, as acknowledged by the company, **that the results of the MAIC of TAFA + LEN v. R-GemOx face considerable uncertainty as important treatment effect modifier and prognostic factors could not be included in the population adjustment**."	prognostic factors and treatment effect modifiers could not be included in the population-adjustment.	

Issue 7 Discussion of the adjustment factor

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 4.2.6.1 page 77, the following statement is included: "It is worth noting here in addition to in Section 3.4 that the reason there is a difference is because of the ITC method employed, i.e. adjustment to estimate the ATE instead of the ATT. If only comparator patients had been selected to match the TAFA+LEN cohort or IPW had been used for all comparators, then the TAFA+LEN data would not have been adjusted as part of the ITC and no "adjustment factor" would be required. The assessment of the *"difference"* seems subjective. The "adjustment factor" was calculated by a Cox regression model fitted to data from all TAFA+LEN patients appending data from the L-MIND matched patients. This approach double	We would ask for the text to be revised with the following: "It is worth noting here in addition to in Section 3.4 that the reason there is a difference is because of the ITC method employed, i.e. **adjustment to estimate the average treatment effect on the treated patients for whom an untreated comparator could be found instead of the ATT. This was motivated by difficulties encountered in the estimation of the ATT in the comparisons conducted against POLA + BR, R2 and CAR-T.** The assessment of the *"difference"* seems subjective. The "adjustment factor" was calculated by a Cox regression model fitted to data from all TAFA+LEN patients appending data from the L-MIND matched patients. This approach double counted some patients since the L-MIND matched patients were also included in the L-MIND enrolled population. **The more standard approach that consisted in estimating Cox regression model on a covariate matched/not matched was**	As discussed earlier we do not believe that the ATE are being estimated here, but instead the average effect on the treated patients for whom an untreated comparator patients could be found. We agree with the ERG that the approach that consists in deriving an HR between the matched and unmatched population is theoretically superior and was initially considered by the company. It was not however implemented in the cost-effectiveness model the PH assumption was found not to hold for most comparisons, meaning that the use of a time-constant HR to make this adjustment would not have been appropriate. The alternative approach, currently implemented in the model, indeed	Not a factual inaccuracy. However, the text has been amended to improve clarity: "It is worth noting here in addition to in Section 3.4 that the reason there is a difference is because of the ITC method employed, i.e. adjustment that appears to estimate the *average treatment effect on those treated with the comparator* instead of the ATT."

counted some patients since the L-MIND matched patients were also included in the L-MIND enrolled population. It is unclear why the original L-MIND dataset adding a covariate matched/not matched was not be used for the analysis. This would have avoided double counting patients. The inverse of this adjustment factor provided a measure of the relationship between the overall L-MIND population against a subset of matched patients, that was further assumed to be applicable to the comparators. This means that the adjustment factor between matched and unmatched patients in TAFA+LEN arm would be the same as the adjustment factor between the matched and unmatched patients in all comparators. Since patient-level data were available for all comparators, the ERG considers that such adjustment factors might have been calculated for each arm, in order to test the assumption of equal adjustment factor across all arms. The adjustment approach relied on the proportional hazard assumption between the L-MIND and	**explored but not pursued as the PH assumption was found not to hold in most comparisons**. The inverse of this adjustment factor provided a measure of the relationship between the overall L-MIND population against a subset of matched patients, that was further assumed to be applicable to the comparators. This means that the adjustment factor between matched and the efficacy population of the L-MIND study would be the same as the adjustment factor between the matched and total comparator populations in all comparators. **Such adjustment factors were calculated for each matched subset of the TAFA + LEN population against the efficacy population for L-MIND, and were used as appropriate to adjust the comparator arms.** The adjustment approach relied on the proportional hazard assumption between the L-MIND and matched populations, **which was evaluated using cumulative hazard plots and global test of Schoenfeld residuals as although the adjustment factors conceptually are not HRs (as they measure an effect between a subset of a population and a population, rather than the effect between a population with a given characteristic and a population without the given characteristic), it is estimated from a Cox regression model and thus has the same statistical properties as an HR.**	does not provide a HR, as a HR would be estimated between a patient population with a given characteristic and another population not having this characteristic and not between a population and a subset of this population as noted by the ERG. However, the numerical estimate that is derived would have the same properties as an HR, and would therefore be submitted to the PH assumption. The PH assumption was evaluated through visualisation of the cumulative hazard plots and global test for Schoenfeld residual, and the PH assumption was found to hold across comparisons. As the subpopulation of the L-MIND study for whom a suitable comparator patient could be found differed from a comparison to another (e.g., the TAFA + LEN patients included in the PSM vs. POLA + BR are not the same patients as the one included the PFSM vs. R2), different adjustment factors were indeed derived and used as appropriate	

matched populations, however it is unclear how this was tested and if some violations were present in the analyses since the company indicated that the adjustment factor was not really a HR.“			

Issue 8 Limitations of RE-MIND2 data for Pola-BR

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Limitations with the Pola-BR RE-MIND2 data In Section 4.2.6.4.1, page 85, the following statement is included: “The company selected the lognormal distribution to model OS in the TAFA+LEN arm but argued that since the mechanism of action of polatuzumab is different to that of both tafasitamab and rituximab plus chemotherapy regimens, selecting a different type of distribution for the pola-BR arm was considered reasonable.” In Section 4.2.6.4.1, page 86, the following statement is included: “The company selected the (adjusted) generalised Gamma distribution as the most plausible candidate to model OS for pola-	For Section 4.2.6.4.1, page 85: “The company selected the lognormal distribution to model OS in the TAFA+LEN arm but argued that since the mechanism of action of polatuzumab is different to that of both tafasitamab and rituximab plus chemotherapy regimens, selecting a different type of distribution for the pola-BR arm was considered reasonable. **However, as acknowledged by the company, all parametric models produced pessimistic long-term extrapolations compared to clinical expert expectations and external data.**” For Section 4.2.6.4.1, page 86: “**For RE-MIND2, t**he company selected the (adjusted) generalised Gamma distribution as the most plausible candidate to model OS for pola-BR. Based on all the evidence presented by the company, the ERG would agree with this choice. However, it should be emphasised that even in this case, model outcomes for	Limitations with the plausibility of the Pola-BR data from RE-MIND2 were recognised by the company within Section B.3.3.1. and Appendix M of the CS, which is not clear from the statements within the ERG report.	Not a factual inaccuracy. The “pessimistic extrapolations” are explicitly mentioned for example on pages 82 and 86 of the ERG report.

BR. Based on all the evidence presented by the company, the ERG would agree with this choice. However, it should be emphasised that even in this case, model outcomes for pola-BR are unlikely to produce (clinically) valid results."	pola-BR are unlikely to produce (clinically) valid results. **The pessimistic nature of the long-term OS predictions based on the RE-MIND2 results for Pola-BR was highlighted by the company in Appendix M of the submission, and used as part of the justification for utilising the MAIC results for Pola-BR in the base case analysis.**"		
<u>Justification for use of MAIC results for Pola-BR in the base case analysis</u> In Table 4.17 (Section 4.2.6.9), the ERG states the following as the justification made by the company when deciding to use the MAIC results for the base case analysis to generate OS and PFS curves for Pola-BR: "MAIC based on clinical expert feedback and lower sample size for RE-MIND2 matched population. Time-varying HRs (apparent violation of PH assumption) with 4-month split."	Amend text to the following: "MAIC based on clinical expert feedback **regarding plausibility of extrapolations from RE-MIND 2, as well as** lower sample size for the RE-MIND2 matched population. Time-varying HRs (apparent violation of PH assumption) with 4-month split."	Plausibility concerns with the Pola-BR extrapolations were noted in Section B.3.3.1. of the CS as a justification for using the MAIC results for the base case analysis, which is not clearly stated in the ERG report.	Changed accordingly
In Section 4.2.6.4.1, page 89, the following statement is included: "The OS adjusted extrapolations for the pola-BR arm were calculated by applying an	We would propose to amend the text to the following: "The OS adjusted extrapolations for the pola-BR arm were calculated by applying an adjusting factor of 0.88 to their unadjusted	Whilst we acknowledge the criticism of the ERG on this point, as discussed earlier we don't believe that ATE were estimated in the analyses of TAFA + LEN v.	Text amended: "…because of the method of adjusting for confounding, as described above."

adjusting factor of 0.88 to their unadjusted counterparts. The ERG questions the validity of this adjustment factor, which is only applied because of a change to the TAFA+LEN cohort due to the matching to estimate the ATE as a method for the original adjustment for confounding. Had a method of adjustment for confounding been implemented that estimated the ATT, whereby there was no change in the TAFA+LEN cohort, but instead in the comparator cohort, then no further adjustment would need to be considered."	counterparts. The ERG questions the validity of this adjustment factor, which is only applied because of a change to the TAFA+LEN cohort due to the matching to estimate the **average treatment effect on treated patients for whom an untreated comparator could be found as a method for the original adjustment for confounding. The company also provided the ATT estimated from IPW which would not need this adjustment. However, the company decided not to use the ATT estimates over concerns about weight dispersion and these were not used in the base case analyses. The ERG acknowledges that the relative efficacy estimates obtained for TAFA + LEN vs. POLA + BR obtained though IPW show a stronger treatment effect in favour of TAFA+LEN compared to estimates obtained through matching (HR of 0.282 under IPTW with MI vs. 0.420 using PSM on 9 covariates with MI on OS)."**	POLA+BR in the base case from RE-MIND 2 but rather the average treatment effect on treated patients for whom an untreated comparator patient could be found. ATT estimates were derived in these comparisons through IPW, and where not used by the company due to concerns over overdispersion of weights, and thus these were not used in the base case.	

Issue 9 Clinical expert feedback for RE-MIND2 extrapolations of BR and R-GemOx

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
<u>Justification for using RE-MIND2 data for BR in the company base case analysis</u> In Table 4.17 (Section 4.2.6.9), the ERG states the following as the justification made by the company when deciding to use	Amend statement to the following: "RE-MIND2 data selected due to larger sample size **and indication from UK clinical experts**	Clinical experts suggested that RE-MIND2 extrapolations were plausible representations of UK clinical practice, which was also part of the company justification for preferring use of RE-MIND2 data for BR.	Changed accordingly

the RE-MIND2 data for the base case analysis for BR: "RE-MIND2 data selected due to larger sample size. PH assumption plausible for OS. Constant HR (2.392) applied to TAFA+LEN curve to estimate BR OS. For PFS, unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution."	**that RE-MIND2 data for BR was plausible in relation to clinical practice**. PH assumption plausible for OS. Constant HR (2.392) applied to TAFA+LEN curve to estimate BR OS. For PFS, unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution."		
<u>Comments about the plausibility of R-GemOx OS and PFS extrapolations in relation to UK clinical practice</u> In Section 4.2.6.4.3, page 92, it is stated by the ERG that, with respect to R-GemOx OS extrapolations for RE-MIND2: "The company also argued that these differences may have been related to underlying differences with the Mounier population and the small sample size in Ionescu-Ittu 2019 (10 patients in R-GemOx). Again, this raised concerns as to whether the sub-population of matched patients in the R-GemOx is representative	Amend statement to the following: "The company also argued that these differences may have been related to underlying differences with the Mounier population and the small sample size in Ionescu-Ittu 2019 (10 patients in R-GemOx). Again, this raised concerns as to whether the sub-population of matched patients in the R-GemOx is representative for UK patients who are expected to be treated with R-GemOx. **However, the company stated that UK clinical experts indicated that the RE-MIND2 parametric survival models for R-GemOx were plausible in relation to clinical practice.**"	ERG report does not acknowledge the company perspective stated in Section B.3.3.1. of the CS that, similar to BR, clinical expert feedback on the plausibility of R-GemOx extrapolations implied that the RE-MIND2 data and associated parametric extrapolations were representative of UK practice.	Not a factual inaccuracy. This text refers to the comparison of the model extrapolations vs. published data. Experts' feedback is discussed above in the same section.

for UK patients who are expected to be treated with R-GemOx.”			
Justification for using RE-MIND2 data for R-GemOx in the company base case analysis In Table 4.17 (Section 4.2.6.9), the ERG states the following as the justification made by the company when deciding to use the RE-MIND2 data for the base case analysis for R-GemOx: “RE-MIND2 data selected due to larger sample size. Limitations with MAIC for comparison against R-GemOx. PH assumption not valid for both OS and PFS. Unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution for OS and PFS.”	Amend text to the following: ““RE-MIND2 data selected due to larger sample size **and indication from UK clinical experts that RE-MIND2 data for R-GemOx was plausible in relation to clinical practice**. Limitations with MAIC for comparison against R-GemOx. PH assumption not valid for both OS and PFS. Unadjusted parametric models fitted to matched BR data were applied using a lognormal distribution for OS and PFS.”	Similar to BR, clinical experts implied that RE-MIND2 extrapolations were plausible representations of UK clinical practice, which was also part of the company justification for preferring use of RE-MIND2 data for R-GemOx.	Changed accordingly

Issue 10 General validity of extrapolations, and comparisons to NICE TA649

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
<u>General statements around face validity and external validity of OS and PFS extrapolations</u> In Table 1.1 of the executive summary, the ERG states the following as one of the key issues identified: "OS/PFS parametric extrapolations lack clinical validity" In Table 1.5, page 18, the ERG summarises Issue 4 as follows: "The ERG considered that there are issues with the validity of the OS/PFS extrapolations, especially (but not exclusively) for the pola-BR arm, which in turn resulted in cost effectiveness results very different to those obtained for example in TA649." In Section 4.2.6.9, page 109, the ERG states the following: "The ERG considers that, in general, the company have used appropriate methods to analyse OS and PFS data by either of the methods selected, i.e. parametric extrapolations of patient-level	We request that the ERG provide more specific comments on which choices made by the company they believe lack face validity with respect to clinical expert opinion and external validity in relation to published (external) data, or clinical validity in general. We also request that the ERG clarify their perspective on the UK clinical expert feedback provided for RE-MIND2 for BR and R-GemOx, and its importance in relation to the external validity of the comparisons to available published data when selecting the most appropriate approach for modelling OS and PFS.	The ERG's comments on the concerns about the validity of extrapolations chosen by the company in their base case submission appear lack specificity, and potentially overstate the possible issues identified by the ERG without acknowledging some of the statements made in the company submission. For Pola-BR, while we acknowledge some of the potential concerns raised by the ERG with respect to the Pola-BR extrapolations, the limitations of the RE-MIND2 data highlighted by UK clinical experts were clearly stated by the company and formed part of the justification for selecting the MAIC results over the RE-MIND2 study for the base-case analysis in alignment with clinical expert feedback, which does not appear to be clearly acknowledged by the ERG in the report. In addition, the ERG does not appear to acknowledge responses to clarification questions provided by the company where it was indicated that the 5-year OS prediction from the modelling	Not a factual inaccuracy. These details are provided throughout the ERG report and summarised in Table 4.18 for OS and Table 4.19 for PFS.

data or the MAIC. However, several concerns have been raised throughout this Section. In particular, the ERG considers that careful attention should have been paid to assess the plausibility of certain choices made by the company, since some of these seem to lack both face and external validity when compared to clinical experts' expectations and to available (external) data. An overview of the ERG concerns and an assessment of the validity of the company's assumptions on OS and PFS is presented in Tables 4.18 and 4.19."		approach selected for pola-BR (11.7%) in the submission were within the range of 5-year OS predictions from the dependent fit standard parametric models for Pola-BR in TA649 (~7-16%). In addition, it is not clear whether the ERG believes that this statement applies to the RE-MIND2 extrapolations selected by the company for BR and R-GemOx. In Table 4.18, the ERG notes that the clinical experts believed the OS extrapolations for BR and R-GemOx were plausible. For BR PFS, R-GemOx OS and R-GemOx PFS, base-case model selection by the company was broadly aligned with the feedback provided by clinical experts. Furthermore, it is implied by the ERG in Tables 4.18 and 4.19 that differences between BR predictions between "all approaches considered by the company" and the GO29365 trial data at 2 years are not substantial. It is also important to note that the RE-MIND2 KM curves for BR extend beyond 2 years for both OS and PFS, and therefore that 2-year model predictions (which provide broadly reasonable visual fits to the observed data) are generally reflective of the actual RE-MIND2	

		study results, rather than parametric model predictions beyond the study duration. Given this, it is unclear in which cases the ERG believes that extrapolations lack **both** face validity with respect to clinical expert opinion and validity with respect to external data. In addition, for BR and R-GemOx, it is unclear whether the ERG has taken the clinical expert feedback into consideration in their selection process for their preferred base-case assumptions (despite highlighting the importance of clinical expert feedback for TAFA+LEN and Pola-BR), how closely the ERG believes that the RE-MIND2 data should match the external studies discussed in the submission and ERG report, and whether the feedback from UK clinical experts should take precedence over comparability to external study data.	
<u>Statement around the cost-effectiveness of Pola-BR vs BR</u> In Table 4.18 (Section 4.2.6.9), the ERG states the following with respect to BR OS extrapolations: "Individual curve fitting is also possible in the model. However,	Include the following amendments, as well as more clearly state which parametric models for RE-MIND2 result in higher OS for BR and more than 2 life years (and whether this was the case in the company base-case analysis or the ERG's preferred OS parametric model for RE-MIND2):	While we agree with the ERG that potential comparisons can be drawn to the results for Pola-BR and BR from TA649, and that Pola-BR is expected to have better clinical outcomes than BR, we strongly disagree with the ERG's statement that the cost-	The first sentence has been changed as follows: "However, some curve choices result in OS BR > OS pola-BR, which seems invalid, since pola-BR has been

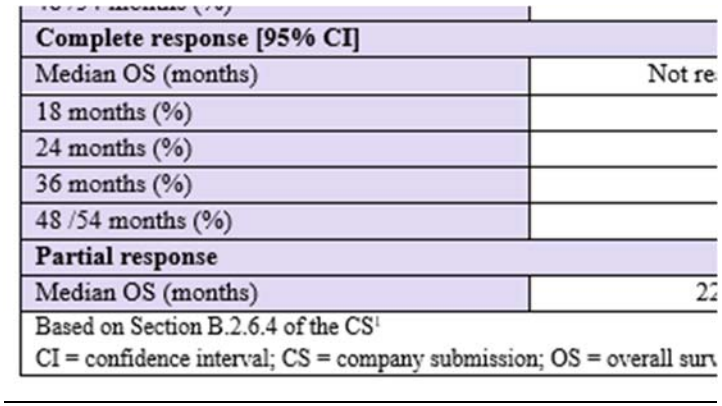
some curve choices result in OS BR > OS pola-BR, which is invalid, since pola-BR has been proven to be (cost-)effective vs. BR. Also, some choices result in more than 2 life years for BR, which according to TA649 is not possible (end of life criteria were applied)."	"Individual curve fitting is also possible in the model. However, some curve choices result in OS BR > OS pola-BR, which **seems** invalid, **given the results of the GO29365 trial**. Also, some choices result in more than 2 life years for BR, which according to TA649 is not possible (end of life criteria were applied), **although this was not the case for the company base-case (where 1.76 total life years were observed for BR)."**	effectiveness of Pola-BR compared to BR is "proven", which does not appear to be clearly justified. In addition, the ERG states with respect to RE-MIND2 model selection that "some choices result in more than 2 life years for BR, which according to TA649 is not possible (end of life criteria were applied)." However, the ERG does not state whether this is true for the company base case (where a constant HR was used to derive OS for BR compared to TAFA+LEN) or whether this is true for the ERG's preferred base case OS parametric model for RE-MIND2 for BR.	accepted to be (cost-)effective vs. BR in TA649". The second sentence is not a factual inaccuracy since the idea was to highlight some potential inconsistencies. Base-case results are discussed later in the ERG report.
<u>Comments on alignment of results between the submission and NICE TA649</u> In Table 1.5, page 18, the ERG states the following with respect to their expectations of the cost-effectiveness results: "Results, especially (but not exclusively) for the pola-BR arm, should be in line with those in TA649."	Amend sentence to the following: "Results for the pola-BR arm should **broadly align** with those in TA649. **In addition, results for BR may be expected to be similar to TA649, although it is important to note that clinical experts indicated the RE-MIND2 data for BR to be plausible representations of clinical practice.**"	The comment lacks specificity, given that the ERG's comments appear to relate specifically to results for pola-BR and BR matching TA649 results, and not necessarily R-GemOx. Particularly for BR, where a different source of data was available for the economic analysis (RE-MIND2), it is also unclear why the ERG necessarily believes that results should exactly match the results of TA649, particularly when some choices of parametric model for RE-MIND2 (and the base-case	The sentence has been changed as follows: "Results for the pola-BR arm should be broadly in line with those in TA649".

		results provided by the company) align with the ERGs broad expectations of fewer than 2 total life years for BR and are not substantially different from those produced using the MAIC results.	

Issue 11 Additional text and data clarifications in the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Appraisal numbers stated for NICE TA649 On both pages 20 and 167, it is stated that: "Results based on the alternative OS assumptions for pola-BR showed large differences with respect to the ERG base-case with QALYs varying from 1.16 to 1.47, values below what is expected from for example **TA647**." On page 158, it is stated that: "Results based on the alternative OS assumptions for pola-BR explored by the ERG (time-varying MAIC and constant HR based on RE-MIND2 data) showed large differences with respect to the ERG base-case. QALYs for the pola-BR arm varied from 1.16 to 1.47, values below what is expected from for example **TA647**."	Change appraisal number from TA647 to TA649.	Incorrect appraisal number stated.	Changed accordingly
Typing error (spelling of 'each') Section 2.2, page 25 "The recommended dosing regimen for tafasitamab is 12 mg/kg body weight administered as an intravenous (IV)	Correct spelling of 'each' "The recommended dosing regimen for tafasitamab is 12 mg/kg body weight administered as an intravenous (IV) infusion according to the following	Correction of typing error	Changed accordingly

infusion according to the following schedule (with ach cycle consisting of 28 days):"	schedule (with **each** cycle consisting of 28 days):"		
Typing error (spelling of 'lenalidomide') Section 2.5, page 27 "*According to the company, "the novel mechanism of action of tafasitamab with lenalidomise is an innovative treatment approach that has been demonstrated to be an effective, well-tolerated…"* Spelling of lenalidomide is incorrect	Correct spelling of 'lenalidomide' "*According to the company, "the novel mechanism of action of tafasitamab with **lenalidomide** is an innovative treatment approach that has been demonstrated to be an effective, well-tolerated…"*	Correction of typing error	Changed accordingly
Typing error ('support' instead of 'supporting') Section 2.5, page 27 "End-of-life criteria are discussed in Section 7 of this report and the ERG identified a key issue regarding the evidence support the end-of-life criteria."	Update text "End-of-life criteria are discussed in Section 7 of this report and the ERG identified a key issue regarding the evidence **supporting** the end-of-life criteria."	Correction of typing error	Changed accordingly
Dosing regimen for tafasitamab In Table 3.4, page 36, the dosing regimen for tafasitamab is stated as follows: "Tafasitamab (MOR00208) Anti-CD19 Antibody, 12 mg/kg, IV infusion, weekly (Cycle 1-3) to bi-weekly (Cycle 4 onwards), 4-week cycles."	Correct text to the following: "Tafasitamab (MOR00208) Anti-CD19 Antibody, 12 mg/kg, IV infusion, weekly (Cycle 1-3, **with additional loading dose on day 4 of Cycle 1**) to bi-weekly (Cycle 4 onwards), 4-week cycles."	Dosing regimen for tafasitamab is incorrectly stated for the first treatment cycle.	Changed accordingly

Table heading consistency Table 3.6, page 43 and Table 3.7, page 45. [95% CI] is missing after the “partial response” heading. 	Update table heading: “Partial response **[95% CI]**”	Update table headings for consistency.	Changed accordingly
Table formatting Table 3.10, page 49. The “median time since first DLBCL diagnosis, months” heading appears as a subcategory of race.	Bold the subheading.	Updating the formatting will make the table easier to read.	Changed accordingly
Typing error Section 3.3. Page 51. According to the CS, “as the pivotal L-MIND study of TAFA+LEN in R/R DLBCL (…) was a single-arm trial, the comparative efficacy of TAFA+LEN was assessed via 1:1 nearest-neighbour (NN) matching with external (synthetic) control arms. These data were generated from two generated in two retrospective cohort studies (RE-MIND [MOR208C206] and RE-MIND2 [MOR208C213]),21, 22 and	Update text. According to the CS, “as the pivotal L-MIND study of TAFA+LEN in R/R DLBCL (…) was a single-arm trial, the comparative efficacy of TAFA+LEN was assessed via 1:1 nearest-neighbour (NN) matching with external (synthetic) control arms. These	Correction of typing error.	Changed accordingly

a matching-adjusted indirect comparison (MAIC) against the published clinical studies of key comparators".	data were **generated in two retrospective** cohort studies (RE-MIND [MOR208C206] and RE-MIND2 [MOR208C213]),21, 22 and a matching-adjusted indirect comparison (MAIC) against the published clinical studies of key comparators".		
Repetition of text In Section 4.2.6.4.1, page 86, the following paragraph is stated twice in a row: "The adjusted OS extrapolations for the pola-BR arm were also compared to clinical trial data from Sehn et al. 2019[27, 51], and confirmed that the company analyses may have largely underestimated OS in relation to the Sehn 2019 data.[50] The company argued that these differences may have been related to underlying differences in the study populations."	Remove the second instance of this paragraph.	Repetition of this paragraph appears to be included accidentally in the report.	Changed accordingly
Representativeness of the Northend 2021 study of the UK population In Section 4.2.6.4.1, page 86, the following statement is provided: "The company argued that the differences in OS between the Northend and Sehn studies may be related to differences in the study design (RCT vs. retrospective analysis of real-world data) and the underlying patient populations. There was also no discussion as to what extent the population in Northend et al. 2021 is representative to the UK patient population.[49] Therefore, it is uncertain	Amend the text as follows: "The company argued that the differences in OS between the Northend and Sehn studies may be related to differences in the study design (RCT vs. retrospective analysis of real-world data) and the underlying patient populations **(with a proportion of patients in Northend et al. 2021 receiving Pola-BR as a bridging therapy**	The ERG report does not state one of the potential limitations with the Northend 2021 study (inclusion of patients receiving Pola-BR as a bridging therapy) highlighted by the company in the submission, which may limit the comparability of the modelled OS for Pola-BR with that shown in Northend 2021. In addition, while we agree with the ERG that more discussion	Changed accordingly

whether a comparison between the modelled and Northend OS for pola-BR is appropriate."	**prior to SCT or CAR-T)**. There was also no discussion as to what extent the population in Northend et al. 2021 is representative to the UK patient population, **although the study is based on retrospective analysis of patients from 28 UK hospitals**.[49] Therefore, it is uncertain whether a comparison between the modelled and Northend OS for pola-BR is appropriate."	could have been added around the generalisability of the Northend 2021 study to the UK, as the Northend 2021 study is based on a UK population of R/R DLBCL patients receiving Pola-BR, we believe it is important to state this in the report.	
<u>PH assumption for BR OS</u> In Section 4.2.6.4.2. of the CS, page 88, the following is stated: "The log cumulative hazard curves for TAFA+LEN and BR crossed at the beginning of the plot. After that, the company considered that the curves appeared parallel. While this might be the case, the interpretation of these plots is subjective and it could also be argued that almost up to the first half of the curves, these seem to converge, which would suggest that the PH assumption would not hold. Similarly, the linear regression for the scaled Schoenfeld residuals was broadly parallel to the 0 line. The P-value of 0.9489 generated from the Schoenfeld residuals test was interpreted by the company as suggestion that the PH assumption was appropriate. The ERG would like to emphasise that failing to reject a null hypothesis (PH in this case) is not the same as accepting the hypothesis as true. An example of this is provided by the company in the	Amend text to the following: "The log cumulative hazard curves for TAFA+LEN and BR crossed at the beginning of the plot. After that, the company considered that the curves appeared parallel. While this might be the case, the interpretation of these plots is subjective and it could also be argued that almost up to the first half of the curves **that the distance between the curves appears to narrow slightly**. Similarly, the linear regression for the scaled Schoenfeld residuals was broadly parallel to the 0 line. The P-value of 0.9489 generated from the Schoenfeld residuals test was interpreted by	ERG comments on convergence of curves on the log cumulative hazard plot are misleading, particularly when the log-cumulative hazard plot is not shown within the report. While the lines for each treatment arm do appear to come together slightly towards the middle of the plot, there is still a very clear gap between the lines, and the term "converge" implies that the lines either meet or come very close together. Statements by the ERG about the company justification for applying a constant HR based on RE-MIND2 to model BR OS are also potentially misleading.	Not a factual inaccuracy. The interpretation of the company and ERG can be different in this case.

assessment of the PH assumption for PFS in pola-BR in Section 4.2.6.7.1. In Appendix M to the CS, the company mentioned that although "the global test of proportionality from the Schoenfeld residuals test generated a non-statistically significant p value (p-value=0.1676), visual inspection of the Schoenfeld residual plot (Figure 95) showed a downward trend in the residuals over time which was non-parallel to the 0 line, suggesting that a proportional hazards assumption was not appropriate".[48] This shows that relying on the P-value only can be misleading. Thus, while the PH assumption between TAFA+LEN and BR might hold, the ERG would prefer to see a plot of the HR over time. If this resulted in a constant line, this would be a clearer indication of PH. However, also in this case the ERG prefers to follow the general recommendations in TSD 14 and since patient-level data are available, relying upon the PH assumption seems unnecessary.[44]"	the company as suggestion that the PH assumption was appropriate. The ERG would like to emphasise that failing to reject a null hypothesis (PH in this case) is not the same as accepting the hypothesis as true. An example of this is provided by the company in the assessment of the PH assumption for PFS in pola-BR in Section 4.2.6.7.1. In Appendix M to the CS, the company mentioned that although "the global test of proportionality from the Schoenfeld residuals test generated a non-statistically significant p value (p-value=0.1676), visual inspection of the Schoenfeld residual plot (Figure 95) showed a downward trend in the residuals over time which was non-parallel to the 0 line, suggesting that a proportional hazards assumption was not appropriate".[48] This shows that relying on the P-value only can be misleading, **although both the size of the p-value as well as interpretations of the log cumulative hazard and Schoenfeld residuals plots offered by the company differ**	It is implied that only the p-value for the Schoenfeld residuals test was used as a justification, despite acknowledging earlier in this section the company's interpretation of the visual plots. Furthermore, the ERG implies that the conclusions of the company with respect to assessing the PH assumption for Pola-BR are also directly applicable to BR OS. Although we agree with the ERG's comments that interpretation of the visual plots can be subjective, given the magnitude of the p-value observed for the Schoenfeld residuals test when conducting the PH assessment for BR OS compared to Pola-BR PFS, and the other observations made by the company with respect to the log cumulative hazard and Schoenfeld residual plots, we do not believe it is fully appropriate to draw a direct parallel between the two scenarios, and that the differences between the company assessments in each case of the visual plots should be more clearly acknowledged.	

	between the PH assessments for BR OS and Pola-BR PFS for RE-MIND2. Thus, while the PH assumption between TAFA+LEN and BR might hold, the ERG would prefer to see a plot of the HR over time. If this resulted in a constant line, this would be a clearer indication of PH. However, also in this case the ERG prefers to follow the general recommendations in TSD 14 and since patient-level data are available, relying upon the PH assumption seems unnecessary.[44]"		
<u>ICER results based on the PAS price</u> Throughout the report, the ICERs presented by the ERG appear to be based on a rounded % reduction in price from the list price, which produces slightly different ICERs compared to using the actual proposed PAS price.	Amend report to include ICER results based on the correct PAS price.	ICERs appear to reflect a rounded % reduction in the list price to produce the PAS price, which is slightly different from the actual proposed PAS price.	Not a factual inaccuracy. At the time of writing the ERG report the available information presented the PAS discount as a percentage to the list price. Given the tiny difference in PAS price used, it was decided in agreement with NICE that redoing all the analyses was not needed.

Technical engagement response form

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal 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 ERG report that are likely to be discussed by the committee. The key issues in the ERG report 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 ERG report.

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 ERG report 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 appraisal, 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Wednesday 6 April 2022**. 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	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Incyte Biosciences UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company's selection of comparators is narrower than the NICE final scope. R-Gem, R-P-MitCEBO, (R-)DECC, pixantrone and BSC were not included in the company submission.	No	We thank the ERG for the opportunity to further discuss the choice of key comparators in the submission. The NICE scope highlights the wide range of chemoimmunotherapy-based options available for management of relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in patients who are not eligible for stem-cell transplant (NTE; NTE R/R DLBCL).(1) A similar list of therapies is also noted in the National Cancer Research Institute (NCRI) submission provided with the technical engagement papers.(2) This wide range of therapies reflects the lack of an established standard of care (SoC) for the NTE R/R DLBCL population: the latest ESMO treatment guidelines (2015) generally recommend platinum and/or gemcitabine-based chemoimmunotherapy regimens, or participation in a clinical trial.(3) NICE guideline NG52 (2016) does not provide clear treatment recommendations for this relapsed or refractory population.(4) A systematic literature review (SLR) by Thuresson, Vander Velde, et al. (2019), of clinical studies in R/R DLBCL, also noted the lack of randomised controlled trials (RCTs) in this setting.(5) This limited availability of high-quality evidence, and the wide range of available treatment regimens, presented challenges in the selection of suitable comparators for TAFA+LEN. Additionally, completing indirect comparative analyses accounting for population heterogeneity for all possible treatments was not practical, and, in many cases, these analyses were not feasible due to difference in population characteristics, study settings or outcome definitions. In preparation for this appraisal, feasibility was completed on the available data to assess suitability for generating comparative evidence.

		On assessment of the available evidence, BR, R-GemOx and POLA+BR were selected as key comparators for the submission, with these choices confirmed by UK Clinical Experts (minutes of the interviews were shared with NICE on 06 December 2021 and discussed in the clarification responses and ERG report factual accuracy check form).(6) Regarding other NTE R/R DLBCL treatments, the following comments were made by the Clinical Experts in response to the question: *"Are there any other comparators you think should be considered for the model?"* Expert 1 noted that, while R-GDP might be used in patients at the "borderline" of fitness for more intensive therapies, this patient population is small, and including R-GDP in the model would add unnecessary complexity. Expert 2 did not think there are any other relevant comparators and noted that, although many other palliative chemotherapy regimens are used, they are probably not relevant for the TAFA+LEN population. Expert 3 noted that additional treatments such as DECC/oral combinations may be used at later therapy lines but would not be valid comparators for the population at 2L and beyond (2L+).(6) POLA+BR was relatively recently introduced to UK clinical practice following the positive NICE recommendation for England and Wales in 2020 (NICE TA649).(7) The NICE TA649 appraisal was based on data from the GO29365 study.(8) Due to this recommendation, the clinical experts consulted by Incyte suggested that, of all the regimens listed during the scoping consultation, POLA+BR was likely to be the most appropriate comparator.(6) R-GemOx was also noted as a frequently-used therapy in the UK and clinical trials internationally.(6) Expert 3 advised that use of polatuzumab vedotin (POLA) may vary between treatment centres.(6) For example, at specialist centres for CAR-T cell therapy, R-GemOx may be used more frequently for patients with NTE R/R DLBCL treated in the 2L setting because the T-cell depleting action of bendamustine-containing regimens should be avoided prior to harvesting T-cells for CAR T-cell therapy.(6) Polatuzumab vedotin (POLA) may also be used as part of 1–2-cycle regimens given as bridging treatments prior to CAR T-cell therapy.(6, 9) BR was the key comparator for POLA+BR in the GO29365 study.(8) In TA649, the NICE technology appraisal for POLA+BR [TA649 Committee Discussion Sections 3.2 and 3.3], the appraisal committee considered that BR is representative of current treatment for NTE R/R DLBCL in the UK.(7) *"…The clinical experts explained that there is no standard of care for patients with relapsed or refractory disease who are not able to have a transplant. A number of low-intensity chemotherapy regimens (with or without rituximab, depending on the amount the patient has already had) are currently used, but there is no evidence to show that one regimen is better*

		than another. The committee concluded that there is no standard of care for relapsed or refractory disease in people who cannot have a haematopoietic stem cell transplant. *…The committee therefore considered whether rituximab with bendamustine could be considered a reasonable proxy for standard of care in the NHS. The clinical experts explained that rituximab with bendamustine is not commonly used to treat diffuse large B cell lymphoma in the UK, and it is not routinely funded. However, it is standard of care in other indications such as chronic lymphocytic leukaemia. The clinical experts explained that there is a lack of information on the relative effectiveness of different treatments used in relapsed or refractory diffuse large B cell lymphoma. However, rituximab with bendamustine would not be expected to have inferior efficacy or tolerability to other treatments and therefore it would be reasonable to use it as a proxy for standard care. The committee concluded that rituximab with bendamustine is a reasonable proxy for standard of care in the NHS in relapsed or refractory diffuse large B cell lymphoma when a haematopoietic stem cell transplant is not an option."* During the Clinical Expert interviews, it was commented that BR is less frequently used in the UK following introduction of POLA+BR.(6) However, the experts noted that BR is relevant as the key comparator for POLA+BR in TA649. Based on this feedback, and because BR was considered representative of SoC for NTE R/R DLBCL in the TA649 appraisal, BR was included as a key comparator for this submission.(6) Inclusion of POLA+BR, R-GemOx and BR in this submission therefore provides an accurate representation of overall treatments and associated outcomes for patients with NTE R/R DLBCL treated in routine clinical practice in the UK, to support appraisal and decision-making for this new treatment combination.
Key issue 2: The SLR of clinical effectiveness evidence was not conducted according to best recommended practice. Problems with the search and study selection might mean that potentially relevant studies might have been missed. Furthermore, there were issues regarding data extraction and quality assessment.	No	Firstly, we would like to thank the ERG for performing the additional quality assessments and for raising these points regarding the SLR. Responses to points raised by the ERG regarding the SLR are provided below, with any relevant additional content provided in Appendix TE1. ***Presentation of search strings*** The ERG made the following comments regarding the searches: ***"****Searches were well structured, transparent and reproducible, although there were issues with documentation in places, where the search strategies had been copied into a tabular format. The Cochrane Manual recommends that "…bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved*

		by each search strategy. The search strategies should not be re-typed, because this can introduce errors"" The original search was manually entered into the bibliographic databases. The whole search, as it appeared in the search history of these databases, was then copied and pasted into the search strategy documentation presented in each SLR report as part of the appendices, and in the company submission. The search documentation was compiled to standard best practices as outlined in PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (https://osf.io/sfc38/) and the Cochrane Handbook for Systematic Reviews of Interventions Chapter 4.5 (https://training.cochrane.org/handbook/current/chapter-04#section-4-5). For the SLR update, the original search documentation was consulted and the search string in its entirety was copied and pasted in the databases. This strategy was chosen to eliminate any discrepancies that may have resulted from manually re-entering the search string. The search output was then copied and pasted directly into the search strategy documentation, as described above and presented in the SLR update report appendix. In order to ease the review process, we attach a reformatted table in Appendix TE1 with the results of the search string for the original SLR and the update. We hope this will eliminate concern regarding the accuracy of the search string. ***Search terminology*** The ERG commented as follows: "*The search strategies contained a population facet (R/R DLBCL), and for the searches of MEDLINE and Embase this was then combined with an additional facet of terms relating to treatments for the condition. The list of comparators was extensive, including many which were not listed in the NICE final scope, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used. However, the intervention, tafasitamab, was not among the drug names in the search strategy, so any studies referring to tafasitamab but not to its comparators will not have been retrieved by the MEDLINE or Embase searches. The Evidence Review Group (ERG) believes that this omission may have resulted in potentially relevant records being missed by the searches, however without re-running the searches, it is unclear what effect this may have had on recall. The abbreviation 'Pola-BR' was also missing from the strategies, although polatuzumab is included as subject indexing and free-text search terms."* Thank you for the opportunity to clarify the search terms considered in the SLR. The search terms polatuzumab vedotin, bendamustine, and rituximab were all included in the search strings. The

		combination POLA BR was not included as this was redundant and did not lead to any additional papers identified by the searches. We have re-confirmed that no papers were excluded due to this search strategy. Tafasitamab was not included in the search terms as at the time of the original SLR, it was not approved for use in the UK. Tafasitamab has been licensed for use with lenalidomide, which was included in the search terms. A subsequent search of PubMed restricted only to the search term "tafasitamab" resulted in 39 studies and confirmed that no citations were missed by the original or update SLRs. All citations captured included the search terms lenalidomide or rituximab, which were part of the original and update SLR search strings. ***Data extraction methodology*** The ERG commented as follows: "*Extraction of study level details and baseline data by a single reviewer followed by independent checking by a second reviewer is acceptable. However, dual, independent data extraction with a pre-specified approach for achieving consensus is the recommended practice for extracting outcome data in order to minimise errors in estimates of effect. The ERG considers that the outcome data and resulting estimates may be at risk of inaccuracies in light of the process employed by the company."* We appreciate the opportunity to further clarify and explain the data extraction methodology used in the SLRs presented in this submission. The data were extracted independently with a pre-specified approach by personnel who were trained on the data extraction process following best practices as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The clinical effectiveness SLR conducted for this submission was comprehensive and identified a total of 8,638 citations originating from peer-reviewed literature and grey literature sources. In order to complete the SLR in an appropriate and relevant timeframe for the submission process, it was necessary to adapt the data extraction process to an acceptable modified practice whereby both extractors (SGB and ACI) acted as reviewers of the others work. Additionally, the data were verified by a third reviewer (KT) during the drafting of the report. Therefore, although the extraction process was not conducted according to best recommended practice, it is fit for purpose with minimal risk of errors. ***Inclusion criteria: language*** The ERG commented: *"The ERG believes that narrowing down the inclusion criteria to only studies published in English or French languages might have missed potentially relevant studies, i.e., has the potential to introduce bias."*

		We apologise for any confusion the protocol may have caused. The original and SLR update searches were not restricted to English and French. This was a screening criterion implemented due to the number of citations returned from the searches. We have subsequently reviewed the search outputs and confirmed that no papers were excluded due to language restriction (they were all excluded based on other PICOS criteria). After the initial screening, only English studies were retained for a second full-text screen and subsequent data extraction. ***Inclusion criteria: Date ranges*** The ERG commented as follows: *"The consideration that economic evidence of tafasitamab may have been published prior to 2010 is inconsistent with the consideration that no evidence of clinical effectiveness was published prior to 2010."* We thank the ERG for highlighting this important point and allowing us to further explain the rationale behind this decision. The treatment of R/R DLBCL is a rapidly evolving area. The decision to use the 2010–2021 dates in the search criteria of the clinical SLR was based on the recent and more relevant clinical treatment guidelines for this disease state. The search strategy focused the many studies identified by the SLR to include all clinical evidence that was relevant to inform the NICE submission. Fewer studies were identified in the economic SLR (N=674 vs. N=8,638 in the clinical SLR), therefore, a wider date range (2000–2021) was searched. ***Use of EMBASE for congress searches*** The ERG commented: *"A good range of databases, clinical trials registers and additional grey literature resources were searched. Searches of conference proceedings were undertaken via Embase, although it is not clear if all relevant conferences are indexed by this database."* We attach an Excel spreadsheet detailing the congresses included in the EMBASE database. Over 7,000 conferences are included, with many focused on lymphoma. We have confirmed that all of the major congresses that focus on cancer and more specifically on lymphoma were searched, including: American Society of Hematology (ASH); American Society of Clinical Oncology (ASCO); European Haematology Association (EHA); European Society for Medical Oncology (ESMO); International Conference of Malignant Lymphoma (ICML); and Value in Health/International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

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<td>Key issue 3:
Questionable validity of ITCs and a number of potentially relevant analyses have not been provided.</td>
<td>Yes</td>
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We appreciate the complexity of the analyses within this submission and thank NICE and the ERG for this opportunity to clarify which analyses are available, provide any relevant additional analyses for completeness and confirm the validity of the ITCs.

Firstly, we provide a visual overview of the analyses available with 1:1 matching, overlap weighting and IPTW methods for each comparator, alongside their location in the submission, and the rationale if any particular analyses were not conducted, in Appendix TE2. We also provide forest plots showing the hazard ratios (HRs) and 95% confidence intervals (CIs) to show consistency of the results with different sensitivity analyses for each comparator in the same appendix.

Secondly, as discussed during the technical engagement call, we have evaluated the feasibility of conducting regression analyses with the RE-MIND2 data through Cox regression models. Results of these analyses were aligned with results obtained with other methodologies and are presented in Appendix TE2b below.

Briefly, Cox-regression models were implemented and used the 9 covariates included in the RE-MIND2 base case adjustment as bias-controlling factors (age, Ann-Arbor staging, refractoriness to last therapy, number of prior lines of therapy, history of primary refractoriness, prior ASCT, elevated LDH, anaemia at baseline, neutropenia at baseline). Due to the reduced size of the cohort of POLA+BR-treated patients in RE-MIND2 with complete profiles (n=36), additional sensitivity models for the comparison of TAFA+LEN vs. POLA+BR using multiple imputation (MI) and using 6 covariates in the adjustment (age, refractoriness to last therapy line, history of primary refractoriness, number of prior lines of therapy, prior treatment with ASCT, and ECOG) with MI were explored.

Results from these analyses should be treated with caution as the proportional hazard assumption was found not to hold for some models. This is summarised in the table below, where a cross indicates a suspicion of non-proportionality of hazards.

<table>
<tr><th></th><th>TAFA+LEN vs. BR</th><th>TAFA+LEN vs. RGemOx</th><th>TAFA+LEN vs. POLA+BR – 9 covariates</th><th>TAFA+LEN vs. POLA+BR – 9 covariates with MI</th><th>TAFA+LEN vs. POLA+BR – 6 covariates with MI</th></tr>
<tr><td>OS</td><td>×</td><td>×</td><td></td><td></td><td></td></tr>
<tr><td>PFS</td><td>×</td><td>×</td><td></td><td></td><td></td></tr>
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		Follow-up analyses are also being conducted and will be shared when available, although we acknowledge that the timelines may not allow consideration of the evidence prior to the Appraisal meeting. Finally, regarding the MAIC of TAFA+LEN compared with POLA+BR in GO29365, we would like to expand on the statistical and clinical rationale for use of the time-varying HR, implemented as piecewise constant hazards with a 4-month split, which forms the company's base case. The ERG note in their report (Table 1.5) that *"Results for the pola-BR arm should be broadly in line with those in TA649."* Accordingly, for the current submission, a constant hazard ratio was implemented for the TAFA+LEN vs. POLA+BR comparison in the ERG's base case. However, the estimates obtained from TA649 were based on extrapolation from a clinical trial, which might not be fully representative of the clinical effectiveness of POLA+BR in a real-world setting where median OS was lower than in TA649 (discussed further in response to key issue 6).(5, 9-11) In addition, testing of the proportional hazard (PH) assumption demonstrated that the PH assumption did not hold when comparing TAFA+LEN and POLA+BR. Upon visual inspection, a change in the pattern of the hazards could be found for TAFA+LEN at approximately 4 months. Furthermore, the choice of a 4-month split for piecewise constant hazards is supported by both statistical and clinical rationale: • There are some major differences in treatment administration between TAFA+LEN and POLA+BR that should be noted. While TAFA+LEN followed by tafasitamab monotherapy is a treat-to-progression regimen, by protocol, POLA+BR can be administered to patients for a maximum of six 21-day cycles. This on-treatment period for POLA+BR lasts approximately 4 months; the use of a separate HR from the fourth month onwards therefore corresponds with the period when patients were no longer receiving treatment with POLA+BR. Investigation of the baseline characteristics of patients still at risk of events (death or progression-free survival [PFS; disease progression or death] events) highlighted that the nature of the L-MIND population still alive and progression-free changed over time. For instance, using a 4-month threshold showed that patients who died or progressed or died early were characterised by worse ECOG performance status and a higher number of prior therapy lines. Hence, there may not have been sufficient time for a response to TAFA+LEN to be achieved. Complete comparison of the baseline characteristics of patients who died or progressed or died within 4 months of treatment

versus patients still alive or alive and progression-free after 4 months are presented in

OS – HR of TAFA + LEN v. RGemOx across analyses

PFS – HR of TAFA + LEN v. RGemOx across analyses

- Appendix TE3. These points provided a statistical rationale for use of piecewise constant HRs using 4 months as a threshold to capture the differential benefit of TAFA+LEN vs. POLA+BR observed in patients still alive or alive and progression-free after 4 months on treatment.
- A potential challenge to using time-varying HRs in the form of piecewise constant HRs lies in the potential for time-assessment bias in surrogate outcomes analyses. Assessment of time

		bias may arise when comparing treatment arms in which different assessment of a surrogate outcome (such as progressive disease) are used.(12) Surrogate outcomes are only observed at the next disease assessment visit and thus a difference in the disease assessment schedules between sources can introduce bias in the assessment of relative efficacy between treatments. In particular, when using piecewise constant HRs, if the splitting point corresponds to a timepoint when only one of the two treatment cohorts had a scheduled surrogate endpoint assessment, some bias in favour of the other treatment could be introduced. However, it is important to note that the design of the L-MIND study and of the GO29365 trial allow an accurate characterisation of progressive disease events at 4 months, as a clinical assessment of PFS was scheduled in L-MIND at around 4 months and in GO29365 at the end of the study treatment administration period. Therefore, it is expected that disease progression events would be accurately captured in both studies without time-assessment bias when using the 4-month split. • In addition, timing of the responses achieved by patients treated with TAFA+LEN or POLA+BR could also explain the change in hazards. Approximately 80% of responses were achieved by 4 months for both treatments, but some responses were achieved much later by patients under TAFA+LEN. The median time to first response with POLA+BR has been reported as 2 months (range: 1.8 to 5.3 months).(13) For TAFA+LEN in L-MIND, median time to first response was 2.05 months, with a wider range of first-response times seen with TAFA+LEN than with POLA+BR (range: 1.7 to 34.7 months); which may be explained by TAFA+LEN being administered until the disease progresses. During the first 4 months, response rates for POLA+BR were 18% higher than for TAFA+LEN, indicating a stronger treatment effect initially. However, while POLA+BR treatment was stopped after 4 months, patients continued receiving TAFA+LEN followed by tafasitamab monotherapy; existing response to TAFA+LEN then deepened over time in some patients. In L-MIND, 25% of complete responses (CRs) with TAFA+LEN were observed after 11.1 months, with a median time to CR of 6.80 months (range: 1.7 to 46.3 months; interquartile range [IQR]: 2.20 to 11.10 months). We have been unable to find equivalent data on time to CR for POLA+BR in GO29365. However, in a real-world study of POLA+BR as a salvage or bridging regimen, the median time of first computed tomography (CT) response assessment was 39 days (~0.3 months), range: 9 to 124 days (up to ~4.1 months). The median time to best CT response was 42 days (~1.4 months), range: 9 to 200 days (up to ~6.6 months).(14) • In addition, duration of response was found to be longer with TAFA+LEN than with POLA+BR from the MAIC results. As a result, the initial advantage of POLA+BR is counterbalanced and reversed by the deepening of the response and the improvement in the duration of response

		in patients treated with TAFA+LEN compared to POLA+BR (HR of 0.34 (0.12, 0.98) [p-value of 0.045]). Thus, the use of different HRs on OS and PFS between the first 4 months on treatment and the months after these 4 months would also be justified to better capture the initial advantage of POLA+BR on response rates, followed by the advantage in favour of TAFA+LEN carried by the improvement of responses overtime and the advantage observed on duration of responses. • The wider range of times to response for some patients treated with TAFA+LEN versus POLA+BR may reflect the difference in treatment duration (~4 months for POLA+BR vs. treat to progression for TAFA+LEN)), and/or the different mechanisms of action of the two agents: POLA+BR is a rituximab-based chemotherapy combination (containing bendamustine). TAFA+LEN is a chemotherapy-free therapy comprising two immunotherapy agents with potentially synergistic mechanisms of action. Response to TAFA+LEN is therefore expected to deepen over time for some patients, whereas chemotherapy-based agents tend to show a faster response which may not commonly deepen over time since therapy regimen is given over a fixed duration. Together, these factors provide a strong clinical and statistical rationale for a time-varying hazard ratio with 4-month piecewise split to capture a differential effect of TAFA+LEN compared with POLA+BR.
Key issue 4: OS/PFS parametric extrapolations lack clinical validity, especially for pola-BR.	Yes	In Table 1.5 of the ERG report, the ERG describes the issue as follows: *"The ERG considers that there are issues with the validity of OS/PFS extrapolations, especially (but not exclusively) for the pola-BR arm, which in turn resulted in cost effectiveness results very different to those obtained for example in TA649."* The ERG also describes the expected effect on the cost-effectiveness estimates as follows: "*Results for the pola-BR arm should be broadly in line with those in TA649".* This suggests that the ERG's concern regarding clinical validity is primarily related to Pola-BR, and that the ERG's perspective is that the results for Pola-BR and BR should broadly align with those from TA649. During the technical engagement call with NICE and the ERG, the ERG confirmed that their primary concern was the validity of OS extrapolations for POLA+BR, with some possible concerns about the extrapolations of BR in relation to results generated in TA649. As such, this implies that the concerns from the ERG regarding the clinical plausibility of extrapolations are narrower than what may be suggested by their summary statement for Key Issue 4 and the description of the issue stated in Table 1.5 of the ERG report. In addition, as the

ERG's concerns about extrapolations appear to be primarily based on comparisons to the extrapolations and results from NICE TA649, this implies that the ERG's perspective on the MAIC-based extrapolations may be more appropriate to classify as "external validity" concerns rather than necessarily "clinical validity" concerns. As such, we would welcome the ERG to provide further confirmation on whether there were other clinical validity considerations involved in their decision-making process.

For the submission, to the best of our knowledge, the most suitable available evidence was utilised for each comparator to perform indirect treatment comparisons in line with NICE guidance.

For the MAIC-based extrapolations for POLA+BR, which were selected instead of RE-MIND2-based extrapolations based on clinical expert feedback, time-varying HRs were chosen for the company base case analysis over a constant HR on the basis of a clear violation of the PH assumption. This was shown by the log-cumulative hazard plots for both OS and PFS (in line with recommendations from NICE DSU TSD 14), where the hazard plots clearly crossed and were non-parallel for the majority of follow-up, with a change in the pattern of TAFA+LEN hazards observed from approximately 4 months. Furthermore, as highlighted in response to Key Issue 3, differences were also observed in the patient characteristics for TAFA+LEN patients in L-MIND who died or progressed within the first 4 months compared to after 4 months, as well as differences between TAFA+LEN and POLA+BR in treatment administration schedules, timing of responses and inclusion of chemotherapy within the dosing regimen; these factors provide a strong clinical and statistical rationale for use of a time-varying hazard ratio with 4-month piecewise split to capture a differential effect of TAFA+LEN compared with POLA+BR.

Furthermore, the table below provides a summary of the MAIC-based extrapolation results in comparison to available UK real-world evidence from Northend 2022 (9) as well as a Japanese study (Terui 2022 (11)); two recent POLA+BR studies identified from a pragmatic literature review that included second line patients:

Comparison of MAIC-based extrapolations against GO29365 trial data and Northend 2022 for Pola-BR.(9, 15)

Outcome	POLA+BR Efficacy Data Source				
	MAIC - time-varying HR (Company base-case)	**MAIC - constant HR (ERG base-case)**	**Northend 2022 - stand-alone treatment cohort (N=76)**	**Northend 2022 - all patients (N=131)**	**Terui 2022 (N=35)**

Median (95% CI) OS, months	14.8	18.7	10.2 (5.2-14.3)	8.2 (5.9-14.3)	Not reached (8.4-NE)
OS at 1 year	57.9%	60.9%	NA	~43%	~59%
Median (95% CI) PFS, months	10.8	15.3	5.4 (3.0-10.8)	4.8 (3.7-9.3)	5.2
PFS at 1 year	39.4%	51.7%	NA	~28%	~38%

Abbreviations: CI = confidence interval; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; NA = not available; OS = overall survival; PFS = progression-free survival.

The table above shows that for OS, available median OS data for the stand-alone treatment cohort from Northend 2022 was substantially lower than MAIC constant HR extrapolation (10.2 months vs 18.7 months) and closer to the median estimate from the time-varying HR extrapolation (14.8 months). Median PFS data from both Northend 2022 (5.4 months) and Terui 2022 (5.2 months) was also much lower than the median PFS estimate produced by the constant HR extrapolation (15.3 months), and closer to the constant HR estimate (10.8 months). This was also the case for the 1-year PFS estimate from Terui 2022 (~38%), which was well aligned with the time-varying HR PFS estimate at 1 year (39.4%) and substantially lower than the constant HR value (51.7%).

While these naïve comparisons against available published data should be interpreted with some caution, the tables above indicate that observed survival for POLA+BR from real-world evidence may be much lower than produced by the extrapolations produced by the constant HRs for OS and PFS generated from the MAIC, and were closer to the time-varying HR values (although these also appeared to potentially overpredict OS and PFS for POLA+BR).

In addition, the statement for Key Issue 4, as well as those provided in Table 1.5 of the ERG report, do not appear to account for the clinical expert feedback on the RE-MIND2 OS extrapolations for BR and R-GemOx, even though the ERG notes in Table 4.18 that the clinical experts believed the OS extrapolations for BR and R-GemOx were plausible. For BR PFS,

		R-GemOx OS and R-GemOx PFS, base-case model selection by the company was broadly aligned with the feedback provided by clinical experts (with BR OS generated in the company base case through a constant HR from RE-MIND2 due to the proportional hazards assumption appearing reasonable). The ERG also indicates in Tables 4.18 and 4.19 that differences between BR predictions between "all approaches considered by the company" and the GO29365 trial data for BR at 2 years are not substantial. It is also worth highlighting that the RE-MIND2 KM curves for BR extend beyond 2 years for both OS and PFS, and therefore the 2-year model predictions (which provide reasonable visual fits to the observed data) are generally reflective of the actual RE-MIND2 study data, rather than parametric model predictions beyond the study duration. We would welcome the opportunity for the ERG to further clarify their concerns around the clinical or external validity of the extrapolations for each comparator, and their perspective on the UK clinical expert feedback collected for the RE-MIND2 study during the appraisal process for BR and R-GemOx.
Key issue 5: The company's assumed reduced price for lenalidomide should not be used.	No	We understand the position taken by the ERG to apply the list price of lenalidomide in the cost utility assessment for this appraisal. And indeed, generic lenalidomide was not available at the time of writing the ERG report. The company acknowledges that the ERG's role is to identify inaccuracies, especially those that can impact patients and/or healthcare spending. From the company's perspective, the spirit of the NICE assessment is to evaluate costs and benefits over the years ahead, not only at the specific instant of submission. Therefore, we included an estimation of the price of generic lenalidomide to reflect the situation in the market on the expected date of reimbursement of tafasitamab by NICE and for the years ahead. Lenalidomide (Revlimid) patent exclusivity was due to expired in Q1 2022. This has prompted product licencing of a range of different lenalidomide generic products as notified publically through the MHRA website. This has prompted a generic tender process which Incyte understands is currently underway – to support the affordable procurement of generic lenalidomide to the Health Service (available at: https://bidstats.uk/tenders/2021/W42/761266484).(16) By the time this appraisal runs its course, the cost of lenalidomide to the NHS is forecast to fall dramatically and the company notes this is already happening in countries like Italy, Spain, France and Ireland where there has been a significant cut to the list price for lenalidomide. [redacted].

		Historically other branded drugs have had price drops to below 10% of their originator price after loss of exclusivity in the UK.(17) Incyte would appreciate the ERG's reconsideration of its position regarding applying the full branded price of lenalidomide in its assessment. If there are any obstacles to this, or concerns that the prices won't drop as these proxies predict, Incyte is willing to engage further on this matter.
Key issue 6: The supporting literature for the company's claim for meeting the end-of-life criteria has limited relevance to the population in the submission.	No	We appreciate the opportunity to clarify that TAFA+LEN qualifies for NICE end-of-life criteria for patients with NTE R/R DLBCL. The end-of-life criteria are as follows: • *Criterion 1:* The treatment is indicated for patients with a short life expectancy, normally less than 24 months. • *Criterion 2:* There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. In this response, we confirm relevant literature supporting survival for patients with NTE R/R DLBCL, discuss the implications of introduction of POLA+BR into the NTE DLBCL treatment pathway and discuss how TAFA+LEN is highly likely to provide more than an additional 3 months of life expectancy compared with current treatments, including POLA+BR. ***End of life criterion 1*** An SLR conducted by Thuresson, Vander Velde, et al. (2019) identified 19 studies of patients with R/R DLBCL, including six randomised controlled trials (RCTs) and 13 prospective, observational, single-arm trials (as noted in Section B.1.3.5 of the company submission).(5) The review reported a median OS range between 5.0 to 22.2 months (n=11 studies).(5) The upper limit of this range is below the 24 months stated in criterion 1. Analysis of a US healthcare database in patients with NTE R/R DLBCL receiving bendamustine, gemcitabine-based chemoimmunotherapy or lenalidomide (N=383, 2011–2018) also showed a median survival time within this range. Median OS was 8.7 months (95% CI: 6.9, 11.1) for all patients and 13.6 months (95% CI: 8.8, 16.1) when considering patients treated at 2L only.(10) Consistent with this range of survival times, median OS in the RE-MIND2 systemic therapies pooled cohort (N=3,454; using L-MIND data cut-off 30 October 2020), was 11.6 months (95% CI: 8.8, 16.1), and OS estimates at 24 months were 36.3% (95% CI: 25.0, 47.6%). These data further indicate that patients with R/R DLBCL meet end-of-life criterion 1.(18) POLA+BR is a recent introduction to the NTE R/R DLBCL treatment pathway. In the GO29365 study, POLA+BR demonstrated superior survival versus BR for patients with NTE R/R DLBCL. In

		GO29365, POLA+BR was associated with a median OS (95% CI) of 12.4 months (9.0, not reached) compared with 4.7 months (3.7, 8.3) with BR.(8) An updated analysis was recently published, which confirmed the results of GO29365, with a median OS of 12.4 months (95% CI: 9.0, 32.0) with POLA+BR vs. 4.7 months (95% CI: 3.7, 8.3) with BR.(15) Median OS in an extension cohort (n=106) was similar at 12.5 months (95% CI: 8.2, 23.1).(15) These median OS values are substantially below the 24 months indicated in end-of-life criterion 1. A pragmatic search highlighted a lack of RCTs or real-world studies for POLA+BR in the 2L+ NTE R/R DLBCL population; a majority of studies identified were conducted in patients at later therapy lines and/or different treatment settings such as bridging to CAR-T cell therapy. A median OS estimate of 10.2 months (95% CI: 5.2, 14.3) was reported in the Northend et al. 2022 retrospective, multicentre UK study in patients receiving POLA+BR as standalone therapy due to ineligibility for CAR T or SCT,(9) below the OS estimate reported in the GO29365 study. Median OS was not reached in a Japanese open-label phase II study (95% CI: 8.4, not evaluable); the median follow-up in this study was 5.4 months.(11) It is important to acknowledge that several factors may make assessment of end-of-life criterion 1 challenging: There is heterogeneity within the NTE R/R DLBCL population, which encompasses a range of patient and disease characteristics that can impact survival. Furthermore, there remains no established SoC in the R/R transplant-ineligible DLBCL population.(2) While many patients receive POLA+BR, this may be as a 2L+ standalone therapy, but treatment may also be received in other settings such as bridging to CAR T.(9) In addition, clinical expert advice indicated that a proportion of patients in the UK are still receiving other therapeutic options, including R-GemOx.(6) Therefore, the patient population should be viewed as a whole when considering end-of-life criterion 1. The REMIND-2 pooled analysis described above is a recent analysis in a large population of patients with NTE R/R DLBCL showing that the median OS substantially below 24 months (median OS: 11.6 months), with approximately 65% of patients surviving less than 24 months.(18) Therefore, TAFA+LEN meets end-of-life criterion 1. ***End of life criterion 2*** Tafasitamab provides more than 3 months life expectancy compared with current treatments and is highly likely to provide more than 3 months life expectancy versus POLA+BR for patients with NTE R/R DLBCL.

		• The RE-MIND2 1:1 matched comparison of TAFA+LEN in L-MIND versus R-GemOx and BR in a retrospective real-world cohort indicated that TAFA+LEN provides an additional OS of 20.6 months (median OS with R-GemOx: 31.6 vs. 11.0 months) and 21.7 months (median OS with BR: 31.6 vs. 9.9 months) vs. BR and R-GemOx respectively.(18). • The OS in L-MIND was 33.5 months, providing an additional 13 months' survival compared with the 22.2-month upper limit of the survival range reported in the SLR by Thuresson, Vander Velde et al. (2020).(5, 19) • Comparison with POLA+BR is more challenging due to variation between the populations in L-MIND and GO29365. Therefore, we consider survival in the adjusted L-MIND population in the MAIC. o Restricted mean survival time (RMST) in the MAIC was 31.96 months (standard error [SE]: 2.52) with TAFA+LEN unadjusted; 30.6 months (SE 4.58) with TAFA+LEN weighted to the GO29365 study population, and 23.36 months (SE 3.6) with POLA+BR, indicating an >8 month increase in survival in this population overall. o Median OS in the MAIC weighted to the GO29365 study population was 34.1 months vs. 12.5 months, which is a 22 months of additional survival time *(non-adjusted L-MIND OS = 33.5 months; the OS curves cross towards the end of follow-up)* This indicates that TAFA+LEN provides more than an additional 3 months survival compared with current treatments, including POLA+BR, and meets end of life criterion 2.

Additional issues

Table 3 Additional issues from the ERG report

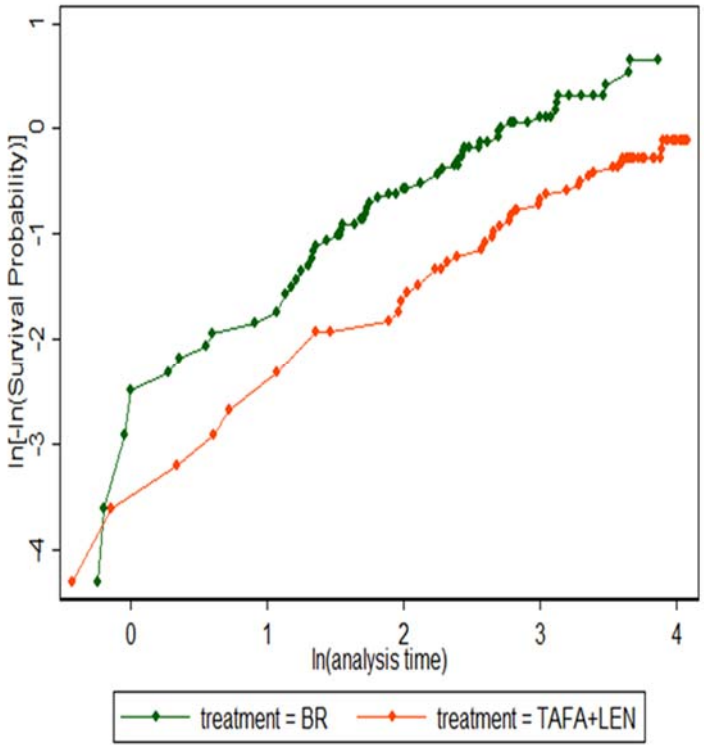
Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Consideration of tafasitamab inclusion in the Cancer Drugs Fund	N/A (Discussion at the technical engagement call)	No	We would like tafasitamab to be considered for inclusion in the Cancer Drugs Fund, should the Appraisal Committee still consider that there remains a high degree of uncertainty. A robust clinical development programme for TAFA+LEN is in progress in DLBCL and other haemato-oncology indications. This clinical development programme forms part of the conditional marketing authorisation in the UK (MHRA) and Europe (EMA). Details of the ongoing studies are provided in Appendix TE4 (updated version of table 19 in document B of the Company Submission) to include estimated completion dates and the FRONT-MIND study. Ongoing studies of tafasitamab in DLBCL are taking place in the R/R setting and the 1L setting. • Ongoing data collection in L-MIND will provide additional maturity to the data, with approximately [redacted] months' longer follow up for clinically relevant endpoints such as OS, PFS and DoR to address uncertainty in survival extrapolations, in addition to longer-term safety data. • The L-MIND2 study is currently being designed. This study will provide data similar to the L-MIND study to fulfil conditions for regulatory approvals • B-MIND will provide comparative efficacy data with TAFA+B vs. BR in the RCT setting. • The FIRST-MIND and FRONT-MIND studies will also assess whether TAFA+LEN could provide added benefit in the 1L DLBCL treatment setting. • An expanded access study for tafasitamab in patients with R/R DLBCL(20) Together, these studies will provide additional patient years of follow up and exposure to tafasitamab to address uncertainty regarding long-term safety of tafasitamab.
Additional issue 2: Generalisability of L-MIND to the UK population with R/R DLBCL who are not eligible for transplant	3.2.1	No	In Section 3.2.1 of their report, the ERG commented on a point in the company's response to the ERG's clarification questions regarding the generalisability of the L-MIND population to the NTE R/R DLBCL population in England and Wales. In the clarification responses, we noted the lack of real-world studies in the NTE R/R DLBCL setting, but discussed the retrospective observational study of pixantrone in 3L+ R/R DLBCL by Eyre et al. (2016),(21) stating that "it is important to note that the observational cohort study and L-MIND are not directly comparable as pixantrone is reimbursed for third- or fourth-line treatment only in the UK, and this is reflected in the

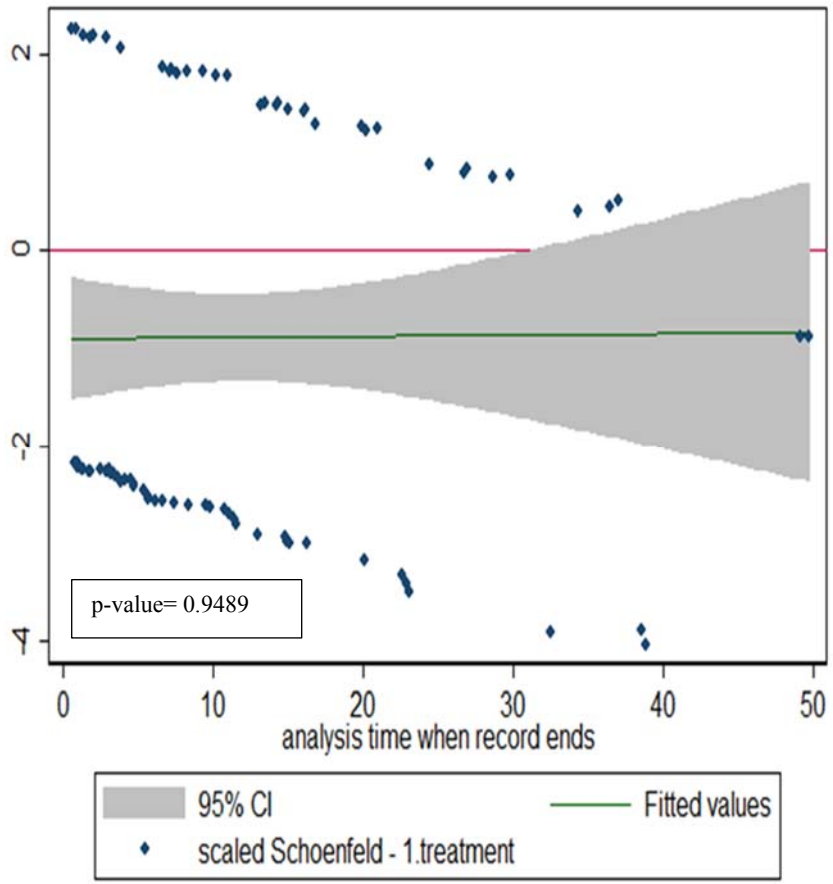
			observational study population, whereas 50% of the L-MIND population were treated in the second-line setting." While the pixantrone observational study provides context for describing the population in UK clinical practice, the study is in patients in the 3L+ setting only and therefore has a higher proportion of patients with primary refractory disease. Therefore, this study is not fully representative of the 2L+ NTE R/R DLBCL population. We acknowledge that the wording "this is in alignment with clinical expert feedback regarding the population in routine clinical practice" provided in clarification may have caused confusion. The clinical experts were referring to the population in the 2L+ setting, where they indicated that there is a slightly higher proportion of patients with refractory disease vs. L-MIND. In the 3L+ setting, as in the Eyre et al. retrospective observational study, more patients with high-risk factors such as refractory disease would be expected. This was not clear in the excerpt cited from the clarification responses. Furthermore, additional baseline characteristics data from the Northend et al. real-world study for the POLA+BR standalone treatment cohort have become available since the company's clarification question responses were submitted (n=78).(9) Baseline characteristics in this standalone therapy cohort who are not eligible for CAR T or ASCT are broadly similar to those in L-MIND. For example, median age was 75 (range 41, 88) versus 72 (IQR: 62, 76) in L-MIND; 55.1% of patients were treated at 2L versus 50% in L-MIND; 57.7% were refractory to their last line of treatment versus 44% in L-MIND; 28.2% had bulky disease versus 19% in L-MIND).(9, 22) This further supports the generalisability of L-MIND to the UK general population with NTE R/R DLBCL.
Additional issue 3: Serious adverse event (SAE) data for the L-MIND and MOR208C201 studies	3.2.1.2, 3.2.2 and 3.6	Yes	The ERG noted that details of the SAEs that occurred in L-MIND and the MOR208C201 study were not provided. We thank the ERG for this comment and provide the SAE data in Appendix TE5 below (L-MIND in Table 20; MOR208C201 in Table 21).
Additional issue 4: Assessment of proportional hazards between TAFA+LEN	4.2.6.4.2	No	In the ERG report, the following statement is made regarding assessment of the PH between TAFA+LEN and BR for the OS extrapolation using the RE-MIND2 data: "*The log cumulative hazard curves for TAFA+LEN of and BR crossed at the beginning of the plot. After that, the company considered that the curves appeared parallel. While this might be the case, the interpretation of these plots is subjective and it could also be*

and BR OS for RE-MIND2			*argued that almost up to the first half of the curves, these seem to converge, which would suggest that the PH assumption would not hold.* *Similarly, the linear regression for the scaled Schoenfeld residuals was broadly parallel to the 0 line. The P-value of 0.9489 generated from the Schoenfeld residuals test was interpreted by the company as suggestion that the PH assumption was appropriate. The ERG would like to emphasise that failing to reject a null hypothesis (PH in this case) is not the same as accepting the hypothesis as true. An example of this is provided by the company in the assessment of the PH assumption for PFS in pola-BR in Section 4.2.6.7.1.* *In Appendix M to the CS, the company mentioned that although "the global test of proportionality from the Schoenfeld residuals test generated a non-statistically significant p value (p-value=0.1676), visual inspection of the Schoenfeld residual plot (Figure 95) showed a downward trend in the residuals over time which was non-parallel to the 0 line, suggesting that a proportional hazards assumption was not appropriate".[48] This shows that relying on the P-value only can be misleading. Thus, while the PH assumption between TAFA+LEN and BR might hold, the ERG would prefer to see a plot of the HR over time. If this resulted in a constant line, this would be a clearer indication of PH. However, also in this case the ERG prefers to follow the general recommendations in TSD 14 and since patient-level data are available, relying upon the PH assumption seems unnecessary.[44]*" We believe that these statements by the ERG about the company justification for applying a constant HR based on RE-MIND2 to model BR OS, as well as comparisons drawn to the PH assessment for POLA+BR PFS for RE-MIND2, may be misleading. Although the ERG appears to acknowledge some of the company's specific interpretation of the visual plots for BR OS, the statement that *"this shows that relying on the P-value only can be misleading"* implies that only the p-value for the Schoenfeld residuals test was used as a justification by the company for the proportional hazards assumption holding for BR OS for RE-MIND2. Furthermore, while we agree with the ERG's comment that interpretation of the visual plots can be subjective, given the magnitude of the p-value observed for the Schoenfeld residuals test when conducting the PH assessment for BR OS compared to POLA+BR PFS, and the other observations made by the company with respect to the log cumulative hazard and Schoenfeld residual plots, we do not believe that it is appropriate to draw a direct parallel between the two scenarios, and that the differences

			between the company assessments of the visual plots should be clearly stated in each case. For BR OS, while the plots crossed very briefly at the start, and the distance between the plots narrowed slightly for a short time near the middle of the observed log survival times, the plots were broadly parallel for the majority of follow-up, with the Schoenfeld residuals plot showing a fitted line for the residuals that was fairly parallel with the 0 line. In contrast, as described in Appendix M of the original company submission, the hazard plots for TAFA+LEN and POLA+BR PFS were clearly non-parallel for a majority of follow-up, with convergence and overlap of the plots near the middle of the observed log survival times, a clear downward trend in the fitted line shown on the Schoenfeld residuals plot, and a substantially lower p-value from the Schoenfeld residual test compared to TAFA+LEN and BR OS (0.1676 vs 0.9489, respectively). Log-cumulative hazard and Schoenfeld residual plots for BR OS and Pola-BR PFS are reproduced below.

			Log Cumulative Hazard Plot for RE-MIND2: OS Plots for TAFA+LEN vs. BR  Abbreviations: BR = bendamustine + rituximab; LEN = lenalidomide; OS = overall survival; TAFA = tafasitamab

Schoenfeld Residuals Plot for RE-MIND2: TAFA+LEN vs. BR OS



Abbreviations: BR = bendamustine + rituximab; CI = confidence interval; OS = overall survival

Log Cumulative Hazard Plot for RE-MIND2: PFS Plots for TAFA+LEN vs. POLA+BR

			 Abbreviations: LEN = lenalidomide; PBR = Pola-BR = polatuzumab + bendamustine + rituximab; PFS = progression-free survival; TAFA = tafasitamab **Schoenfeld Residuals Plot for RE-MIND2: TAFA+LEN vs. Pola-BR PFS**

			 Abbreviations: CI = confidence interval; PFS = progression-free survival; Pola-BR = polatuzumab + bendamustine + rituximab

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4. Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report 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)
• Key Issue 4 (validation of survival extrapolations) • Key Issue 5 (LEN list price discount)	Company base case prior to technical engagement: • Generalised gamma survival model for TAFA+LEN PFS • MAIC with time-varying HRs for POLA+BR OS and PFS • Use of RE-MIND2 to model BR survival outcomes (constant HR for OS, lognormal model for PFS, KM curve for TTD) • [redacted] discount on LEN list price • Inclusion of CAR-T as a subsequent treatment • 7.5 treatment cycles of R-GemOx as a subsequent treatment • Median treatment durations from available studies for modelling duration of subsequent therapies	Incyte has utilised the same inputs and assumptions as the ERG preferred base case, with the following exceptions: • Use of the generalised gamma parametric survival model for TAFA+LEN PFS, instead of lognormal • Application of MAIC time-varying HRs for POLA+BR OS and PFS, rather than constant HRs • Use of an [redacted] discount on the LEN list price, [redacted], rather than no discount ([redacted] discount previously used for the original submission) • Change in the submitted PAS discount on the TAFA list price to [redacted], instead of [redacted]	• Base-case ICERs for TAFA+LEN vs each comparator using previous PAS price discount for tafasitamab of [redacted] (based on revised economic model submitted during clarification questions): o POLA+BR: [redacted] o BR: [redacted] o R-GemOx: [redacted] • New base case ICERs for TAFA+LEN vs each comparator (additional details provided below): o POLA+BR: [redacted] o BR: [redacted] o R-GemOx: [redacted]

	• Progressed disease (PD) health state disease management cost of £3,550.65 per model cycle for R-GemOx, based on NICE TA567 ERG preferred base case: • Lognormal survival model for TAFA+LEN PFS • MAIC with constant HRs for POLA+BR OS and PFS • Use of MAIC results to model BR survival outcomes (constant HR for OS and PFS, median treatment duration from clinical trial to model TTD) • List price with no discount for LEN • Exclusion of CAR-T as a subsequent treatment • 7.5 treatment cycles of R-GemOx as a subsequent treatment • Minimum of maximal and median durations for subsequent therapies		

	• Same PD health state disease management costs for R-GemOx as other comparators (£1,571.25 per model cycle)		

Base case deterministic results:

The base-case cost-effectiveness results for TAFA+LEN and each model comparator (pola-BR, BR and R-GemOx) are presented in Table 1. While TAFA+LEN generated increased total costs against each model comparator, it also produced substantial increases in total life years (2.88-3.49) and QALYs ([redacted]). Undiscounted life year gains for TAFA+LEN were 3.97, 4.66 and 4.41 vs Pola-BR, BR and R-GemOx, respectively.

The ICERs for TAFA+LEN against Pola-BR, BR and R-GemOx were [redacted], [redacted] and [redacted] per QALY, respectively.

Table 1. Base-case results

Intervention	Total costs (£)	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	[redacted]	5.08	[redacted]	-	-	-	-
Pola-BR	[redacted]	2.20	1.45	[redacted]	2.88	[redacted]	[redacted]
BR	[redacted]	1.60	1.04	[redacted]	3.49	[redacted]	[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]	3.26	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; LYG = life year gained; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

Incremental analysis results are shown below in Table 2. [redacted].

Table 2: Base case results – full incremental analysis

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs previous non-dominated alternative
R-GemOx	[redacted]	1.16	-	-	-
BR	[redacted]	1.04	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	1.45	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Tafa+Len, tafasitamab + lenalidomide; Pola-BR, polatuzumab + bendamustine + rituximab; BR, bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaplatin; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis results:

Mean probabilistic results are presented in Table 3 alongside the deterministic base-case results. Mean PSA total costs for TAFA+LEN and R-GemOx were fairly similar to the deterministic results from the base-case analysis, with values within 2.0% of the base-case estimates, while mean PSA costs were higher for Pola-BR and BR by 6.3% and 12.3%, respectively. Similarly, mean PSA total QALYs were fairly close to the base case analysis for TAFA+LEN and R-GemOx (within 1.5% of the base case values), while mean PSA total QALYs were also slightly higher for pola-BR and BR than the deterministic base-case results (8.7% and 10.8%, respectively).

Table 3. Mean PSA results

Intervention	Deterministic results		Mean PSA results	
	Total costs	**Total QALYs**	**Total costs (95% CI)**	**Total QALYs (95% CI)**
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	1.45	[redacted]	1.58 (0.64 to 3.38)
BR	[redacted]	1.04	[redacted]	1.15 (0.34 to 2.69)
R-GemOx	[redacted]	1.16	[redacted]	1.18 (0.88 to 1.55)

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; ICER = incremental cost-effectiveness ratio; LYG = life year gained; pola-BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

The distribution of incremental costs and QALYs for TAFA+LEN vs. pola-BR, BR and R-GemOx is shown in Figure 1, Figure 2, Figure 3, respectively.

Figure 1. PSA cost-effectiveness plane for TAFA+LEN vs. pola-BR

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 2. PSA cost-effectiveness plane for TAFA+LEN vs. BR

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 3. PSA cost-effectiveness plane for TAFA+LEN vs. R-GemOx

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The cost-effectiveness acceptability curve (CEAC) for TAFA+LEN vs. pola-BR, BR and R-GemOx is shown in Figure 4 for willingness to pay (WTP) thresholds between £0 and £200,000 per QALY, in increments of £4,000 per QALY. The CEAC indicates that .

Figure 4. CEAC

Deterministic sensitivity analysis results:

Tornado diagrams illustrating the key drivers of ICER values in the comparison are shown in Figure 5, Figure 6 and

Figure 7. [redacted]

[redacted]

Figure 5. Tornado diagram of ICER results for TAFA+LEN vs. pola-BR

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 6. Tornado diagram of ICER results for TAFA+LEN vs. BR

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 7. Tornado diagram of ICER results for TAFA+LEN vs. R-GemOx

Abbreviations: 2L+ - second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Scenario analysis results:

Scenarios exploring alternative long-term extrapolations and data sources for survival parameters, cure assumptions, utilities and vial sharing, along with shorter model time horizons and lower discount rates, are summarised in Table 4.

Scenarios with the largest increases in the ICER were shorter time horizons (and for BR, and for R-GemOx for five and 10-year time horizons, respectively), use of the Weibull model for TAFA+LEN OS (to across

comparators), use of the log-normal model for TAFA+LEN PFS ([redacted] to [redacted]), use of MAIC constant HRs for pola-BR ([redacted] increase in ICER vs. pola-BR) and applying MAIC HRs and median TTD data for R-GemOx ([redacted] increase in ICER vs. R-GemOx).

Scenarios generating the largest decreases in the ICER were the cure assumption scenarios, with scenarios 16 and 17 generating the largest ICER decreases of between [redacted] to [redacted] across comparators, as well as use of RE-MIND2 data for pola-BR ([redacted]), health state utilities from NICE TA567 ([redacted] to [redacted]) and assuming vial-sharing for all IV therapies ([redacted] to [redacted]). Shorter time horizons of 5 and 10 years decreased the ICER for TAFA+LEN compared to pola-BR by [redacted] and [redacted], respectively.

Table 4. Scenario analysis results

Scenario #	Scenario	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
-	**Base-Case**	[redacted]	[redacted]	[redacted]
1	5-year time horizon	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	[redacted]	[redacted]
3	1.5% discount rate for costs and outcomes	[redacted]	[redacted]	[redacted]
4	TAFA+LEN OS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
5	TAFA+LEN OS parametric model: Weibull	[redacted]	[redacted]	[redacted]
6	TAFA+LEN PFS parametric model: log-normal	[redacted]	[redacted]	[redacted]
7	Pola-BR: apply MAIC HRs with 11-month split for OS and PFS	[redacted]	[redacted]	[redacted]

Scenario #	Scenario	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
8	Pola-BR: apply constant MAIC HRs for OS and PFS	[redacted]	[redacted]	[redacted]
9	Pola-BR: apply RE-MIND2 survival data (generalised gamma for OS, exponential for PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
10	BR: apply RE-MIND2 survival data (lognormal for OS and PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
11	R-GemOx OS parametric model: Gompertz	[redacted]	[redacted]	[redacted]
12	R-GemOx PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
13	Applying MAIC HR estimates for OS/PFS and median TTD duration for R-GemOx	[redacted]	[redacted]	[redacted]
14	Fixed 2-year cure point with 78.6% of PFS patients at 2 year achieving cure: general population mortality only	[redacted]	[redacted]	[redacted]
15	Scenario 14 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
16	Scenario 15 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
17	Scenario 16 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
18	Cure point at crossing of OS and PFS curves: general population mortality only	[redacted]	[redacted]	[redacted]

Scenario #	Scenario	ICER vs. pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
19	Scenario 18 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
20	Scenario 19 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
21	Scenario 20 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
22	Utility of 0.83 for PFS and 0.71 for PD based on NICE TA567	[redacted]	[redacted]	[redacted]
23	Vial sharing for all IV administered treatments	[redacted]	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PFS = progression-free survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R=GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = Tafasitamab + lenalidomide; TTD = time to treatment discontinuation

Appendix

Appendix Contents

OS – HR of TAFA + LEN v. RGemOx across analyses

PFS – HR of TAFA + LEN v. RGemOx across analyses

- Appendix TE3. Supportive information for use of time-varying hazard ratios
- Appendix TE4. Overview of ongoing studies with tafasitamab
-

- Appendix TE5. Serious adverse event data for L-MIND and MOR208C201
-

Appendix TE1. SLR additional supportive materials

TE1A: Clinical SLR original search

Pubmed – Database

Table 5. Pubmed Search Strategy - Date of Search: Feb 4, 2021

Criteria number	Search string	Number of hits
87	#86 NOT (Comment[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR in vitro techniques[MeSH])	2,705
86	#84 NOT #85	2,792
85	case report*[Title] or case stud*[Title]	310,265
84	#83 NOT Case Reports[Publication Type]	2,825
83	#82 NOT (Animals[MeSH Terms] NOT Humans[MeSH Terms])	3,416
82	#79 AND #9 From 2011 - 2021	3,455
80	#79 AND #9	7,049
79	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78	824,756
78	"ASHAP protocol"[Supplementary Concept] OR "LNH 87 protocol"[Supplementary Concept] OR "CEPP protocol"[Supplementary Concept] OR "CHOP protocol"[Supplementary Concept] OR "R-CHOP protocol"[Supplementary Concept] OR "DHAOx protocol"[Supplementary Concept] OR "DHAP protocol"[Supplementary Concept] OR "EPOCH protocol"[Supplementary Concept] OR "ESHAP regimen"[Supplementary Concept] OR "GDP protocol"[Supplementary Concept] OR "gemcitabine-oxaliplatin regimen"[Supplementary Concept] OR "ICE protocol 1"[Supplementary Concept] OR "IEV protocol"[Supplementary Concept] OR "MINE regimen"[Supplementary Concept] OR "BEAM regimen"[Supplementary Concept]	4,721
77	Palliative Care[MeSH Terms] OR "best supportive care"[All Fields] OR "supportive care"[All Fields] OR "palliative care"[All Fields]	93,294
76	ASHAP[Title/Abstract] OR R-ASHAP[Title/Abstract] OR RASHAP[Title/Abstract] OR ACVBP[Title/Abstract] OR "LNH 87 protocol"[Title/Abstract] OR R-ACVBP[Title/Abstract] OR RACVBP[Title/Abstract] OR R-BENDA[Title/Abstract] OR RBENDA[Title/Abstract] OR CEOP[Title/Abstract] OR R-CEOP[Title/Abstract] OR RCEOP[Title/Abstract] OR CEPP[Title/Abstract] OR R-CEPP O RCEPP[Title/Abstract] OR CHOP[Title/Abstract] OR R-CHOP[Title/Abstract] OR RCHOP[Title/Abstract] OR "R2 CHOP"[Title/Abstract] OR DHAOX[Title/Abstract] OR R-DHAOX[Title/Abstract] OR RDHAOX[Title/Abstract] OR DHAP[Title/Abstract] OR R-DHAP[Title/Abstract] OR	255,108

Criteria number	Search string	Number of hits
	RDHAP[Title/Abstract] OR EPOCH[Title/Abstract] OR R-EPOCH[Title/Abstract] OR REPOCH[Title/Abstract] OR DA-EPOCH[Title/Abstract] OR DA-EPOCH-R[Title/Abstract] OR DAEPOCHR[Title/Abstract] OR ESHAP[Title/Abstract] OR R-ESHAP[Title/Abstract] OR RESHAP[Title/Abstract] OR GDP[Title/Abstract] OR R-GDP[Title/Abstract] OR RGDP[Title/Abstract] OR GemOx[Title/Abstract] OR "gemcitabine-oxaliplatin regimen"[Title/Abstract] OR R-GemOx[Title/Abstract] OR RGemOx[Title/Abstract] OR ICE[Title/Abstract] OR R-ICE[Title/Abstract] OR RICE[Title/Abstract] OR IEV[Title/Abstract] OR R-IEV[Title/Abstract] OR RIEV[Title/Abstract] OR IGEV[Title/Abstract] OR R-IGEV[Title/Abstract] OR RIGEV[Title/Abstract] OR MINE[Title/Abstract] OR R-MINE[Title/Abstract] OR RMINE[Title/Abstract] OR BEAM[Title/Abstract] OR "Mini-BEAM"[Title/Abstract] OR R-BEAM[Title/Abstract] OR RBEAM[Title/Abstract]	
75	Tisagenlecleucel OR CTL019 OR Kymriah	334
74	Tisagenlecleucel [Supplementary Concept]	96
73	Lisocabtagene OR "liso-cel"	18
72	Axicabtagene OR "Axi-Cel" OR KTE C19 OR Yescarta	230
71	Axicabtagene Ciloleucel [Supplementary Concept]	48
70	Pixantrone OR BBR 2778 OR BBR2778 OR Pixuvri	108
69	Pixantrone [Supplementary Concept]	82
68	Melphalan* OR Alkeran OR Evomela OR L-PAM OR L Sarcolysine OR Melfalano OR Phenylalanine mustard OR Medphalan OR Sarkolysin* OR Merphalan	11,381
67	Melphalan[MeSH Terms]	7,822
66	Carmustin* OR "BCNU" OR "BiCNU" OR Gliadel OR FIVB OR Nitrumon	5,434
65	Carmustine[MeSH Terms]	4,022
64	Mitoxantron* OR Mitozantrone OR Novantron* OR DHAQ OR NSC 279836 OR NSC279836 OR NSC 287836 OR NSC287836 OR NSC 299195 OR NSC299195 OR NSC 301739* OR NSC301739* OR Mitroxone OR Pralifan OR CL 232325 OR CL232325 OR Ralenova OR Onkotrone	6,426
63	Mitoxantrone[MeSH Terms]	4,282
62	Mesna OR Mesnex OR Uromitexan OR ASTA D 7093 OR ASTAD 7093 OR Ziken OR Mistabron* OR Mucofluid OR Mitexan OR UCB 3983 OR UCB3983 OR Uromitexan OR Mesnum	1,828
61	Mesna[MeSH Terms]	1,183
60	Obinutuzumab OR GA101 OR GA 101 OR Afutuzumab OR Gazyva* OR RO 5072759 OR RO5072759 OR R 7159 OR R7159 OR GA 101	592
59	Obinutuzumab [Supplementary Concept]	293
58	Epirubicin* OR Ellence OR Pharmorubicin OR Epiadriamycin OR Pidorubicin* OR 4' Epidoxorubicin OR 4' Epi Doxorubicin OR 4' Epi Adriamycin OR 4' Epiadriamycin OR 4' Epi DXR OR EPI cell OR EPIcell OR Epilem OR IMI 28 OR IMI28 OR NSC 256942 OR NSC256942 OR Farmorubicin*	11,329
57	Epirubicin[MeSH Terms]	5,254

Criteria number	Search string	Number of hits
56	Ifosfamid* OR Ifex OR Iphosphamide OR Isofosfamide OR Isophosphamide OR Isosfamide OR Iso Endoxan OR Holoxan OR NSC 109,724 OR NSC109,724 OR NSC 109724 OR NSC109724 OR Asta Z 4942	7,399
55	Ifosfamide[MeSH Terms]	4,822
54	PCI 32765 OR PCI32765 OR Ibrutinib OR Imbruvica OR Ibrutix OR CRA 032765	2,437
53	PCI 32765 [Supplementary Concept]	1,239
52	Vinorelbin* OR Navelbine OR KW 2307 OR KW2307	4,244
51	Vinorelbine[MeSH Terms]	2,725
50	Gemcitabin* OR Gemzar OR LY 188011	17,798
49	Gemcitabine [Supplementary Concept]	11,214
48	Dexamethasone* OR Dextenza OR Ozurdex OR Dexpak OR MK 125 OR Dexametasona OR Decadron OR Baycadron OR Methylfluorprednisolone OR Hexadecadrol OR Decameth OR Decaspray OR Dexasone OR Maxidex OR Millicorten OR Oradexon OR Decaject OR Hexadrol	74,053
47	Dexamethasone[MeSH Terms]	52,018
46	Oxaliplatin* OR Eloxatin* OR Oxalatoplatin* OR L-OHP Cpd OR ACT 078	12,515
45	Oxaliplatin[MeSH Terms]	6,725
44	Lenalidomid* OR CDC501 OR CDC 501 OR CDC5013 OR CDC 5013 OR ENMD0997 OR ENMD 0997 OR Revlimid OR Linamide OR Ladevina OR IMiD3 Cpd OR CC 5013 OR CC5013 OR Revimid	5,200
43	Lenalidomide[MeSH Terms]	2,776
42	Procarbazin* OR Matulane OR Natulan OR Indicarb	4,212
41	Procarbazine[MeSH Terms]	3,266
40	Vincristin* OR Leurocristine OR Oncovin* OR Vincasar OR Marqibo OR Cellcristin OR Citomid OR Onkocristin OR Farmistin OR Vintec OR Vincrisul	32,191
39	Vincristine[MeSH Terms]	23,448
38	Etoposid* OR Etopophos OR Toposar OR VePesid OR Eposin OR Eposide OR Demethyl Epipodophyllotoxin Ethylidine Glucoside OR Eto GRY OR Exitop OR Lastet OR NSC 141540 OR NSC141540 OR Onkoposid OR Riboposid OR VP 16 213 OR VP 16213 OR VP 16 OR VP16 OR Celltop OR Etopos OR Etomedac	28,573
37	Etoposide[MeSH Terms]	16,849
36	Brentuximab Vedotin OR Adcetris OR cAC10 vcMMAE OR cAC10vcMMAE OR CAC10 1006 OR CAC101006 OR SGN 35 OR SGN35	1,071
35	Brentuximab Vedotin[MeSH Terms]	611
34	Polatuzumab Vedotin OR Polivy OR RG 7596 OR RG7596 OR ACD 79BVCMMAE OR ACD79B VCMMAE OR ACD 79B VCMMAE OR FCU 2711 OR FCU2711 OR DCDS 4501A OR DCDS4501A OR RO 5541077000 OR RO 5541077 000 OR RO5541077 000	249
33	Polatuzumab Vedotin [Supplementary Concept]	14

Criteria number	Search string	Number of hits
32	Bendamustin* OR Treanda OR Treakisym OR Ribomustin OR Levact OR Bendeka OR Ribomustine OR Belrapzo OR Cytostasan OR IMET 3393 OR Zimet 3393	1,439
31	Bendamustine Hydrochloride[MeSH Terms]	837
30	Prednison* OR Prednisolone OR Deltasone OR "Liquid Pred" OR Orasone OR Sterapred OR Dehydrocortisone OR delta-Cortisone OR Rectodelt OR Ultracorten OR Winpred OR Cortan OR Cortancyl OR Panafcort OR Cutason OR Decortin OR Dacortin OR Decortisyl OR Encorton* OR Enkortolon OR Kortancyl OR Meticorten OR Panasol OR Predni Tablinen OR Prednidib OR Predniment OR Pronisone OR Sone	117,656
29	Prednisolone[MeSH Terms]	51,644
28	Prednisone[MeSH Terms]	39,739
27	Bleomycin* OR Blenoxane OR Bleocin OR Bleomicin* OR BLEO cell OR BLEOcell OR Bleolem OR Blanoxan	20,748
26	Bleomycin[MeSH Terms]	15,581
25	Vindesin* OR Eldisine OR Desacetylvinblastine amide OR Enison OR NSC 245467 OR NSC245467	1,870
24	Vindesine[MeSH Terms]	1,287
23	Cyclophosphamid* OR Cytophosphan* OR Endoxan OR Cytoxan OR Neosar OR Procytox OR Revimmune OR Cycloblastin OR Ciclofosfamid* OR Sendoxan OR B 518 OR B518 OR NSC 26271 OR NSC26271 OR Cyclophosphane	75,600
21	Cyclophosphamide[MeSH Terms]	54,173
20	Rituximab OR Rituxan OR Mabthera OR Truxima OR Riximyo OR Ruxience OR IDEC C2B8 OR GP2013	25,087
19	Rituximab[MeSH Terms]	15,221
18	Methylprednisolon* OR Medrol OR A-methaPred OR Metipred OR Urbason	27,560
17	Methylprednisolone[MeSH Terms]	19,759
16	Doxorubicin* OR Hydroxydaunorubicin OR Daunorubicin OR Adriamycin OR Caelyx OR Myocet OR Doxil OR Rubex OR Farmiblastina OR Ribodoxo OR Adriblastin* OR Adrimedac OR DOXO cell OR Doxolem OR Doxotec OR Onkodox	89,210
15	Doxorubicin[MeSH Terms]	57,948
14	Cytarabin* OR Cytosine Arabinoside OR Cytosar OR Depocyt OR Citarabina OR Arabinofuranosyl Cytidine OR Tarabine OR AraC OR Ara C OR Arabinosylcytosine OR Arabinofuranosylcytosine OR Aracytidine OR Aracytine OR Cytonal	21,788
13	Cytarabine[MeSH Terms]	14,788
12	Cisplatin* OR Carboplat* OR Platamin OR Neoplatin OR Cismaplat OR CDDP OR Cis-diamminedichloridoplatinum OR Cis-DDP OR Platino* OR Paraplatin* OR CBDCA OR NSC-119875 OR JM-8 OR JM8 OR NSC-241240 OR NSC241240 OR Platinum Diamminodichloride OR Cis-Platinum OR Dichlorodiammineplatinum OR Biocisplatinum OR Platidiam OR Platinwas OR Ribocarbo OR Neocarbo OR Carbosin OR Carbotec OR Ercar OR Nealorin OR Blastocarb	93,145
11	Carboplatin[MeSH Terms]	11,863
10	Cisplatin[MeSH Terms]	52,943

Criteria number	Search string	Number of hits
9	#8 AND #5	17,491
8	#6 OR #7	2,041,343
7	Recurr*[Title/Abstract] OR Reoccurr*[Title/Abstract] OR Relaps*[Title/Abstract] OR Refractory[Title/Abstract] OR Resist*[Title/Abstract] OR "R R"[Title/Abstract] OR "RR"[Title/Abstract] OR "R/R"[Title/Abstract]	1,979,056
6	Recurrence[MeSH Terms]	186,991
5	#1 OR #4	89,536
4	#2 AND #3	81,306
3	Diffuse[Title/Abstract] OR B Cell[Title/Abstract] OR Large Cell[Title/Abstract] OR Non Hodgkin*[Title/Abstract]	292,575
2	lymphoma[Title/Abstract] OR lymphomas[Title/Abstract]	182,412
1	Lymphoma, Large B-Cell, Diffuse[MeSH Terms]	20,173

Lines*#22 and #81 are missing. They have been deleted within the search since they contained mistakes. These twolines were not combined with any other lines and/or incorporated into the search strategy. The numbering in Pubmed does not reset once a line is deleted so it appears as above.

Embase – Database

Table 6. Embase Search Strategy - Date of search: Feb 4, 2021

Criteria number	Search string	Number of hits
#88	#86 NOT #87	3,338
#87	#86 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it) [2016-2021]/py	4,507
#86	#84 NOT #85	7,845
#85	#84 AND ('editorial'/it OR 'letter'/it)	126
#84	#82 NOT #83	7,971
#83	#82 AND ('case report'/de OR 'case study'/de)	1,840
#82	#80 NOT #81	9,811
#81	#80 AND ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'cell culture'/de OR 'in vitro study'/de OR 'in vivo study'/de OR 'mouse model'/de OR 'nonhuman'/de)	1,546
#80	#78 NOT #79	11,357
#79	'animal'/exp NOT 'human'/exp	5,563,525
#78	#8 AND #76 AND [2011-2021]/py	11,631
#77	#8 AND #76	17,813
#76	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75	1,622,291
#75	ashap OR 'r ashap' OR rashap OR acvbp OR 'lnh 87 protocol' OR 'r acvbp' OR racvbp OR rbenda OR 'r benda' OR ceop OR 'r ceop' OR rceop OR cepp OR 'r cepp' OR rcepp OR 'chop'/exp OR chop OR 'r chop'/exp OR 'r chop' OR 'rchop'/exp OR rchop OR 'r2 chop' OR dhaox OR 'r dhaox' OR rdhaox OR dhap OR 'r dhap' OR rdhap OR 'epoch'/exp OR epoch OR 'r epoch'/exp OR 'r epoch' OR 'repoch'/exp OR repoch OR 'da epoch'/exp OR 'da epoch' OR 'da epoch r'/exp OR 'da epoch r' OR daepochr OR eshap OR 'r eshap' OR reshap OR 'gdp'/exp OR gdp OR 'r gdp' OR rgdp OR gemox OR 'gemcitabine-oxaliplatin regimen' OR 'r gemox' OR rgemox OR 'ice'/exp OR ice OR 'r ice' OR 'rice'/exp OR rice OR iev OR 'r iev' OR riev OR igev OR 'r igev' OR rigev OR 'mine'/exp OR mine OR 'r mine' OR rmine OR beam OR 'mini-beam' OR 'r beam' OR rbeam OR 'best supportive care'/exp OR 'palliative therapy'/exp OR ((care NEAR/2 ('best support*' OR palliative)):ti,ab,kw)	520,802
#74	tisagenlecleucel:ti,ab,kw OR ctl019:ti,ab,kw OR kymriah:ti,ab,kw	674
#73	'tisagenlecleucel t'/de	1,054
#72	isocabtagene:ti,ab,kw OR 'liso-cel':ti,ab,kw	46
#71	'lisocabtagene maraleucel'/de	126

Criteria number	Search string	Number of hits
#70	axicabtagene:ti,ab,kw OR 'axi-cel':ti,ab,kw OR 'kte c19':ti,ab,kw OR yescarta:ti,ab,kw	540
#69	'axicabtagene ciloleucel'/de	727
#68	pixantrone:ti,ab,kw OR 'bbr 2778':ti,ab,kw OR bbr2778:ti,ab,kw OR pixuvri:ti,ab,kw	190
#67	'pixantrone'/de	265
#66	melphalan*:ti,ab,kw OR alkeran:ti,ab,kw OR evomela:ti,ab,kw OR 'l pam':ti,ab,kw OR 'l sarcolysine':ti,ab,kw OR melfalano:ti,ab,kw OR 'phenylalanine mustard':ti,ab,kw OR medphalan:ti,ab,kw OR sarkolysin*:ti,ab,kw OR merphalan:ti,ab,kw	15,174
#65	'melphalan'/de	38,681
#64	carmustin*:ti,ab,kw OR 'bcnu':ti,ab,kw OR 'bicnu':ti,ab,kw OR gliadel:ti,ab,kw OR fivb:ti,ab,kw OR nitrumon:ti,ab,kw	5,459
#63	'carmustine'/de	19,136
#62	mitoxantron*:ti,ab,kw OR mitozantrone:ti,ab,kw OR novantron*:ti,ab,kw OR dhaq:ti,ab,kw OR 'nsc 279836':ti,ab,kw OR nsc279836:ti,ab,kw OR 'nsc 287836':ti,ab,kw OR nsc287836:ti,ab,kw OR 'nsc 299195':ti,ab,kw OR nsc299195:ti,ab,kw OR 'nsc 301739*':ti,ab,kw OR nsc301739*:ti,ab,kw OR mitroxone:ti,ab,kw OR pralifan:ti,ab,kw OR 'cl 232325':ti,ab,kw OR cl232325:ti,ab,kw OR ralenova:ti,ab,kw OR onkotrone:ti,ab,kw	7,760
#61	'mitoxantrone'/de	23,687
#60	mesna:ti,ab,kw OR mesnex:ti,ab,kw OR 'asta d 7093':ti,ab,kw OR 'astad 7093':ti,ab,kw OR ziken:ti,ab,kw OR mistabron*:ti,ab,kw OR mucofluid:ti,ab,kw OR mitexan:ti,ab,kw OR 'ucb 3983':ti,ab,kw OR ucb3983:ti,ab,kw OR uromitexan:ti,ab,kw OR mesnum:ti,ab,kw	1,782
#59	'mesna'/de	6,050
#58	obinutuzumab:ti,ab,kw OR ga101:ti,ab,kw OR 'ga 10':ti,ab,kw OR afutuzumab:ti,ab,kw OR gazyva*:ti,ab,kw OR 'ro 5072759':ti,ab,kw OR ro5072759:ti,ab,kw OR 'r 7159':ti,ab,kw OR r7159:ti,ab,kw OR 'ga 101':ti,ab,kw	1,548
#57	'obinutuzumab'/de	2,493
#56	epirubicin*:ti,ab,kw OR ellence:ti,ab,kw OR pharmorubicin:ti,ab,kw OR epiadriamycin:ti,ab,kw OR pidorubicin*:ti,ab,kw OR '4 epidoxorubicin':ti,ab,kw OR '4 epi doxorubicin':ti,ab,kw OR '4 epi adriamycin':ti,ab,kw OR '4 epiadriamycin':ti,ab,kw OR '4 epi dxr':ti,ab,kw OR 'epi cell':ti,ab,kw OR epicell:ti,ab,kw OR epilem:ti,ab,kw OR 'imi 28':ti,ab,kw OR imi28:ti,ab,kw OR 'nsc 256942':ti,ab,kw OR nsc256942:ti,ab,kw OR farmorubicin*:ti,ab,kw	8,973
#55	'epirubicin'/de	29,324
#54	ifosfamid*:ti,ab,kw OR ifex:ti,ab,kw OR iphosphamide:ti,ab,kw OR isofosfamide:ti,ab,kw OR isophosphamide:ti,ab,kw OR isosfamide:ti,ab,kw OR 'iso endoxan':ti,ab,kw OR holoxan:ti,ab,kw OR 'nsc 109 724':ti,ab,kw OR 'nsc109 724':ti,ab,kw OR 'nsc 109724':ti,ab,kw OR nsc109724:ti,ab,kw OR 'asta z 4942':ti,ab,kw	9,084
#53	'ifosfamide'/de	31,025
#52	'pci 32765':ti,ab,kw OR pci32765:ti,ab,kw OR ibrutinib:ti,ab,kw OR imbruvica:ti,ab,kw OR ibrutix:ti,ab,kw OR 'cra 032765':ti,ab,kw	5,334
#51	'ibrutinib'/de	7,141

Criteria number	Search string	Number of hits
#50	vinorelbin*:ti,ab,kw OR navelbine:ti,ab,kw OR 'kw 2307':ti,ab,kw OR kw2307:ti,ab,kw	6,493
#49	'vinorelbine tartrate'/de	18,425
#48	gemcitabin*:ti,ab,kw OR gemzar:ti,ab,kw OR 'ly 188011':ti,ab,kw	30,136
#47	'gemcitabine'/de	59,089
#46	dexamethasone*:ti,ab,kw OR dextenza:ti,ab,kw OR ozurdex:ti,ab,kw OR dexpak:ti,ab,kw OR 'mk 125':ti,ab,kw OR dexametasona:ti,ab,kw OR decadron:ti,ab,kw OR baycadron:ti,ab,kw OR methylfluorprednisolone:ti,ab,kw OR hexadecadrol:ti,ab,kw OR decameth:ti,ab,kw OR decaspray:ti,ab,kw OR dexasone:ti,ab,kw OR maxidex:ti,ab,kw OR millicorten:ti,ab,kw OR oradexon:ti,ab,kw OR decaject:ti,ab,kw OR hexadrol:ti,ab,kw	81,447
#45	'dexamethasone'/de	157,601
#44	'brentuximab vedotin':ti,ab,kw OR adcetris:ti,ab,kw OR 'cac10 vcmmae':ti,ab,kw OR cac10vcmmae:ti,ab,kw OR 'cac10 1006':ti,ab,kw OR cac101006:ti,ab,kw OR 'sgn 35':ti,ab,kw OR sgn35:ti,ab,kw	2,269
#43	oxaliplatin*:ti,ab,kw OR eloxatin*:ti,ab,kw OR oxalatoplatin*:ti,ab,kw OR 'l-ohp cpd':ti,ab,kw OR 'act 078':ti,ab,kw	20,253
#42	'oxaliplatin'/de	41,397
#41	lenalidomid*:ti,ab,kw OR cdc501:ti,ab,kw OR 'cdc 501':ti,ab,kw OR cdc5013:ti,ab,kw OR 'cdc 5013':ti,ab,kw OR enmd0997:ti,ab,kw OR 'enmd 0997':ti,ab,kw OR revlimid:ti,ab,kw OR linamide:ti,ab,kw OR ladevina:ti,ab,kw OR 'imid3 cpd':ti,ab,kw OR 'cc 5013':ti,ab,kw OR cc5013:ti,ab,kw OR revimid:ti,ab,kw	12,645
#40	'lenalidomide'/de	19,942
#39	procarbazin*:ti,ab,kw OR matulane:ti,ab,kw OR natulan:ti,ab,kw OR indicarb:ti,ab,kw	3,006
#38	'procarbazine'/de	16,522
#37	vincristin*:ti,ab,kw OR leurocristine:ti,ab,kw OR oncovin*:ti,ab,kw OR vincasar:ti,ab,kw OR marqibo:ti,ab,kw OR cellcristin:ti,ab,kw OR citomid:ti,ab,kw OR onkocristin:ti,ab,kw OR farmistin:ti,ab,kw OR vintec:ti,ab,kw OR vincrisul:ti,ab,kw	27,766
#36	'vincristine'/de	103,671
#35	etoposid*:ti,ab,kw OR etopophos:ti,ab,kw OR toposar:ti,ab,kw OR vepesid:ti,ab,kw OR eposin:ti,ab,kw OR eposide:ti,ab,kw OR 'demethyl epipodophyllotoxin ethylidine glucoside':ti,ab,kw OR 'eto gry':ti,ab,kw OR exitop:ti,ab,kw OR lastet:ti,ab,kw OR 'nsc 141540':ti,ab,kw OR nsc141540:ti,ab,kw OR onkoposid:ti,ab,kw OR riboposid:ti,ab,kw OR 'vp 16 213':ti,ab,kw OR 'vp 16213':ti,ab,kw OR 'vp 16':ti,ab,kw OR vp16:ti,ab,kw OR celltop:ti,ab,kw OR etopos:ti,ab,kw OR etomedac:ti,ab,kw	34,648
#34	'etoposide'/de	89,343
#33	'brentuximab vedotin'/de	3,830
#32	'polatuzumab vedotin':ti,ab,kw OR polivy:ti,ab,kw OR 'rg 7596':ti,ab,kw OR rg7596:ti,ab,kw OR 'acd 79bvcmmae':ti,ab,kw OR 'acd79b vcmmae':ti,ab,kw OR 'acd 79b vcmmae':ti,ab,kw OR 'fcu 2711':ti,ab,kw OR fcu2711:ti,ab,kw OR 'dcds 4501a':ti,ab,kw OR dcds4501a:ti,ab,kw OR 'ro 5541077000':ti,ab,kw OR 'ro 5541077 000':ti,ab,kw OR 'ro5541077 000':ti,ab,kw	209
#31	'polatuzumab vedotin'/de	291

Criteria number	Search string	Number of hits
#30	bendamustin*:ti,ab,kw OR treanda:ti,ab,kw OR treakisym:ti,ab,kw OR ribomustin:ti,ab,kw OR levact:ti,ab,kw OR bendeka:ti,ab,kw OR ribomustine:ti,ab,kw OR belrapzo:ti,ab,kw OR cytostasan:ti,ab,kw OR 'imet 3393':ti,ab,kw OR 'zimet 3393':ti,ab,kw	4,182
#29	'bendamustine'/de	6,974
#28	prednison*:ti,ab,kw OR prednisolone:ti,ab,kw OR deltasone:ti,ab,kw OR 'liquid pred':ti,ab,kw OR orasone:ti,ab,kw OR sterapred:ti,ab,kw OR dehydrocortisone:ti,ab,kw OR 'delta cortisone':ti,ab,kw OR rectodelt:ti,ab,kw OR ultracorten:ti,ab,kw OR winpred:ti,ab,kw OR cortan:ti,ab,kw OR cortancyl:ti,ab,kw OR panafcort:ti,ab,kw OR cutason:ti,ab,kw OR decortin:ti,ab,kw OR dacortin:ti,ab,kw OR decortisyl:ti,ab,kw OR encorton*:ti,ab,kw OR enkortolon:ti,ab,kw OR kortancyl:ti,ab,kw OR meticorten:ti,ab,kw OR panasol:ti,ab,kw OR 'predni tablinen':ti,ab,kw OR prednidib:ti,ab,kw OR predniment:ti,ab,kw OR pronisone:ti,ab,kw OR sone:ti,ab,kw	91,933
#27	'prednisolone'/de	134,239
#26	'prednisone'/de	181,543
#25	bleomycin*:ti,ab,kw OR blenoxane:ti,ab,kw OR bleocin:ti,ab,kw OR bleomicin*:ti,ab,kw OR 'bleo cell':ti,ab,kw OR bleocell:ti,ab,kw OR bleolem:ti,ab,kw OR blanoxan:ti,ab,kw	22,626
#24	'bleomycin'/exp	50,782
#23	vindesin*:ti,ab,kw OR eldisine:ti,ab,kw OR 'desacetylvinblastine amide':ti,ab,kw OR enison:ti,ab,kw OR 'nsc 245467':ti,ab,kw OR nsc245467:ti,ab,kw	1,802
#22	'vindesine'/de	7,665
#21	cyclophosphamid*:ti,ab,kw OR cytophosphan*:ti,ab,kw OR endoxan:ti,ab,kw OR cytoxan:ti,ab,kw OR neosar:ti,ab,kw OR procytox:ti,ab,kw OR revimmune:ti,ab,kw OR cycloblastin:ti,ab,kw OR ciclofosfamid*:ti,ab,kw OR sendoxan:ti,ab,kw OR 'b 518':ti,ab,kw OR b518:ti,ab,kw OR 'nsc 26271':ti,ab,kw OR nsc26271:ti,ab,kw OR cyclophosphane:ti,ab,kw	80,251
#20	'cyclophosphamide'/de	224,273
#19	rituximab:ti,ab,kw OR rituxan:ti,ab,kw OR mabthera:ti,ab,kw OR truxima:ti,ab,kw OR riximyo:ti,ab,kw OR ruxience:ti,ab,kw OR 'idec c2b8':ti,ab,kw OR gp2013:ti,ab,kw	49,077
#18	'rituximab'/de	83,364
#17	methylprednisolon*:ti,ab,kw OR medrol:ti,ab,kw OR 'a methapred':ti,ab,kw OR metipred:ti,ab,kw OR urbason:ti,ab,kw	28,350
#16	'methylprednisolone'/de	99,765
#15	doxorubicin*:ti,ab,kw OR hydroxydaunorubicin:ti,ab,kw OR daunorubicin:ti,ab,kw OR adriamycin:ti,ab,kw OR caelyx:ti,ab,kw OR myocet:ti,ab,kw OR doxil:ti,ab,kw OR rubex:ti,ab,kw OR farmiblastina:ti,ab,kw OR ribodoxo:ti,ab,kw OR adriblastin*:ti,ab,kw OR adrimedac:ti,ab,kw OR 'doxo cell':ti,ab,kw OR doxolem:ti,ab,kw OR doxotec:ti,ab,kw OR onkodox:ti,ab,kw	87,912
#14	'doxorubicin'/de	193,682
#13	cytarabin*:ti,ab,kw OR 'cytosine arabinoside':ti,ab,kw OR cytosar:ti,ab,kw OR depocyt:ti,ab,kw OR citarabina:ti,ab,kw OR 'arabinofuranosyl cytidine':ti,ab,kw OR tarabine:ti,ab,kw OR arac:ti,ab,kw OR 'ara c':ti,ab,kw OR arabinosylcytosine:ti,ab,kw OR arabinofuranosylcytosine:ti,ab,kw OR aracytidine:ti,ab,kw OR aracytine:ti,ab,kw OR cytonal:ti,ab,kw	24,855

Criteria number	Search string	Number of hits
#12	'cytarabine'/de	63,132
#11	cisplatin*:ti,ab,kw OR carboplat*:ti,ab,kw OR platamin:ti,ab,kw OR neoplatin:ti,ab,kw OR cismaplat:ti,ab,kw OR cddp:ti,ab,kw OR 'cis diamminedichloridoplatinum':ti,ab,kw OR 'cis ddp':ti,ab,kw OR platino*:ti,ab,kw OR paraplatin*:ti,ab,kw OR cbdca:ti,ab,kw OR 'nsc 119875':ti,ab,kw OR 'jm 8':ti,ab,kw OR jm8:ti,ab,kw OR 'nsc 241240':ti,ab,kw OR nsc241240:ti,ab,kw OR 'platinum diamminodichloride':ti,ab,kw OR 'cis platinum':ti,ab,kw OR dichlorodiammineplatinum:ti,ab,kw OR biocisplatinum:ti,ab,kw OR platidiam:ti,ab,kw OR platinwas:ti,ab,kw OR ribocarbo:ti,ab,kw OR neocarbo:ti,ab,kw OR carbosin:ti,ab,kw OR carbotec:ti,ab,kw OR ercar:ti,ab,kw OR nealorin:ti,ab,kw OR blastocarb:ti,ab,kw	120,493
#10	'carboplatin'/de	71,650
#9	'cisplatin'/de	188,774
#8	#7 AND #3	30,394
#7	#4 OR #5 OR #6	2,823,103
#6	recurr*:ti,ab,kw OR reoccurr*:ti,ab,kw OR relaps*:ti,ab,kw OR refractory:ti,ab,kw OR resist*:ti,ab,kw OR 'r r':ti,ab,kw OR 'rr':ti,ab,kw OR 'r/r':ti,ab,kw	2,732,421
#5	'cancer recurrence'/de	220,930
#4	'recurrent disease'/de	186,794
#3	#1 OR #2	113,212
#2	(lymphoma* NEAR/5 ('b cell' OR 'large cell' OR diffuse OR 'non hodgkin*')):ti,ab,kw	110,104
#1	'diffuse large b cell lymphoma'/exp	14,744

Cochrane Library – Database

Table 7. Cochrane Library database – Date of search: Feb. 4, 2021

CENTRAL: 1139 results

Criteria number	Search string	Number of hits
#1	MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees	413
#2	Lymphoma* NEAR/8 (Diffuse OR (B NEAR Cell) OR "Large Cell" OR (Non Near Hodgkin*)):ti,ab,kw	5,035
#3	#1 OR #2	5,035
#4	MeSH descriptor: [Recurrence] this term only	12,121
#5	(Recurr* OR Reoccurr* OR Relaps* OR Refractory OR Resist* OR "R R" OR "RR" OR "R/R"):ti,ab,kw	193,195
#6	#4 OR #5	193,195
#7	#3 AND #6 with Publication Year from 2011 to 2021, with Cochrane Library publication date Between Jan 2011 and Jan 2021, in Trials	1,139

Clinical trials.gov

Table 8. Clinical trials.gov database – Date of search: Feb. 4, 2021

Clinical trials.gov	refractory OR recurrent OR relapsed | Diffuse Large B Cell Lymphoma | First posted from 01/01/2011 to 02/05/2021	488 results

Grey Literature

Table 9. Grey Literature Search

Canadian Agency for Drugs and Technologies in Health (CADTH). Search https://www.cadth.ca/search?keywords	Feb 7, 2021 diffuse b cell lymphoma	4 results
National Institute for Health and Care Excellence (NICE). http://www.nice.org.uk/	Feb 7, 2021 diffuse b cell lymphoma	6 results
Scottish Medicines Consortium https://www.scottishmedicines.org.uk/	Feb 7, 2021 diffuse b cell lymphoma	5 results
All Wales Medicines Strategy Group (AWMSG) http://www.awmsg.org/	Feb 7, 2021 diffuse b cell lymphoma	1 result
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, (IQWiG) https://www.iqwig.de/	Feb 7, 2021 Browsed publications	5 results
HAS https://www.has-sante.fr/	Feb 7, 2021 lymphoma	1 result
Pharmaceutical Benefits Advisory Committee (PBAC) https://pbac.pbs.gov.au/	Feb 7, 2021 Browsed site	0 result
ESMO https://www.esmo.org/	April 11, 2021 Diffuse AND lymphoma	58 results
ICER https://icer.org/	April 11, 2021 lymphoma	2 results

Complete Database

Table 10. Complete Database Results

Database	Total Hits	After Duplicates Removed
Medline (Pubmed)	2705	2582
Embase	3338	1484
Embase Conference Abstracts	2707	1913
Cochrane Library	1139	1000
Clinical trials.gov	488	488
CADTH	4	4
NICE	6	6
SMC	5	5
AWMSG	1	1
IQWIG	5	5
HAS	1	1
PBAC	0	0
ESMO	58	58
ICER	2	2
TOTAL	**10459**	**7549**

TE1B: Clinical SLR Update search

Pubmed – Database

Table 11. Pubmed Search Strategy - Date of Search: June 28, 2021

Criteria number	Search string	Number of hits
#89	Search: #86 OR #88	162
#88	Search: #84 AND #87	162
#87	Search: 2021/02/04:2021/06[edat]	618,870
#86	Search: #84 AND #85	161
#85	Search: 2021/02/04:2021/06[crdt]	634,599
#84	Search: #83 NOT (Comment[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR in vitro techniques[MeSH])	5,721
#83	Search: #81 NOT #82	5,863
#82	Search: case report*[Title] or case stud*[Title]	321,241
#81	Search: #80 NOT Case Reports[Publication Type]	5,898
#80	Search: #79 NOT (Animals[MeSH Terms] NOT Humans[MeSH Terms])	7,232
#79	Search: #78 AND #9	7,320
#78	Search: #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77	845,149
#77	Search: "ASHAP protocol"[Supplementary Concept] OR "LNH 87 protocol"[Supplementary Concept] OR "CEPP protocol"[Supplementary Concept] OR "CHOP protocol"[Supplementary Concept] OR "R-CHOP protocol"[Supplementary Concept] OR "DHAOx protocol"[Supplementary Concept] OR "DHAP protocol"[Supplementary Concept] OR "EPOCH protocol"[Supplementary Concept] OR "ESHAP regimen"[Supplementary Concept] OR "GDP protocol"[Supplementary Concept] OR "gemcitabine-oxaliplatin regimen"[Supplementary Concept] OR "ICE protocol 1"[Supplementary Concept] OR "IEV protocol"[Supplementary Concept] OR "MINE regimen"[Supplementary Concept] OR "BEAM regimen"[Supplementary Concept]	4,814
#76	Search: Palliative Care[MeSH Terms] OR "best supportive care"[All Fields] OR "supportive care"[All Fields] OR "palliative care"[All Fields]	96,595
#75	Search: ASHAP[Title/Abstract] OR R-ASHAP[Title/Abstract] OR RASHAP[Title/Abstract] OR ACVBP[Title/Abstract] OR "LNH 87 protocol"[Title/Abstract] OR R-ACVBP[Title/Abstract] OR RACVBP[Title/Abstract] OR R-BENDA[Title/Abstract] OR RBENDA[Title/Abstract] OR CEOP[Title/Abstract] OR R-CEOP[Title/Abstract] OR RCEOP[Title/Abstract] OR CEPP[Title/Abstract] OR R-CEPP O RCEPP[Title/Abstract] OR CHOP[Title/Abstract] OR R-CHOP[Title/Abstract] OR RCHOP[Title/Abstract] OR "R2 CHOP"[Title/Abstract] OR DHAOX[Title/Abstract] OR R-DHAOX[Title/Abstract] OR	262,760

Criteria number	Search string	Number of hits
	RDHAOX[Title/Abstract] OR DHAP[Title/Abstract] OR R-DHAP[Title/Abstract] OR RDHAP[Title/Abstract] OR EPOCH[Title/Abstract] OR R-EPOCH[Title/Abstract] OR REPOCH[Title/Abstract] OR DA-EPOCH[Title/Abstract] OR DA-EPOCH-R[Title/Abstract] OR DAEPOCHR[Title/Abstract] OR ESHAP[Title/Abstract] OR R-ESHAP[Title/Abstract] OR RESHAP[Title/Abstract] OR GDP[Title/Abstract] OR R-GDP[Title/Abstract] OR RGDP[Title/Abstract] OR GemOx[Title/Abstract] OR "gemcitabine-oxaliplatin regimen"[Title/Abstract] OR R-GemOx[Title/Abstract] OR RGemOx[Title/Abstract] OR ICE[Title/Abstract] OR R-ICE[Title/Abstract] OR RICE[Title/Abstract] OR IEV[Title/Abstract] OR R-IEV[Title/Abstract] OR RIEV[Title/Abstract] OR IGEV[Title/Abstract] OR R-IGEV[Title/Abstract] OR RIGEV[Title/Abstract] OR MINE[Title/Abstract] OR R-MINE[Title/Abstract] OR RMINE[Title/Abstract] OR BEAM[Title/Abstract] OR "Mini-BEAM"[Title/Abstract] OR R-BEAM[Title/Abstract] OR RBEAM[Title/Abstract]	
#74	Search: Tisagenlecleucel OR CTL019 OR Kymriah	376
#73	Search: Tisagenlecleucel [Supplementary Concept]	119
#72	Search: Lisocabtagene OR "liso-cel"	26
#71	Search: Axicabtagene OR "Axi-Cel" OR KTE C19 OR Yescarta	269
#70	Search: Axicabtagene Ciloleucel [Supplementary Concept]	81
#69	Search: Pixantrone OR BBR 2778 OR BBR2778 OR Pixuvri	111
#68	Search: Pixantrone [Supplementary Concept]	85
#67	Search: Melphalan* OR Alkeran OR Evomela OR L-PAM OR L Sarcolysine OR Melfalano OR Phenylalanine mustard OR Medphalan OR Sarkolysin* OR Merphalan	11,491
#66	Search: Melphalan[MeSH Terms]	7,914
#65	Search: Carmustin* OR "BCNU" OR "BiCNU" OR Gliadel OR FIVB OR Nitrumon	5,470
#64	Search: Carmustine[MeSH Terms]	4,040
#63	Search: Mitoxantron* OR Mitozantrone OR Novantron* OR DHAQ OR NSC 279836 OR NSC279836 OR NSC 287836 OR NSC287836 OR NSC 299195 OR NSC299195 OR NSC 301739* OR NSC301739* OR Mitroxone OR Pralifan OR CL 232325 OR CL232325 OR Ralenova OR Onkotrone	6,486
#62	Search: Mitoxantrone[MeSH Terms]	4,309
#61	Search: Mesna OR Mesnex OR Uromitexan OR ASTA D 7093 OR ASTAD 7093 OR Ziken OR Mistabron* OR Mucofluid OR Mitexan OR UCB 3983 OR UCB3983 OR Uromitexan OR Mesnum	1,833
#60	Search: Mesna[MeSH Terms]	1,186
#59	Search: Obinutuzumab OR GA101 OR GA 101 OR Afutuzumab OR Gazyva* OR RO 5072759 OR RO5072759 OR R 7159 OR R7159 OR GA 101	638
#58	Search: Obinutuzumab [Supplementary Concept]	331
#57	Search: Epirubicin* OR Ellence OR Pharmorubicin OR Epiadriamycin OR Pidorubicin* OR 4' Epidoxorubicin OR 4' Epi Doxorubicin OR 4' Epi Adriamycin OR 4' Epiadriamycin OR 4' Epi DXR OR EPI cell OR EPIcell OR Epilem OR IMI 28 OR IMI28 OR NSC 256942 OR NSC256942 OR Farmorubicin*	11,526
#56	Search: Epirubicin[MeSH Terms]	5,305

Criteria number	Search string	Number of hits
#55	Search: Ifosfamid* OR Ifex OR Iphosphamide OR Isofosfamide OR Isophosphamide OR Isosfamide OR Iso Endoxan OR Holoxan OR NSC 109,724 OR NSC109,724 OR NSC 109724 OR NSC109724 OR Asta Z 4942	7,477
#54	Search: Ifosfamide[MeSH Terms]	4,863
#53	Search: PCI 32765 OR PCI32765 OR Ibrutinib OR Imbruvica OR Ibrutix OR CRA 032765	2,652
#52	Search: PCI 32765 [Supplementary Concept]	1,375
#51	Search: Vinorelbin* OR Navelbine OR KW 2307 OR KW2307	4,291
#50	Search: Vinorelbine[MeSH Terms]	2,755
#49	Search: Gemcitabin* OR Gemzar OR LY 188011	18,279
#48	Search: Gemcitabine [Supplementary Concept]	11,491
#47	Search: Dexamethasone* OR Dextenza OR Ozurdex OR Dexpak OR MK 125 OR Dexametasona OR Decadron OR Baycadron OR Methylfluorprednisolone OR Hexadecadrol OR Decameth OR Decaspray OR Dexasone OR Maxidex OR Millicorten OR Oradexon OR Decaject OR Hexadrol	75,395
#46	Search: Dexamethasone[MeSH Terms]	52,760
#45	Search: Oxaliplatin* OR Eloxatin* OR Oxalatoplatin* OR L-OHP Cpd OR ACT 078	13,022
#44	Search: Oxaliplatin[MeSH Terms]	7,029
#43	Search: Lenalidomid* OR CDC501 OR CDC 501 OR CDC5013 OR CDC 5013 OR ENMD0997 OR ENMD 0997 OR Revlimid OR Linamide OR Ladevina OR IMiD3 Cpd OR CC 5013 OR CC5013 OR Revimid	5,402
#42	Search: Lenalidomide[MeSH Terms]	2,944
#41	Search: Procarbazin* OR Matulane OR Natulan OR Indicarb	4,236
#40	Search: Procarbazine[MeSH Terms]	3,277
#39	Search: Vincristin* OR Leurocristine OR Oncovin* OR Vincasar OR Marqibo OR Cellcristin OR Citomid OR Onkocristin OR Farmistin OR Vintec OR Vincrisul	32,566
#38	Search: Vincristine[MeSH Terms]	23,733
#37	Search: Etoposid* OR Etopophos OR Toposar OR VePesid OR Eposin OR Eposide OR Demethyl Epipodophyllotoxin Ethylidine Glucoside OR Eto GRY OR Exitop OR Lastet OR NSC 141540 OR NSC141540 OR Onkoposid OR Riboposid OR VP 16 213 OR VP 16213 OR VP 16 OR VP16 OR Celltop OR Etopos OR Etomedac	28,970
#36	Search: Etoposide[MeSH Terms]	17,053
#35	Search: Brentuximab Vedotin OR Adcetris OR cAC10 vcMMAE OR cAC10vcMMAE OR CAC10 1006 OR CAC101006 OR SGN 35 OR SGN35	1,133
#34	Search: Brentuximab Vedotin[MeSH Terms]	655
#33	Search: Polatuzumab Vedotin OR Polivy OR RG 7596 OR RG7596 OR ACD 79BVCMMAE OR ACD79B VCMMAE OR ACD 79B VCMMAE OR FCU 2711 OR FCU2711 OR DCDS 4501A OR DCDS4501A OR RO 5541077000 OR RO 5541077 000 OR RO5541077 000	259
#32	Search: Polatuzumab Vedotin [Supplementary Concept]	27

Criteria number	Search string	Number of hits
#31	Search: Bendamustin* OR Treanda OR Treakisym OR Ribomustin OR Levact OR Bendeka OR Ribomustine OR Belrapzo OR Cytostasan OR IMET 3393 OR Zimet	1,954
#30	Search: Bendamustine Hydrochloride[MeSH Terms]	892
#29	Search: Prednison* OR Prednisolone OR Deltasone OR "Liquid Pred" OR Orasone OR Sterapred OR Dehydrocortisone OR delta-Cortisone OR Rectodelt OR Ultracorten OR Winpred OR Cortan OR Cortancyl OR Panafcort OR Cutason OR Decortin OR Dacortin OR Decortisyl OR Encorton* OR Enkortolon OR Kortancyl OR Meticorten OR Panasol OR Predni Tablinen OR Prednidib OR Predniment OR Pronisone OR Sone	119,167
#28	Search: Prednisolone[MeSH Terms]	52,137
#27	Search: Prednisone[MeSH Terms]	40,083
#26	Search: Bleomycin* OR Blenoxane OR Bleocin OR Bleomicin* OR BLEO cell OR BLEOcell OR Bleolem OR Blanoxan	21,051
#25	Search: Bleomycin[MeSH Terms]	15,801
#24	Search: Vindesin* OR Eldisine OR Desacetylvinblastine amide OR Enison OR NSC 245467 OR NSC245467	1,878
#23	Search: Vindesine[MeSH Terms]	1,289
#22	Search: Cyclophosphamid* OR Cytophosphan* OR Endoxan OR Cytoxan OR Neosar OR Procytox OR Revimmune OR Cycloblastin OR Ciclofosfamid* OR Sendoxan OR B 518 OR B518 OR NSC 26271 OR NSC26271 OR Cyclophosphane	76,615
#21	Search: Cyclophosphamide[MeSH Terms]	54,830
#20	Search: Rituximab OR Rituxan OR Mabthera OR Truxima OR Riximyo OR Ruxience OR IDEC C2B8 OR GP2013	26,095
#19	Search: Rituximab[MeSH Terms]	15,962
#18	Search: Methylprednisolon* OR Medrol OR A-methaPred OR Metipred OR Urbason	28,097
#17	Search: Methylprednisolone[MeSH Terms]	19,988
#16	Search: Doxorubicin* OR Hydroxydaunorubicin OR Daunorubicin OR Adriamycin OR Caelyx OR Myocet OR Doxil OR Rubex OR Farmiblastina OR Ribodoxo OR Adriblastin* OR Adrimedac OR DOXO cell OR Doxolem OR Doxotec OR Onkodox	90,961
#15	Search: Doxorubicin[MeSH Terms]	59,558
#14	Search: Cytarabin* OR Cytosine Arabinoside OR Cytosar OR Depocyt OR Citarabina OR Arabinofuranosyl Cytidine OR Tarabine OR AraC OR Ara C OR Arabinosylcytosine OR Arabinofuranosylcytosine OR Aracytidine OR Aracytine OR Cytonal	22,044
#13	Search: Cytarabine[MeSH Terms]	14,983
#12	Search: Cisplatin* OR Carboplat* OR Platamin OR Neoplatin OR Cismaplat OR CDDP OR Cis-diamminedichloridoplatinum OR Cis-DDP OR Platino* OR Paraplatin* OR CBDCA OR NSC-119875 OR JM-8 OR JM8 OR NSC-241240 OR NSC241240 OR Platinum Diamminodichloride OR Cis-Platinum OR Dichlorodiammineplatinum OR Biocisplatinum OR Platidiam OR Platinwas OR Ribocarbo OR Neocarbo OR Carbosin OR Carbotec OR Ercar OR Nealorin OR Blastocarb	95,039
#11	Search: Carboplatin[MeSH Terms]	12,077
#10	Search: Cisplatin[MeSH Terms]	54,018

Criteria number	Search string	Number of hits
#9	Search: #8 AND #5	18,141
#8	Search: #6 OR #7	2,097,718
#7	Search: Recurr*[Title/Abstract] OR Reoccurr*[Title/Abstract] OR Relaps*[Title/Abstract] OR Refractory[Title/Abstract] OR Resist*[Title/Abstract] OR "R R"[Title/Abstract] OR "RR"[Title/Abstract] OR "R/R"[Title/Abstract]	2,034,845
#6	Search: Recurrence[MeSH Terms]	190,016
#5	Search: #1 OR #4	92,049
#4	Search: #2 AND #3	83,775
#3	Search: Diffuse[Title/Abstract] OR B Cell[Title/Abstract] OR Large Cell[Title/Abstract] OR Non Hodgkin*[Title/Abstract]	299,673
#2	Search: lymphoma[Title/Abstract] OR lymphomas[Title/Abstract]	186,110
#1	Search: Lymphoma, Large B-Cell, Diffuse[MeSH Terms]	20,785

Embase – Database

Table 12 Embase Search Strategy - Date of Search: June 29, 2021

Criteria number	Search string	Number of hits
#80	#78 NOT #79	481
#79	#78 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	553
#78	#8 AND #76 AND [4-2-2021]/sd NOT [2-7-2021]/sd	1,034
#77	#8 AND #76	18,721
#76	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75	1,665,593
#75	ashap OR 'r ashap' OR rashap OR acvbp OR 'lnh 87 protocol' OR 'r acvbp' OR racvbp OR rbenda OR 'r benda' OR ceop OR 'r ceop' OR rceop OR cepp OR 'r cepp' OR rcepp OR 'chop'/exp OR chop OR 'r chop'/exp OR 'r chop' OR 'rchop'/exp OR rchop OR 'r2 chop' OR dhaox OR 'r dhaox' OR rdhaox OR dhap OR 'r dhap' OR rdhap OR 'epoch'/exp OR epoch OR 'r epoch'/exp OR 'r epoch' OR 'repoch'/exp OR repoch OR 'da epoch'/exp OR 'da epoch' OR 'da epoch r'/exp OR 'da epoch r' OR daepochr OR eshap OR 'r eshap' OR reshap OR 'gdp'/exp OR gdp OR 'r gdp' OR rgdp OR gemox OR 'gemcitabine-oxaliplatin regimen' OR 'r gemox' OR rgemox OR 'ice'/exp OR ice OR 'r ice' OR 'rice'/exp OR rice OR iev OR 'r iev' OR riev OR igev OR 'r igev' OR rigev OR 'mine'/exp OR mine OR 'r mine' OR rmine OR beam OR 'mini-beam' OR 'r beam' OR rbeam OR 'best supportive care'/exp OR 'palliative therapy'/exp OR ((care NEAR/2 ('best support*' OR palliative)):ti,ab,kw)	536,783
#74	tisagenlecleucel:ti,ab,kw OR ctl019:ti,ab,kw OR kymriah:ti,ab,kw	799
#73	'tisagenlecleucel t'/de	1,231
#72	isocabtagene:ti,ab,kw OR 'liso-cel':ti,ab,kw	64
#71	'lisocabtagene maraleucel'/de	155
#70	axicabtagene:ti,ab,kw OR 'axi-cel':ti,ab,kw OR 'kte c19':ti,ab,kw OR yescarta:ti,ab,kw	660
#69	'axicabtagene ciloleucel'/de	871
#68	pixantrone:ti,ab,kw OR 'bbr 2778':ti,ab,kw OR bbr2778:ti,ab,kw OR pixuvri:ti,ab,kw	196
#67	'pixantrone'/de	274
#66	melphalan*:ti,ab,kw OR alkeran:ti,ab,kw OR evomela:ti,ab,kw OR 'l pam':ti,ab,kw OR 'l sarcolysine':ti,ab,kw OR melfalano:ti,ab,kw OR 'phenylalanine mustard':ti,ab,kw OR medphalan:ti,ab,kw OR sarkolysin*:ti,ab,kw OR merphalan:ti,ab,kw	15,525
#65	'melphalan'/de	39,428
#64	carmustin*:ti,ab,kw OR 'bcnu':ti,ab,kw OR 'bicnu':ti,ab,kw OR gliadel:ti,ab,kw OR fivb:ti,ab,kw OR nitrumon:ti,ab,kw	5,512
#63	'carmustine'/de	19,316

Criteria number	Search string	Number of hits
#62	mitoxantron*:ti,ab,kw OR mitozantrone:ti,ab,kw OR novantron*:ti,ab,kw OR dhaq:ti,ab,kw OR 'nsc 279836':ti,ab,kw OR nsc279836:ti,ab,kw OR 'nsc 287836':ti,ab,kw OR nsc287836:ti,ab,kw OR 'nsc 299195':ti,ab,kw OR nsc299195:ti,ab,kw OR 'nsc 301739*':ti,ab,kw OR nsc301739*:ti,ab,kw OR mitroxone:ti,ab,kw OR pralifan:ti,ab,kw OR 'cl 232325':ti,ab,kw OR cl232325:ti,ab,kw OR ralenova:ti,ab,kw OR onkotrone:ti,ab,kw	7,834
#61	'mitoxantrone'/de	24,001
#60	mesna:ti,ab,kw OR mesnex:ti,ab,kw OR 'asta d 7093':ti,ab,kw OR 'astad 7093':ti,ab,kw OR ziken:ti,ab,kw OR mistabron*:ti,ab,kw OR mucofluid:ti,ab,kw OR mitexan:ti,ab,kw OR 'ucb 3983':ti,ab,kw OR ucb3983:ti,ab,kw OR uromitexan:ti,ab,kw OR mesnum:ti,ab,kw	1,793
#59	'mesna'/de	6,137
#58	obinutuzumab:ti,ab,kw OR ga101:ti,ab,kw OR 'ga 10':ti,ab,kw OR afutuzumab:ti,ab,kw OR gazyva*:ti,ab,kw OR 'ro 5072759':ti,ab,kw OR ro5072759:ti,ab,kw OR 'r 7159':ti,ab,kw OR r7159:ti,ab,kw OR 'ga 101':ti,ab,kw	1,689
#57	'obinutuzumab'/de	2,746
#56	epirubicin*:ti,ab,kw OR ellence:ti,ab,kw OR pharmorubicin:ti,ab,kw OR epiadriamycin:ti,ab,kw OR pidorubicin*:ti,ab,kw OR '4 epidoxorubicin':ti,ab,kw OR '4 epi doxorubicin':ti,ab,kw OR '4 epi adriamycin':ti,ab,kw OR '4 epiadriamycin':ti,ab,kw OR '4 epi dxr':ti,ab,kw OR 'epi cell':ti,ab,kw OR epicell:ti,ab,kw OR epilem:ti,ab,kw OR 'imi 28':ti,ab,kw OR imi28:ti,ab,kw OR 'nsc 256942':ti,ab,kw OR nsc256942:ti,ab,kw OR farmorubicin*:ti,ab,kw	9,085
#55	'epirubicin'/de	29,860
#54	ifosfamid*:ti,ab,kw OR ifex:ti,ab,kw OR iphosphamide:ti,ab,kw OR isofosfamide:ti,ab,kw OR isophosphamide:ti,ab,kw OR isosfamide:ti,ab,kw OR 'iso endoxan':ti,ab,kw OR holoxan:ti,ab,kw OR 'nsc 109 724':ti,ab,kw OR 'nsc109 724':ti,ab,kw OR 'nsc 109724':ti,ab,kw OR nsc109724:ti,ab,kw OR 'asta z 4942':ti,ab,kw	9,225
#53	'ifosfamide'/de	31,603
#52	'pci 32765':ti,ab,kw OR pci32765:ti,ab,kw OR ibrutinib:ti,ab,kw OR imbruvica:ti,ab,kw OR ibrutix:ti,ab,kw OR 'cra 032765':ti,ab,kw	5,821
#51	'ibrutinib'/de	7,824
#50	vinorelbin*:ti,ab,kw OR navelbine:ti,ab,kw OR 'kw 2307':ti,ab,kw OR kw2307:ti,ab,kw	6,571
#49	'vinorelbine tartrate'/de	18,758
#48	gemcitabin*:ti,ab,kw OR gemzar:ti,ab,kw OR 'ly 188011':ti,ab,kw	30,794
#47	'gemcitabine'/de	60,879
#46	dexamethasone*:ti,ab,kw OR dextenza:ti,ab,kw OR ozurdex:ti,ab,kw OR dexpak:ti,ab,kw OR 'mk 125':ti,ab,kw OR dexametasona:ti,ab,kw OR decadron:ti,ab,kw OR baycadron:ti,ab,kw OR methylfluorprednisolone:ti,ab,kw OR hexadecadrol:ti,ab,kw OR decameth:ti,ab,kw OR decaspray:ti,ab,kw OR dexasone:ti,ab,kw OR maxidex:ti,ab,kw OR millicorten:ti,ab,kw OR oradexon:ti,ab,kw OR decaject:ti,ab,kw OR hexadrol:ti,ab,kw	83,493
#45	'dexamethasone'/de	162,388

Criteria number	Search string	Number of hits
#44	'brentuximab vedotin':ti,ab,kw OR adcetris:ti,ab,kw OR 'cac10 vcmmae':ti,ab,kw OR cac10vcmmae:ti,ab,kw OR 'cac10 1006':ti,ab,kw OR cac101006:ti,ab,kw OR 'sgn 35':ti,ab,kw OR sgn35:ti,ab,kw	2,431
#43	oxaliplatin*:ti,ab,kw OR eloxatin*:ti,ab,kw OR oxalatoplatin*:ti,ab,kw OR 'l-ohp cpd':ti,ab,kw OR 'act 078':ti,ab,kw	20,833
#42	'oxaliplatin'/de	42,949
#41	lenalidomid*:ti,ab,kw OR cdc501:ti,ab,kw OR 'cdc 501':ti,ab,kw OR cdc5013:ti,ab,kw OR 'cdc 5013':ti,ab,kw OR enmd0997:ti,ab,kw OR 'enmd 0997':ti,ab,kw OR revlimid:ti,ab,kw OR linamide:ti,ab,kw OR ladevina:ti,ab,kw OR 'imid3 cpd':ti,ab,kw OR 'cc 5013':ti,ab,kw OR cc5013:ti,ab,kw OR revimid:ti,ab,kw	13,186
#40	'lenalidomide'/de	20,921
#39	procarbazin*:ti,ab,kw OR matulane:ti,ab,kw OR natulan:ti,ab,kw OR indicarb:ti,ab,kw	3,053
#38	'procarbazine'/de	16,690
#37	vincristin*:ti,ab,kw OR leurocristine:ti,ab,kw OR oncovin*:ti,ab,kw OR vincasar:ti,ab,kw OR marqibo:ti,ab,kw OR cellcristin:ti,ab,kw OR citomid:ti,ab,kw OR onkocristin:ti,ab,kw OR farmistin:ti,ab,kw OR vintec:ti,ab,kw OR vincrisul:ti,ab,kw	28,315
#36	'vincristine'/de	105,225
#35	etoposid*:ti,ab,kw OR etopophos:ti,ab,kw OR toposar:ti,ab,kw OR vepesid:ti,ab,kw OR eposin:ti,ab,kw OR eposide:ti,ab,kw OR 'demethyl epipodophyllotoxin ethylidine glucoside':ti,ab,kw OR 'eto gry':ti,ab,kw OR exitop:ti,ab,kw OR lastet:ti,ab,kw OR 'nsc 141540':ti,ab,kw OR nsc141540:ti,ab,kw OR onkoposid:ti,ab,kw OR riboposid:ti,ab,kw OR 'vp 16 213':ti,ab,kw OR 'vp 16213':ti,ab,kw OR 'vp 16':ti,ab,kw OR vp16:ti,ab,kw OR celltop:ti,ab,kw OR etopos:ti,ab,kw OR etomedac:ti,ab,kw	35,330
#34	'etoposide'/de	91,125
#33	'brentuximab vedotin'/de	4,125
#32	'polatuzumab vedotin':ti,ab,kw OR polivy:ti,ab,kw OR 'rg 7596':ti,ab,kw OR rg7596:ti,ab,kw OR 'acd 79bvcmmae':ti,ab,kw OR 'acd79b vcmmae':ti,ab,kw OR 'acd 79b vcmmae':ti,ab,kw OR 'fcu 2711':ti,ab,kw OR fcu2711:ti,ab,kw OR 'dcds 4501a':ti,ab,kw OR dcds4501a:ti,ab,kw OR 'ro 5541077000':ti,ab,kw OR 'ro 5541077 000':ti,ab,kw OR 'ro5541077 000':ti,ab,kw	242
#31	'polatuzumab vedotin'/de	348
#30	bendamustin*:ti,ab,kw OR treanda:ti,ab,kw OR treakisym:ti,ab,kw OR ribomustin:ti,ab,kw OR levact:ti,ab,kw OR bendeka:ti,ab,kw OR ribomustine:ti,ab,kw OR belrapzo:ti,ab,kw OR cytostasan:ti,ab,kw OR 'imet 3393':ti,ab,kw OR 'zimet 3393':ti,ab,kw	4,400
#29	'bendamustine'/de	7,355
#28	prednison*:ti,ab,kw OR prednisolone:ti,ab,kw OR deltasone:ti,ab,kw OR 'liquid pred':ti,ab,kw OR orasone:ti,ab,kw OR sterapred:ti,ab,kw OR dehydrocortisone:ti,ab,kw OR 'delta cortisone':ti,ab,kw OR rectodelt:ti,ab,kw OR ultracorten:ti,ab,kw OR winpred:ti,ab,kw OR cortan:ti,ab,kw OR cortancyl:ti,ab,kw OR panafcort:ti,ab,kw OR cutason:ti,ab,kw OR decortin:ti,ab,kw OR dacortin:ti,ab,kw OR decortisyl:ti,ab,kw OR encorton*:ti,ab,kw OR enkortolon:ti,ab,kw OR kortancyl:ti,ab,kw OR meticorten:ti,ab,kw OR panasol:ti,ab,kw OR 'predni tablinen':ti,ab,kw OR prednidib:ti,ab,kw OR predniment:ti,ab,kw OR pronisone:ti,ab,kw OR sone:ti,ab,kw	94,327

Criteria number	Search string	Number of hits
#27	'prednisolone'/de	137,275
#26	'prednisone'/de	185,366
#25	bleomycin*:ti,ab,kw OR blenoxane:ti,ab,kw OR bleocin:ti,ab,kw OR bleomicin*:ti,ab,kw OR 'bleo cell':ti,ab,kw OR bleocell:ti,ab,kw OR bleolem:ti,ab,kw OR blanoxan:ti,ab,kw	23,086
#24	'bleomycin'/exp	51,544
#23	vindesin*:ti,ab,kw OR eldisine:ti,ab,kw OR 'desacetylvinblastine amide':ti,ab,kw OR enison:ti,ab,kw OR 'nsc 245467':ti,ab,kw OR nsc245467:ti,ab,kw	1,809
#22	'vindesine'/de	7,712
#21	cyclophosphamid*:ti,ab,kw OR cytophosphan*:ti,ab,kw OR endoxan:ti,ab,kw OR cytoxan:ti,ab,kw OR neosar:ti,ab,kw OR procytox:ti,ab,kw OR revimmune:ti,ab,kw OR cycloblastin:ti,ab,kw OR ciclofosfamid*:ti,ab,kw OR sendoxan:ti,ab,kw OR 'b 518':ti,ab,kw OR b518:ti,ab,kw OR 'nsc 26271':ti,ab,kw OR nsc26271:ti,ab,kw OR cyclophosphane:ti,ab,kw	82,019
#20	'cyclophosphamide'/de	228,744
#19	rituximab:ti,ab,kw OR rituxan:ti,ab,kw OR mabthera:ti,ab,kw OR truxima:ti,ab,kw OR riximyo:ti,ab,kw OR ruxience:ti,ab,kw OR 'idec c2b8':ti,ab,kw OR gp2013:ti,ab,kw	50,967
#18	'rituximab'/de	86,863
#17	methylprednisolon*:ti,ab,kw OR medrol:ti,ab,kw OR 'a methapred':ti,ab,kw OR metipred:ti,ab,kw OR urbason:ti,ab,kw	28,679
#16	'methylprednisolone'/de	103,036
#15	doxorubicin*:ti,ab,kw OR hydroxydaunorubicin:ti,ab,kw OR daunorubicin:ti,ab,kw OR adriamycin:ti,ab,kw OR caelyx:ti,ab,kw OR myocet:ti,ab,kw OR doxil:ti,ab,kw OR rubex:ti,ab,kw OR farmiblastina:ti,ab,kw OR ribodoxo:ti,ab,kw OR adriblastin*:ti,ab,kw OR adrimedac:ti,ab,kw OR 'doxo cell':ti,ab,kw OR doxolem:ti,ab,kw OR doxotec:ti,ab,kw OR onkodox:ti,ab,kw	89,871
#14	'doxorubicin'/de	197,750
#13	cytarabin*:ti,ab,kw OR 'cytosine arabinoside':ti,ab,kw OR cytosar:ti,ab,kw OR depocyt:ti,ab,kw OR citarabina:ti,ab,kw OR 'arabinofuranosyl cytidine':ti,ab,kw OR tarabine:ti,ab,kw OR arac:ti,ab,kw OR 'ara c':ti,ab,kw OR arabinosylcytosine:ti,ab,kw OR arabinofuranosylcytosine:ti,ab,kw OR aracytidine:ti,ab,kw OR aracytine:ti,ab,kw OR cytonal:ti,ab,kw	25,383
#12	'cytarabine'/de	64,276
#11	cisplatin*:ti,ab,kw OR carboplat*:ti,ab,kw OR platamin:ti,ab,kw OR neoplatin:ti,ab,kw OR cismaplat:ti,ab,kw OR cddp:ti,ab,kw OR 'cis diamminedichloridoplatinum':ti,ab,kw OR 'cis ddp':ti,ab,kw OR platino*:ti,ab,kw OR paraplatin*:ti,ab,kw OR cbdca:ti,ab,kw OR 'nsc 119875':ti,ab,kw OR 'jm 8':ti,ab,kw OR jm8:ti,ab,kw OR 'nsc 241240':ti,ab,kw OR nsc241240:ti,ab,kw OR 'platinum diamminodichloride':ti,ab,kw OR 'cis platinum':ti,ab,kw OR dichlorodiammineplatinum:ti,ab,kw OR biocisplatinum:ti,ab,kw OR platidiam:ti,ab,kw OR platinwas:ti,ab,kw OR ribocarbo:ti,ab,kw OR neocarbo:ti,ab,kw OR carbosin:ti,ab,kw OR carbotec:ti,ab,kw OR ercar:ti,ab,kw OR nealorin:ti,ab,kw OR blastocarb:ti,ab,kw	122,539
#10	'carboplatin'/de	73,757
#9	'cisplatin'/de	193,089
#8	#7 AND #3	31,831

Criteria number	Search string	Number of hits
#7	#4 OR #5 OR #6	2,901,990
#6	recurr*:ti,ab,kw OR reoccurr*:ti,ab,kw OR relaps*:ti,ab,kw OR refractory:ti,ab,kw OR resist*:ti,ab,kw OR 'r r':ti,ab,kw OR 'rr':ti,ab,kw OR 'r/r':ti,ab,kw	2,809,200
#5	'cancer recurrence'/de	232,125
#4	'recurrent disease'/de	190,953
#3	#1 OR #2	116,966
#2	(lymphoma* NEAR/5 ('b cell' OR 'large cell' OR diffuse OR 'non hodgkin*')):ti,ab,kw	113,501
#1	'diffuse large b cell lymphoma'/exp	16,474

Cochrane Library – Database

Table 13 Cochrane Library database – Date of search: June 28, 2021

Criteria number	Search string	Number of hits
#1	MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees	425
#2	Lymphoma* NEAR/8 (Diffuse OR (B NEAR Cell) OR "Large Cell" OR (Non Near Hodgkin*)):ti,ab,kw	5162
#3	#1 OR #2	5162
#4	MeSH descriptor: [Recurrence] this term only	12286
#5	(Recurr* OR Reoccurr* OR Relaps* OR Refractory OR Resist* OR "R R" OR "RR" OR "R/R"):ti,ab,kw	198607
#6	#4 OR #5	198607
#7	#3 AND #6 with Publication Year from 2021 to 2021, in Trials	23

Clinical trials.gov

Table 14 Clinical trials.gov database – Date of search: June 28, 2021

Clinical trials.gov	Search of: refractory OR recurrent OR relapsed | Diffuse Large B Cell Lymphoma | First posted from 02/04/2021 to 06/26/2021	30 results

Grey Literature

Table 15 Grey Literature Search - Date of Search: June 29, 2021

Canadian Agency for Drugs and Technologies in Health (CADTH). Search https://www.cadth.ca/search?keywords	June 29, 2021 1 result	diffuse b cell lymphoma
National Institute for Health and Care Excellence (NICE). http://www.nice.org.uk/	June 29, 2021 0 results	diffuse b cell lymphoma
Scottish Medicines Consortium https://www.scottishmedicines.org.uk/	June 29, 2021 0 results	diffuse b cell lymphoma
All Wales Medicines Strategy Group (AWMSG) http://www.awmsg.org/	June 29, 2021 0 result	diffuse b cell lymphoma
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, (IQWiG) https://www.iqwig.de/	June 29, 2021 0 results	Browsed publications
HAS https://www.has-sante.fr/	June 29, 2021 1 results	lymphoma
Pharmaceutical Benefits Advisory Committee (PBAC) https://pbac.pbs.gov.au/	June 29, 2021 0 results	Browsed site
ESMO https://www.esmo.org/	June 29, 2021 results	Diffuse AND lymphoma
ICER https://icer.org/	June 29, 2021 0 results	lymphoma

Complete Database

Table 16 Complete Database Results

Database	Total Hits	After Duplicates Removed
Medline (Pubmed)	162	38
Embase	481	448
Embase Conference Abstracts	553	549
Cochrane Library	23	21
Clinical trials.gov	30	30
CADTH	1	1
NICE	0	0
SMC	0	0
AWMSG	0	0
IQWIG	0	0
HAS	1	1
PBAC	0	0
ESMO	0	0
ICER	0	0
TOTAL	**1251**	**1088**

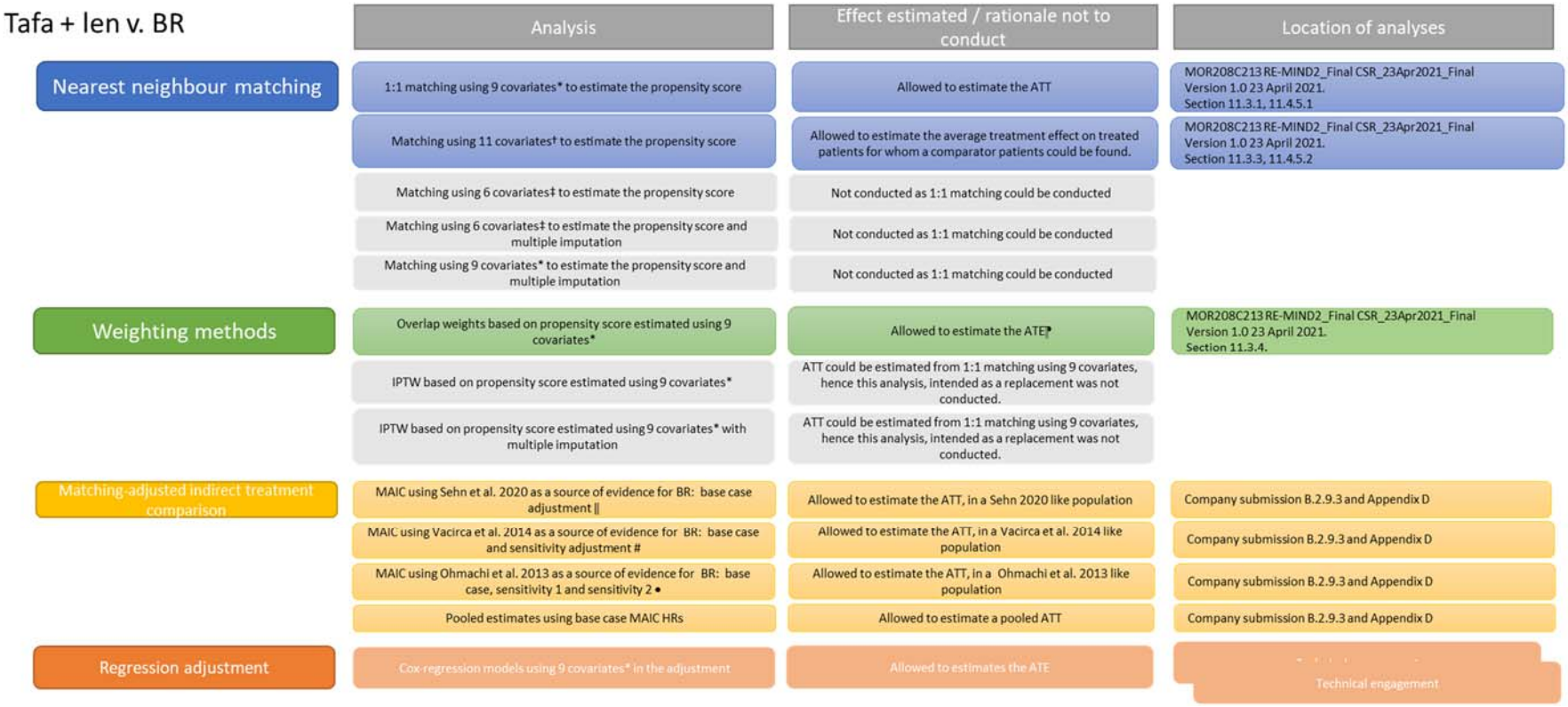
Appendix TE2. Overview of ITC analyses

Summary of Analyses

Tafa + len v. POLA + BR

	Analysis	Effect estimated / rationale not to conduct	Location of analyses
Nearest neighbour matching	1:1 matching using 9 covariates* to estimate the propensity score	Could not be conducted as less comparator patients were recruited compared to treated patients	
	Matching using 11 covariates† to estimate the propensity score	Could not be conducted as less comparator patients were recruited compared to treated patients	
	Matching using 6 covariates‡ to estimate the propensity score	Allowed to estimate the average treatment effect on treated patients for whom a comparator patients could be found.	MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 Version 1.0 Aug 2021. Section 7.1.2 and 7.1.3
	Matching using 6 covariates‡ to estimate the propensity score and multiple imputation	Allowed to estimate the average treatment effect on treated patients for whom a comparator patients could be found.	MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 Version 1.0 Aug 2021. Section 7.1.2 and 7.1.3
	Matching using 9 covariates* to estimate the propensity score and multiple imputation	Allowed to estimate the average treatment effect on treated patients for whom a comparator patients could be found.	MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 Version 1.0 Aug 2021. Section 7.1.2 and 7.1.3
Weighting methods	Overlap weights based on propensity score estimated using 9 covariates*	Allowed to estimate the ATE⁋	MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 TLFs p315
	IPTW based on propensity score estimated using 9 covariates*	Allowed to estimate the ATT. Results of these analyses should interpreted with caution due the observed imbalances in treatment cohorts.	MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 Version 1.0 Aug 2021. Section 7.1.2 and 7.1.3
	IPTW based on propensity score estimated using 9 covariates* with multiple imputation	Allowed to estimate the ATT. Results of these analyses should interpreted with caution due the observed imbalances in treatment cohorts	MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 Version 1.0 Aug 2021. Section 7.1.2 and 7.1.3
Matching-adjusted indirect treatment comparison	MAIC using Sehn et al. 2020 as a source of evidence for POLA + BR: base case adjustment ‖	Allowed to estimate the ATT, in a Sehn 2020 like population	Company submission B.2.9.3 and Appendix D
	MAIC using Sehn et al. 2020 as a source of evidence for POLA + BR: sensitivity adjustment 1 #	Allowed to estimate the ATT, in a Sehn 2020 like population	Company submission Appendix D
	MAIC using Sehn et al. 2020 as a source of evidence for POLA + BR: sensitivity adjustment 2 #	Allowed to estimate the ATT, in a Sehn 2020 like population	Company submission Appendix D
Regression adjustment	Cox-regression models using 9 covariates* in the adjustment	Allowed to estimates the ATE	Technical engagement
	Cox-regression models using 9 covariates‡ in the adjustment with MI	Allowed to estimates the ATE	Technical engagement
	Cox-regression models using 6 covariates‡ in the adjustment with MI	Allowed to estimates the ATE	Technical engagement

* age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline.
† age, ECOG, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, history of primary progression, history of early relapse, prior ASCT, anaemia at baseline, neutropenia at baseline.
‡ age, ECOG, refractoriness to last therapy, primary refractoriness, number of prior lines of therapy and prior treatment with ASCT
⁋ analyses conducted on the primary outcome only: OS
‖ age, transformed indolent lymphoma, centrally confirmed DLBCL histology, ECOG, IPI, number of prior lines of therapy, refractoriness to last therapy line, prior treatment with ASCT
Sensitivity 1: age, sex, transformed indolent lymphoma, centrally confirmed DLBCL histology, ECOG, IPI, Ann-Arbor stage, bulky disease at baseline number of prior lines of therapy, refractoriness to last therapy line, prior treatment with ASCT, duration of response to prior line; Sensitivity 2: same factors except duration of response to prior line



Tafa + len v. BR	Analysis	Effect estimated / rationale not to conduct	Location of analyses
Nearest neighbour matching	1:1 matching using 9 covariates* to estimate the propensity score	Allowed to estimate the ATT	MOR208C213 RE-MIND2_Final CSR_23Apr2021_Final Version 1.0 23 April 2021. Section 11.3.1, 11.4.5.1
	Matching using 11 covariates† to estimate the propensity score	Allowed to estimate the average treatment effect on treated patients for whom a comparator patients could be found.	MOR208C213 RE-MIND2_Final CSR_23Apr2021_Final Version 1.0 23 April 2021. Section 11.3.3, 11.4.5.2
	Matching using 6 covariates‡ to estimate the propensity score	Not conducted as 1:1 matching could be conducted	
	Matching using 6 covariates‡ to estimate the propensity score and multiple imputation	Not conducted as 1:1 matching could be conducted	
	Matching using 9 covariates* to estimate the propensity score and multiple imputation	Not conducted as 1:1 matching could be conducted	
Weighting methods	Overlap weights based on propensity score estimated using 9 covariates*	Allowed to estimate the ATE⁋	MOR208C213 RE-MIND2_Final CSR_23Apr2021_Final Version 1.0 23 April 2021. Section 11.3.4.
	IPTW based on propensity score estimated using 9 covariates*	ATT could be estimated from 1:1 matching using 9 covariates, hence this analysis, intended as a replacement was not conducted.	
	IPTW based on propensity score estimated using 9 covariates* with multiple imputation	ATT could be estimated from 1:1 matching using 9 covariates, hence this analysis, intended as a replacement was not conducted.	
Matching-adjusted indirect treatment comparison	MAIC using Sehn et al. 2020 as a source of evidence for BR: base case adjustment ‖	Allowed to estimate the ATT, in a Sehn 2020 like population	Company submission B.2.9.3 and Appendix D
	MAIC using Vacirca et al. 2014 as a source of evidence for BR: base case and sensitivity adjustment #	Allowed to estimate the ATT, in a Vacirca et al. 2014 like population	Company submission B.2.9.3 and Appendix D
	MAIC using Ohmachi et al. 2013 as a source of evidence for BR: base case, sensitivity 1 and sensitivity 2 •	Allowed to estimate the ATT, in a Ohmachi et al. 2013 like population	Company submission B.2.9.3 and Appendix D
	Pooled estimates using base case MAIC HRs	Allowed to estimate a pooled ATT	Company submission B.2.9.3 and Appendix D
Regression adjustment	Cox-regression models using 9 covariates* in the adjustment	Allowed to estimates the ATE	Technical engagement

* age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline.
† age, ECOG, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, history of primary progression, history of early relapse, prior ASCT, anaemia at baseline, neutropenia at baseline.
‡ age, ECOG, refractoriness to last therapy, primary refractoriness, number of prior lines of therapy and prior treatment with ASCT
⁋ analyses conducted on the primary outcome only: OS
‖ age, transformed indolent lymphoma, centrally confirmed DLBCL histology, ECOG, IPI, number of prior lines of therapy, refractoriness to last therapy line, prior treatment with ASCT. No sensitivity could be conducted due to small ESS
Base case: age, sex, ECOG, IPI, Ann-Arbor stage number of prior lines, prior treatment with ASCT; Sensitivity: same factors with more granular adjustment (e.g. adjustment for % of patients with ECOG 1 and 2, instead of ECOG 1-2). Analyses only conducted on PFS as no OS data was available
• Base case: Age, proportion of elderly patients, ECOG, IPI, history of transformed indolent lymphoma, number of prior lines, prior treatment with ASCT, refractoriness to last line of therapy; Sensitivity 1: same factors as base case except the proportion of elderly patients, with the addition, of sex, LDH levels and Ann-Arbor staging; Sensitivity 2: same factors as base case except proportion of elderly patients. Analyses only conducted on PFS as no OS data was available

Tafa + len v. RGemOx	Analysis	Effect estimated / rationale not to conduct	Location of analyses
Nearest neighbour matching	1:1 matching using 9 covariates* to estimate the propensity score	Allowed to estimate the ATT	MOR208C213 RE-MIND2_Final CSR_23Apr2021_Final Version 1.0 23 April 2021. Section 11.3.1, 11.4.5.1
	Matching using 11 covariates† to estimate the propensity score	Allowed to estimate the average treatment effect on treated patients for whom a comparator patients could be found.	MOR208C213 RE-MIND2_Final CSR_23Apr2021_Final Version 1.0 23 April 2021. Section 11.3.3, 11.4.5.2
	Matching using 6 covariates ‡ to estimate the propensity score	Not conducted as 1:1 matching could be conducted	
	Matching using 6 covariates‡ to estimate the propensity score and multiple imputation	Not conducted as 1:1 matching could be conducted	
	Matching using 9 covariates* to estimate the propensity score and multiple imputation	Not conducted as 1:1 matching could be conducted	
Weighting methods	Overlap weights based on propensity score estimated using 9 covariates*	Allowed to estimate the ATE ⁋	MOR208C213 RE-MIND2_Final CSR_23Apr2021_Final Version 1.0 23 April 2021. Section 11.3.4.
	IPTW based on propensity score estimated using 9 covariates*	ATT could be estimated from 1:1 matching using 9 covariates, hence this analysis, intended as a replacement was not conducted.	
	IPTW based on propensity score estimated using 9 covariates* with multiple imputation	ATT could be estimated from 1:1 matching using 9 covariates, hence this analysis, intended as a replacement was not conducted.	
Matching-adjusted indirect treatment comparison	MAIC using Mounier et al. 2013 as a source of evidence for RGemOx ‖	Allowed to estimate the ATT, in a Mounier et al. 2013 like-population. This analysis is only provided as a scenario as the MAIC faced considerable uncertainty.	Company submission B.2.9.3 and Appendix D
Regression adjustment	Cox-regression models using 9 covariates* in the adjustment	Allowed to estimates the ATE	Technical engagement

* age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline.
† age, ECOG, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, history of primary progression, history of early relapse, prior ASCT, anaemia at baseline, neutropenia at baseline.
‡ age, ECOG, refractoriness to last therapy, primary refractoriness, number of prior lines of therapy and prior treatment with ASCT
⁋ analyses conducted on the primary outcome only: OS
‖ age, ECOG, IPI, cell of origin of the disease, number of patients with 3 or more prior lines, prior treatment with ASCT

Balancing of populations

Tafa + len v. PBR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following matching on 6 covariates

Factor	Level	TAFA + LEN (N=24)	POLA + BR (N=24)	SMD
Age	<70	6 (25.0)	6 (25.0)	0.00
	≥70	18 (75.0)	18 (75.0)	
Refractoriness to last therapy	Yes	17 (70.8)	17 (70.8)	0.00
	No	7 (29.2)	7 (29.2)	
Number of prior lines	1	8 (33.3)	8 (33.3)	0.00
	2-3	16 (66.7)	16 (66.7)	
History of primary refractoriness	Yes	8 (33.3)	8 (33.3)	0.00
	No	16 (66.7)	16 (66.7)	
Prior ASCT	Yes	0	0	Not estimable
	No	24 (100.0)	24 (100.0)	
ECOG	0-1	22 (91.7)	22 (91.7)	0.00
	≥2	2 (8.3)	2 (8.3)	

Source: MOR208C213 TLF, Table 14.1.6.26

RE-MIND2: Baseline characteristics following matching on 6 covariates with MI

Factor	Level	TAFA + LEN (N=39)	POLA + BR (N=39)	SMD
Age	<70	[redacted]	[redacted]	[redacted]
	≥70	[redacted]	[redacted]	
Refractoriness to last therapy	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Number of prior lines	1	[redacted]	[redacted]	[redacted]
	2-3	[redacted]	[redacted]	
History of primary refractoriness	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Prior ASCT	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
ECOG	0-1	[redacted]	[redacted]	[redacted]
	≥2	[redacted]	[redacted]	
	Missing	[redacted]	[redacted]	

* Because of data missingness on the covariates, SMD could not be derived.
Source: MOR208C213 TLF, Table 14.1.5.28

Abbreviations: ASCT = autologous stem cell transplant; ECOG = eastern collaborative oncology group; ND = not defined; POLA + BR = platuzumab + bendamustine + rituximab; SMD = standardised mean difference; TAFA + LEN = tafasitamab + lenalidomide

Tafa + len v. PBR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following weighting using overlap weights	Baseline characteristics following weighting using MAIC
By construction, this method allows to achieve perfect balancing of the cohorts. Age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline were included in the derivation of the weights	By construction, this method allows to achieve perfect balancing of the cohorts: • In base case analyses Age, centrally confirmed DLBCL histology, proportion of patients with transformed indolent lymphoma, ECOG, IPI, number of prior lines of therapy, refractoriness to last therapy line and prior treatment with ASCT were included in the weight derivation. • In sensitivity 1 age, sex, transformed indolent lymphoma, centrally confirmed DLBCL histology, ECOG, IPI, Ann-Arbor stage, bulky disease at baseline number of prior lines of therapy, refractoriness to last therapy line, prior treatment with ASCT, duration of response to prior line were included in the weight derivation. • In sensitivity 2 the same factors as included in sensitivity 1 except duration of response to prior line were included in the weight derivation

Tafa + len v. PBR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following matching on 9 covariates with MI

Factor	Level	TAFA + LEN (N=39); n (%)	POLA + BR (N=39); n (%)	SMD
Age	<70	[redacted]	[redacted]	[redacted]
	≥70	[redacted]	[redacted]	
Ann-Arbor stage	I/II	[redacted]	[redacted]	[redacted]
	III/IV	[redacted]	[redacted]	
	Missing	[redacted]	[redacted]	
Refractoriness to last therapy	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Number of prior lines	1	[redacted]	[redacted]	[redacted]
	2-3	[redacted]	[redacted]	
History of primary refractoriness	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Prior ASCT	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	

Factor	Level	TAFA + LEN (N=39); n (%)	POLA + BR (N=39); n (%)	SMD
Elevated LDH	LDH>ULN	[redacted]	[redacted]	[redacted]
	LDH≤ULN	[redacted]	[redacted]	
	Missing	[redacted]	[redacted]	
Neutropenia	ANC < 1.5×10^9/L	[redacted]	[redacted]	[redacted]
	ANC ≥ 1.5×10^9/L	[redacted]	[redacted]	
	Missing	[redacted]	[redacted]	
Anaemia	Hb < 10g/dL	[redacted]	[redacted]	[redacted]
	Hb ≥ 10g/dL	[redacted]	[redacted]	
	Missing	[redacted]	[redacted]	

* Because of data missingness on the covariates, SMD could not be derived.
Source: MOR208C213 TLF, Table 14.1.5.27

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; Hb = Haemoglobin; LDH = lactate dehydrogenase; ND = not defined; POLA + BR = polatuzumab + bendamustine + rituximab; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. PBR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following IPTW on 9 covariates

Factor	Level	TAFA + LEN (N=76); n (%)	POLA + BR (Weighted N=72); n (%)	SMDs
Age	<65	[redacted]	[redacted]	[redacted]
	≥65	[redacted]	[redacted]	
Ann-Arbor stage	I/II	[redacted]	[redacted]	[redacted]
	III/IV	[redacted]	[redacted]	
Refractoriness to last therapy	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Number of prior lines	1	[redacted]	[redacted]	[redacted]
	2-3	[redacted]	[redacted]	
History of primary refractoriness	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Prior ASCT	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	

Factor	Level	TAFA + LEN (N=76)	POLA + BR (Weighted N=72); n (%)	SMDs
Elevated LDH	LDH>ULN	[redacted]	[redacted]	[redacted]
	LDH≤ULN	[redacted]	[redacted]	
Neutropenia	ANC < 1.5×10^9/L	[redacted]	[redacted]	[redacted]
	ANC ≥ 1.5×10^9/L	[redacted]	[redacted]	
Anaemia	Hb < 10g/dL	[redacted]	[redacted]	[redacted]
	Hb ≥ 10g/dL	[redacted]	[redacted]	

*SMD on Age ≥70

Source: New analyses; MOR208C213_Statistical Report_posthoc_final_AUGUST 2021 Version 1.0 Aug 2021, table 66.

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; Hb = Haemoglobin; LDH = lactate dehydrogenase; POLA + BR = polatuzumab + bendamustine + rituximab; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. PBR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following IPTW on 9 covariates with MI

Factor	Level	TAFA + LEN (N=76); n (%)	POLA + BR (Weighted N=91); n (%)	SMD
Age	<65	[redacted]	[redacted]	[redacted]
	≥65	[redacted]	[redacted]	
Ann-Arbor stage	Missing	[redacted]	[redacted]	[redacted]
	I/II	[redacted]	[redacted]	
	III/IV	[redacted]	[redacted]	
Refractoriness to last therapy	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Number of prior lines	1	[redacted]	[redacted]	[redacted]
	2-3	[redacted]	[redacted]	
History of primary refractoriness	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Prior ASCT	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	

Factor	Level	TAFA + LEN (N=76); n (%)	POLA + BR (Weighted N=91); n (%)	SMD
Elevated LDH	Missing	[redacted]	[redacted]	[redacted]
	LDH>ULN	[redacted]	[redacted]	
	LDH≤ULN	[redacted]	[redacted]	
Neutropenia	Missing	[redacted]	[redacted]	[redacted]
	ANC < 1.5×10^9/L	[redacted]	[redacted]	
	ANC ≥ 1.5×10^9/L	[redacted]	[redacted]	
Anaemia	Missing	[redacted]	[redacted]	[redacted]
	Hb < 10g/dL	[redacted]	[redacted]	
	Hb ≥ 10g/dL	[redacted]	[redacted]	

* Because of data missingness on the covariates, SMD could not be derived.
Source: New analyses;

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; Hb = Haemoglobin; LDH = lactate dehydrogenase; ND = not defined; POLA + BR = polatuzumab + bendamustine + rituximab; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. BR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following 1:1 matching on 9 covariates

Factor	Level	TAFA + LEN (N=75) ; n (%)	BR (N=75); n (%)	SMD
Age	<70	33 (44.0)	33 (44.0)	0.0
	≥70	42 (56.0)	42 (56.0)	
Ann-Arbor stage	I/II	18 (24.0)	19 (25.3)	0.03
	III/IV	57 (76.0)	56 (74.7)	
Refractoriness to last therapy	Yes	33 (44.0)	32 (42.7)	0.03
	No	42 (56.0)	43 (57.3)	
Number of prior lines	1	39 (52.0)	39 (52.0)	0.00
	2-3	36 (48.0)	36 (48.0)	
History of primary refractoriness	Yes	14 (18.7)	19 (25.3)	0.16
	No	61 (81.3)	56 (74.7)	
Prior ASCT	Yes	9 (12.0)	14 (18.7)	0.19
	No	66 (88.0)	61 (81.3)	

Factor	Level	TAFA + LEN (N=75); n (%)	BR (N=75); n (%)	SMD
Elevated LDH	LDH>ULN	41 (54.7)	37 (49.3)	0.11
	LDH≤ULN	34 (45.3)	38 (50.7)	
Neutropenia	ANC < 1.5×10^9/L	2 (2.7)	4 (5.3)	0.14
	ANC ≥ 1.5×10^9/L	73 (97.3)	71 (94.7)	
Anaemia	Hb < 10g/dL	6 (8.0)	5 (6.7)	0.05
	Hb ≥ 10g/dL	69 (92.0)	70 (93.3)	

Source: MOR208C213 TLF Table 14.1.6.8 - BR

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; BR = bendamustine + rituximab; Hb = Haemoglobin; LDH = lactate dehydrogenase; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. BR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following matching on 11 covariates

Factor	Level	TAFA + LEN (N=65); n (%)	BR (N=65); n (%)	SMD
Age	<70	[redacted]	[redacted]	[redacted]
	≥70	[redacted]	[redacted]	
Ann-Arbor stage	I/II	[redacted]	[redacted]	[redacted]
	III/IV	[redacted]	[redacted]	
Refractoriness to last therapy	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Number of prior lines	1	[redacted]	[redacted]	[redacted]
	2-3	[redacted]	[redacted]	
Prior ASCT	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Elevated LDH	LDH>ULN	[redacted]	[redacted]	[redacted]
	LDH≤ULN	[redacted]	[redacted]	

Factor	Level	TAFA + LEN (N=65); n (%)	BR (N=65); n (%)	SMD
Neutropenia	ANC<1.5×10^9/L	[redacted]	[redacted]	[redacted]
	ANC≥1.5×10^9/L	[redacted]	[redacted]	
Anaemia	Hb<10g/dL	[redacted]	[redacted]	[redacted]
	Hb≥10g/dL	[redacted]	[redacted]	
Primary progressive	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Early relapse	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
ECOG	0-1	[redacted]	[redacted]	[redacted]
	>=2	[redacted]	[redacted]	

Source: MOR208C213 TLF Table 14.1.6.10

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; BR = bendamustine + rituximab; Hb = Haemoglobin; LDH = lactate dehydrogenase; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. BR – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following weighting using overlap weights

By construction, this method allows to achieve perfect balancing of the cohorts. Age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline were included in the derivation of the weights

Tafa + len v. BR – Balancing of cohorts following population adjustment

Baseline characteristics following weighting using MAIC v. BR using Sehn et al.2020 as source of evidence

By construction, this method allows to achieve perfect balancing of the cohorts. Age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline were included in the derivation of the weights

Baseline characteristics following weighting using MAIC v. BR using Vacirca et al. 2014 as source of evidence

By construction, this method allows to achieve perfect balancing of the cohorts. In the base case Age, sex, ECOG, IPI, Ann-Arbor stage, number of prior lines of therapy and prior treatment with ASCT were included in the weight derivation. In the sensitivity model, the same set of factors were used but with a more granular adjustment (e.g. adjustment for proportion of patients with ECOG1 and ECOG2 at baseline instead of ECOG 1-2)

Baseline characteristics following weighting using MAIC v. BR using Ohmachi et al. 2014 as source of evidence

By construction, this method allows to achieve perfect balancing of the cohorts.

- In base case analyses age, ECOG, IPI, history of transformed indolent lymphoma, refractoriness to last therapy line, number of prior lines of therapy and prior treatment with ASCT were included in weight derivations.
- In sensitivity 1, to the base case adjustment was added an adjustment on sex, LDH levels and Ann-Arbor stage and the adjustment on the proportion of elderly patients (higher in L-MIND) was removed.
- In sensitivity 2, the same factors as in the base case adjustment were considered except the proportion of elderly patients (higher in L-MIND).

Tafa + len v. R-GemOx – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following 1:1 matching on 9 covariates

Factor	Level	TAFA + LEN (N=74); n (%)	R-GemOx (N=74); n (%)	SMD
Age	<70	31 (41.9)	26 (35.1)	0.14
	≥70	43 (58.1)	48 (64.9)	
Ann-Arbor stage	I/II	18 (24.3)	15 (20.3)	0.10
	III/IV	56 (75.7)	59 (79.7)	
Refractoriness to last therapy	Yes	33 (44.6)	29 (39.2)	0.11
	No	41 (55.4)	45 (60.8)	
Number of prior lines	1	39 (52.7)	41 (55.4)	0.05
	2-3	35 (47.3)	33 (44.6)	
History of primary refractoriness	Yes	14 (18.9)	14 (18.9)	0.00
	No	60 (81.1)	60 (81.1)	
Prior ASCT	Yes	8 (10.8)	8 (10.8)	0.00
	No	66 (89.2)	66 (89.2)	
Elevated LDH	LDH>ULN	41 (55.4)	48 (64.9)	0.19
	LDH≤ULN	33 (44.6)	26 (35.1)	
Neutropenia	ANC < 1.5×10^9/L	2 (2.7)	5 (6.8)	0.19
	ANC ≥ 1.5×10^9/L	72 (97.3)	69 (93.2)	
Anaemia	Hb < 10g/dL	6 (8.1)	5 (6.8)	0.05
	Hb ≥ 10g/dL	68 (91.9)	69 (93.2)	

Source: MOR208C213 TLF Table 14.1.6.8 – R-GemOx

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; Hb = Haemoglobin; LDH = lactate dehydrogenase; R-GemOx = rituximab + gemcitabine + oxaliplatin; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. R-GemOx – Balancing of cohorts following population adjustment

RE-MIND2: Baseline characteristics following matching on 11 covariates

Factor	Level	TAFA + LEN (N=59); n (%)	R-GemOx (N=59); n (%)	SMD
Age	<70	[redacted]	[redacted]	[redacted]
	≥70	[redacted]	[redacted]	
Ann-Arbor stage	I/II	[redacted]	[redacted]	[redacted]
	III/IV	[redacted]	[redacted]	
Refractoriness to last therapy	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Number of prior lines	1	[redacted]	[redacted]	[redacted]
	2-3	[redacted]	[redacted]	
Prior ASCT	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Elevated LDH	LDH>ULN	[redacted]	[redacted]	[redacted]
	LDH≤ULN	[redacted]	[redacted]	

Factor	Level	TAFA + LEN (N=65); n (%)	R-GemOx (N=59); n (%)	SMD
Neutropenia	ANC<1.5×10⁹/L	[redacted]	[redacted]	[redacted]
	ANC≥1.5×10⁹/L	[redacted]	[redacted]	
Anaemia	Hb<10g/dL	[redacted]	[redacted]	[redacted]
	Hb≥10g/dL	[redacted]	[redacted]	
Primary progressive	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
Early relapse	Yes	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	
ECOG	0-1	[redacted]	[redacted]	[redacted]
	>=2	[redacted]	[redacted]	

Source: MOR208C213 TLF Table 14.1.6.10 – R-GemOx

Abbreviations: ANC = absolute neutrophil counts; ASCT = autologous stem cell transplant; Hb = Haemoglobin; LDH = lactate dehydrogenase; R-GemOx = rituximab + gemcitabine + oxaliplatin; SMD = standardised mean difference; TAFA + LEN = Tafasitimab + lenalidomide; ULN = upper limit of normal.

Tafa + len v. R-GemOx – Balancing of cohorts following population adjustment

Baseline characteristics following weighting using MAIC

By construction, this method allows to achieve perfect balancing of the cohorts. In particular age, ECOG, IPI, cell of origin of the disease, number of patients with 3 or more prior lines, prior treatment with ASCT were included in the adjustment. Importantly, no adjustment on refractoriness to last therapy line or on the proportion of patients with 1 or 2 prior lines of therapy could be made.

RE-MIND2: Baseline characteristics following weighting using overlap weights

By construction, this method allows to achieve perfect balancing of the cohorts. Age, Ann-Arbor stage, elevated LDH, number of prior lines of therapy, refractoriness to last therapy line, primary refractoriness, prior ASCT, anaemia at baseline, neutropenia at baseline were included in the derivation of the weights

Forest plot of results

OS – HR of TAFA + LEN v. PBR across analyses

PFS – HR of TAFA + LEN v. PBR across analyses

OS – HR of TAFA + LEN v. BR across analyses

PFS – HR of TAFA + LEN v. BR across analyses

OS – HR of TAFA + LEN v. RGemOx across analyses

PFS – HR of TAFA + LEN v. RGemOx across analyses

Appendix TE3. Supportive information for use of time-varying hazard ratios

Table 17. Baseline characteristics of L-MIND patients according to OS status at 4 months

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death <= 4 months (N=11)	Death > 4 months (N=69)	p value	Death <= 4 months (Sum of weights =6.6)	Death > 4 months (Sum of weights =22.5)	p value
Age >= 65 years			0.907			0.341
Yes	8 (72.7%)	49 (71.0%)		73.5%	52.8%	
No	3 (27.3%)	20 (29.0%)		26.5%	47.2%	
Sex			0.552			0.551
Female	6 (54.5%)	31 (44.9%)		48.5%	35.7%	
Male	5 (45.5%)	38 (55.1%)		51.5%	64.3%	
Race			0.922			0.716
Asian	0 (0.0%)	1 (1.4%)		0.0%	0.5%	
White	10 (90.9%)	62 (89.9%)		70.6%	84.0%	
Missing	1 (9.1%)	6 (8.7%)		29.4%	15.6%	
ECOG			**0.003**			**0.017**
0	0 (0.0%)	29 (42.0%)		0.0%	53.5%	
1	8 (72.7%)	37 (53.6%)		52.6%	37.8%	
2	3 (27.3%)	3 (4.3%)		47.4%	8.7%	
ANNA (I,II,III,IV)			0.837			0.708
STAGE I	0 (0.0%)	4 (5.8%)		0.0%	11.9%	
STAGE II	2 (18.2%)	14 (20.3%)		13.5%	16.8%	
STAGE III	2 (18.2%)	14 (20.3%)		36.8%	20.5%	

STAGE IV	7 (63.6%)	37 (53.6%)		49.8%	50.9%	
ANNA (I-II,III-IV)			0.574			0.428
I and II	2 (18.2%)	18 (26.1%)		13.5%	28.7%	
III and IV	9 (81.8%)	51 (73.9%)		86.5%	71.3%	
IPI			**0.033**			0.458
0	1 (9.1%)	4 (5.8%)		6.2%	12.4%	
1	1 (9.1%)	10 (14.5%)		6.2%	16.0%	
2	0 (0.0%)	24 (34.8%)		0.0%	26.2%	
3	3 (27.3%)	21 (30.4%)		33.1%	25.7%	
4	5 (45.5%)	9 (13.0%)		48.3%	17.5%	
5	1 (9.1%)	1 (1.4%)		6.3%	2.2%	
IPI>=3			**0.023**			0.054
Yes	9 (81.8%)	31 (44.9%)		87.7%	45.4%	
No	2 (18.2%)	38 (55.1%)		12.3%	54.7%	
LDH levels >= ULN			0.054			0.12
Yes	9 (81.8%)	35 (50.7%)		87.7%	54.3%	
No	2 (18.2%)	34 (49.3%)		12.3%	45.7%	
Histology = NHL DLBCL			0.892			0.616
Yes	10 (90.9%)	60 (87.0%)		98.7%	93.9%	
No	1 (9.1%)	8 (11.6%)		1.3%	6.1%	
Missing	0 (0.0%)	1 (1.4%)		0.0%	0.0%	
Histology = TIL			0.234			0.999
Yes	0 (0.0%)	8 (11.6%)		0.0%	0.0%	
No	11 (100.0%)	61 (88.4%)		100.0%	100.0%	
Cell of origin of the disease			0.633			0.784
GCB	0 (0.0%)	8 (11.6%)		0.0%	10.3%	
ABC	3 (27.3%)	17 (24.6%)		27.8%	27.2%	

Unclassified Phenotype	0 (0.0%)	5 (7.2%)		0.0%	10.0%	
Not Evaluable	1 (9.1%)	4 (5.8%)		7.3%	7.2%	
Missing	7 (63.6%)	35 (50.7%)		64.8%	45.4%	
Bulky disease at baseline (>= 7.5 cm)			**0.009**			**0.004**
Yes	5 (45.5%)	9 (13.0%)		57.6%	7.7%	
No	6 (54.5%)	60 (87.0%)		42.4%	92.3%	
Number of prior lines of therapies (Continuous)			**0.006**			**0.001**
Mean	2.09	1.51		2.30	1.74	
SD	0.83	0.61		0.65	0.31	
Median	2	1		2.00	2.00	
Number of prior lines of therapies (Categorical)			**0.016**			0.158
1	2 (18.2%)	38 (55.1%)		14.5%	31.3%	
2	7 (63.6%)	27 (39.1%)		48.8%	63.5%	
3	1 (9.1%)	4 (5.8%)		29.4%	5.1%	
4	1 (9.1%)	0 (0.0%)		7.3%	0.0%	
Prior ASCT			0.204			0.09
Yes	0 (0.0%)	9 (13.0%)		0.0%	32.4%	
No	11 (100.0%)	60 (87.0%)		100.0%	67.6%	
Duration of response to last therapy			0.111			0.328
<= 12 months	10 (90.9%)	40 (58.0%)		98.7%	71.2%	
> 12 months	1 (9.1%)	28 (40.6%)		1.3%	27.1%	
Unknown	0 (0.0%)	1 (1.4%)		0.0%	1.7%	

Refractoriness: To last therapy line			0.152			0.845
Yes	7 (63.6%)	28 (40.6%)		77.9%	74.2%	
No	4 (36.4%)	41 (59.4%)		22.1%	25.9%	
Refractoriness: Primary refractoriness			**0.015**			0.113
Yes	5 (45.5%)	10 (14.5%)		42.3%	14.0%	
No	6 (54.5%)	59 (85.5%)		57.7%	86.0%	
Note:	p-value from test on categorical variables obtained from Chi-squared tests p-value from test on continuous variable obtained from ANOVA			p-value from test on categorical variables obtained from Chi-squared tests p-value from test on continuous variable obtained from ANOVA		

Table 18. Baseline characteristics of L-MIND patients according to PFS status at 4 months

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	Death/Progression > 4 months (N=57)	p value	Death/Progression <= 4 months (Sum of weights =11.6)	Death/Progression > 4 months (Sum of weights =17.5)	p value
Age >= 65 years			0.832			0.914
Yes	16 (69.6%)	41 (71.9%)		58.7%	56.7%	
No	7 (30.4%)	16 (28.1%)		41.3%	43.3%	
Sex			0.857			0.724
Female	11 (47.8%)	26 (45.6%)		34.7%	41.2%	
Male	12 (52.2%)	31 (54.4%)		65.3%	58.8%	
Race			0.572			0.894
Asian	0 (0.0%)	1 (1.8%)		0.0%	0.6%	
White	20 (87.0%)	52 (91.2%)		77.7%	83.0%	
Missing	3 (13.0%)	4 (7.0%)		22.3%	16.4%	
ECOG			0.228			0.62
0	5 (21.7%)	24 (42.1%)		30.4%	48.6%	
1	16 (69.6%)	29 (50.9%)		49.2%	35.9%	

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	**Death/Progression > 4 months (N=57)**	**p value**	**Death/Progression <= 4 months (Sum of weights =11.6)**	**Death/Progression > 4 months (Sum of weights =17.5)**	**p value**
2	2 (8.7%)	4 (7.0%)		20.4%	15.6%	
ANNA (I,II,III,IV)			0.787			0.486
STAGE I	1 (4.3%)	3 (5.3%)		3.8%	12.7%	
STAGE II	5 (21.7%)	11 (19.3%)		28.0%	8.1%	
STAGE III	3 (13.0%)	13 (22.8%)		22.7%	25.2%	
STAGE IV	14 (60.9%)	30 (52.6%)		45.5%	54.0%	
ANNA (I-II,III-IV)			0.887			0.504
I and II	6 (26.1%)	14 (24.6%)		31.8%	20.9%	
III and IV	17 (73.9%)	43 (75.4%)		68.2%	79.2%	
IPI			0.112			0.398
0	2 (8.7%)	3 (5.3%)		7.3%	13.4%	
1	2 (8.7%)	9 (15.8%)		21.3%	8.7%	
2	4 (17.4%)	20 (35.1%)		4.6%	30.6%	

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	Death/Progression > 4 months (N=57)	p value	Death/Progression <= 4 months (Sum of weights =11.6)	Death/Progression > 4 months (Sum of weights =17.5)	p value
3	7 (30.4%)	17 (29.8%)		27.2%	27.6%	
4	6 (26.1%)	8 (14.0%)		31.8%	19.6%	
5	2 (8.7%)	0 (0.0%)		7.8%	0.0%	
IPI>=3			0.084			0.299
Yes	15 (65.2%)	25 (43.9%)		66.8%	47.2%	
No	8 (34.8%)	32 (56.1%)		33.3%	52.8%	
LDH levels >= ULN			0.243			0.82
Yes	15 (65.2%)	29 (50.9%)		64.4%	60.3%	
No	8 (34.8%)	28 (49.1%)		35.6%	39.7%	
Histology = NHL DLBCL			0.365			0.388
Yes	22 (95.7%)	48 (84.2%)		99.3%	92.2%	
No	1 (4.3%)	8 (14.0%)		0.7%	7.8%	
Missing	0 (0.0%)	1 (1.8%)		0.0%	0.0%	

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	**Death/Progression > 4 months (N=57)**	**p value**	**Death/Progression <= 4 months (Sum of weights =11.6)**	**Death/Progression > 4 months (Sum of weights =17.5)**	**p value**
Histology = TIL			0.058			0.999
Yes	0 (0.0%)	8 (14.0%)		0.0%	0.0%	
No	23 (100.0%)	49 (86.0%)		100.0%	100.0%	
Cell of origin of the disease			0.534			0.689
GCB	3 (13.0%)	5 (8.8%)		10.2%	6.4%	
ABC	7 (30.4%)	13 (22.8%)		23.2%	30.1%	
Unclassified Phenotype	0 (0.0%)	5 (8.8%)		0.0%	12.9%	
Not Evaluable	2 (8.7%)	3 (5.3%)		5.9%	8.1%	
Missing	11 (47.8%)	31 (54.4%)		60.8%	42.5%	
Bulky disease at baseline (>= 7.5 cm)			0.199			0.082
Yes	6 (26.1%)	8 (14.0%)		34.6%	8.8%	
No	17 (73.9%)	49 (86.0%)		65.4%	91.3%	

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	**Death/Progression > 4 months (N=57)**	**p value**	**Death/Progression <= 4 months (Sum of weights =11.6)**	**Death/Progression > 4 months (Sum of weights =17.5)**	**p value**
Number of prior lines of therapies (Continuous)			**0.042**			**0.002**
Mean	1.83	1.49		2.14	1.68	
SD	0.72	0.63		0.47	0.33	
Median	2	1		2	2	
Number of prior lines of therapies (Categorical)			0.053			0.316
1	7 (30.4%)	33 (57.9%)		11.0%	38.5%	
2	14 (60.9%)	20 (35.1%)		68.0%	54.9%	
3	1 (4.3%)	4 (7.0%)		16.8%	6.6%	
4	1 (4.3%)	0 (0.0%)		4.2%	0.0%	
Prior ASCT			0.646			0.728
Yes	2 (8.7%)	7 (12.3%)		21.6%	27.3%	
No	21 (91.3%)	50 (87.7%)		78.4%	72.7%	

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	Death/Progression > 4 months (N=57)	p value	Death/Progression <= 4 months (Sum of weights =11.6)	Death/Progression > 4 months (Sum of weights =17.5)	p value
Duration of response to last therapy			0.369			0.644
<= 12 months	17 (73.9%)	33 (57.9%)		71.1%	81.7%	
> 12 months	6 (26.1%)	23 (40.4%)		28.9%	16.2%	
Unknown	0 (0.0%)	1 (1.8%)		0.0%	2.1%	
Refractoriness: To last therapy line			0.144			0.553
Yes	13 (56.5%)	22 (38.6%)		80.9%	71.1%	
No	10 (43.5%)	35 (61.4%)		19.2%	28.9%	
Refractoriness: Primary refractoriness			0.286			0.39
Yes	6 (26.1%)	9 (15.8%)		28.4%	15.3%	
No	17 (73.9%)	48 (84.2%)		71.6%	84.8%	

	L-MIND unweighted population			L-MIND weighted population, using base case weights for the MAIC against POLA + BR		
	Death/Progression <= 4 months (N=23)	**Death/Progression > 4 months (N=57)**	**p value**	**Death/Progression <= 4 months (Sum of weights =11.6)**	**Death/Progression > 4 months (Sum of weights =17.5)**	**p value**
Note:	p-value from test on categorical variables obtained from Chi-squared tests			p-value from test on categorical variables obtained from Chi-squared tests		

Appendix TE4. Overview of ongoing studies with tafasitamab

Table 19. Clinical development programme for tafasitamab

Study	Phase	Therapy	Line of Tx	Cancer type	Recruiting countries	Enrolment (n)	Status	Estimated completion
DLBCL								
NCT04134936 MOR208C107 FIRST-MIND	Ib	Tafasitamab or TAFA+LEN in addition to R-CHOP	1L	DLBCL	Austria, Belgium, Czech Republic, Germany, Portugal, US	Estimated: 60	Ongoing, not recruiting	Primary: Aug 2021 Study: Jan 2023
NCT04824092 MOR208C310 FRONT-MIND	III	TAFA+LEN+ R-CHOP vs. R-CHOP	1L	DLBCL (High–intermediate and high risk)	Argentina, Australia, Austria, Colombia, Czechia, US, France, Germany, Hungary, Ireland, Israel, Italy, Republic of Korea, Malaysia, New Zealand, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, Taiwan, Thailand, Turkey, Ukraine, UK	Estimated: 880	Ongoing, recruiting	Primary: Jun 2025 Study: May 2026
NCT02399085 MOR208C203 L-MIND	II	TAFA+LEN	2L/ 3L	R/R DLBCL	Spain, Poland, Italy, Hungary, Germany, France, Czech Republic, Belgium, UK, US	81	Ongoing, not recruiting	Study follow-up: Nov 2022

Study	Phase	Therapy	Line of Tx	Cancer type	Recruiting countries	Enrolment (n)	Status	Estimated completion
NCT02763319 MOR208C204 B-MIND	II/III	Tafasitamab + bendamustine vs. BR	2L/ 3L	R/R DLBCL	Australia, Austria, Canada, Croatia, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Korea, New Zealand, Poland, Portugal, Romania, Serbia, Singapore, Spain, Taiwan, Turkey, UK, US	Estimated: 450	Ongoing, recruiting	Primary: Mar 2022 Study: Mar 2024
NCT04300803 MOR208N001	Expanded access	Tafasitamab	2L+	R/R DLBCL	US	NA	Approved for marketing	N/A
Other therapy R/R DLBCL								
NCT04150328 MOR208C206 RE-MIND	Retro-spective	LEN monotherapy vs. TAFA+LEN	2L/ 3L	R/R DLBCL	France, Italy, Spain, US	490	Completed	N/A
NCT04697160 MOR208C213 RE-MIND2	Retro-spective	Systemic therapies vs. TAFA+LEN	2L+	R/R DLBCL	Australia, Austria, Canada, Denmark, France, Germany, Italy, South Korea, Spain, Taiwan, UK, US	3,454	Completed	N/A
Other cancers								
NCT01685021 MOR208C202	2a	Tafasitamab	2L+	R/R B-ALL	US	22	Terminated	N/A

Study	Phase	Therapy	Line of Tx	Cancer type	Recruiting countries	Enrolment (n)	Status	Estimated completion
NCT02639910 MOR208C205 COSMOS	2	Tafasitamab + idelalisib or venetoclax	2L+	R/R CLL/SLL (previously treated with BTKi)	Italy, Poland, Germany, Austria, UK, US	24	Completed	Completed in December 2021
NCT01161511 XmAb5574-01	1	Tafasitamab	2L+	R/R CLL/SLL	US	27	Completed	N/A
NCT02005289 NCI-2013-02082 OSU-13031	2	TAFA+LEN	1L/ 2L	R/R CLL, SLL or PLL or older pts w/untreated CLL, SLL, or PLL	US	41	Ongoing, not recruiting	Primary: December 2021 Study: December 2022
NCT01685008 MOR208C201	2a	Tafasitamab	2L+	R/R NHL	Belgium, Germany, Hungary, Italy, Poland, Spain, US	92	Ongoing, not recruiting	December 2021

Sources: NCT04134936(23); NCT02399085(24); NCT02763319(25); NCT04150328(26); NCT04300803(20); NCT01685021(27); NCT02639910(28); NCT01161511(29); NCT02005289(30); NCT01685008(31); NCT04697160(25)

Abbreviations: B-ALL = B-cell acute lymphoblastic leukaemia; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin lymphoma; PLL = prolymphocytic leukaemia; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; Tx = treatment; UK = United Kingdom; US = United States

Appendix TE5. Serious adverse event data for L-MIND and MOR208C201

SAE data for L-MIND are provided in Table 20 and for MOR208C201 are provided in Table 21.

In L-MIND, 81 treatment-emergent SAEs were reported in 43 patients; the most common of which were pneumonia, febrile neutropenia, pulmonary embolism and bronchitis.

Table 20. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	TAFA + LEN (N = 81)	
	n (%)	Event
Any TEAE	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]
Bronchopulmonary aspergillosis	[redacted]	[redacted]
Cytomegalovirus infection reactivation	[redacted]	[redacted]
Enterobacter bacteraemia	[redacted]	[redacted]
Escherichia bacteraemia	[redacted]	[redacted]
Febrile infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Klebsiella sepsis	[redacted]	[redacted]
Neutropenic sepsis	[redacted]	[redacted]
Parainfluenzae virus infection	[redacted]	[redacted]

System Organ Class Preferred Term	TAFA + LEN (N = 81)	
	n (%)	Event
Progressive multifocal leukoencephalopathy	[redacted]	[redacted]
Respiratory syncytial virus infection	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Soft tissue infection	[redacted]	[redacted]
Streptococcal sepsis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Urinary tract infection enterococcal	[redacted]	[redacted]
Varicella zoster virus infection	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Cervicobrachial syndrome	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]
Facial paralysis	[redacted]	[redacted]
Sciatica	[redacted]	[redacted]
Transient global amnesia	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Agranulocytosis	[redacted]	[redacted]
Cardiac Disorders	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]

System Organ Class Preferred Term	TAFA + LEN (N = 81)	
	n (%)	Event
Myocardial ischaemia	[redacted]	[redacted]
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Bowen's disease	[redacted]	[redacted]
Myelodysplastic syndrome	[redacted]	[redacted]
Myeloproliferative neoplasm	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]
Tumour flare	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Disorders	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]
Pathological fracture	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]

System Organ Class Preferred Term	TAFA + LEN (N = 81)	
	n (%)	Event
Injury, Poisoning and Procedural Complications	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]
Lower limb fracture	[redacted]	[redacted]
Wound complication	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Hepatobiliary Disorders	[redacted]	[redacted]
Biliary colic	[redacted]	[redacted]
Renal and Urinary Disorders	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]

AE = adverse event; LEN = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in SAF; n = number of patients in each category; PT = preferred term; SAF = safety analysis set; SOC = System Organ Class; TEAE = treatment-emergent adverse event. Percentages are based on the number of patients in the SAF, N. Treatment-emergent AEs were defined as any AE reported in the following time interval (including the lower and upper limits): date of first administration of study treatment; date of last administration of study treatment + 30 days, or if they were considered to be related to the study drug. MedDRA (Version 21.0) coding dictionary was used. A patient with more than 1 TEAE within a PT was counted once for that PT. A patient with more than 1 TEAE within a SOC was counted once for that SOC. A patient was counted only once for the maximum toxicity under each SOC and PT but all events are presented.

Table 21. Treatment Emergent Severe Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	FL (N=34)	DLBCL (N=35)	MCL (N=12)	Other indolent NHL (N=11)
	n (%)	n (%)	n (%)	n (%)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Agranulocytosis	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	FL (N=34)	DLBCL (N=35)	MCL (N=12)	Other indolent NHL (N=11)
	n (%)	n (%)	n (%)	n (%)
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Mitral valve incompetence	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]		[redacted]
Oedema	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Bile duct obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]
Genital herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	FL (N=34)	DLBCL (N=35)	MCL (N=12)	Other indolent NHL (N=11)
	n (%)	n (%)	n (%)	n (%)
Respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Fracture	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Lumbar vertebral fracture	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood lactate dehydrogenase increased	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	FL (N=34)	DLBCL (N=35)	MCL (N=12)	Other indolent NHL (N=11)
	n (%)	n (%)	n (%)	n (%)
Myelodysplastic syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on tafasitamab with lenalidomide in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 ERG report that are likely to be discussed by the committee. The key issues in the ERG report 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 ERG report (section 1.1). 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) 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.

Clinical expert statement

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **Wednesday 6 April 2022.** 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating relapsed or refractory diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew DAVIES
2. Name of organisation	University of Southampton and University Hospitals Southampton
3. Job title or position	Professor of Haematological Oncology and Honorary Consultant
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☒ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or tafasitamab with lenalidomide? ☐ 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)	☒ 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 diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure relapsed or refractory diffuse large B-cell lymphoma, or prevent progression or disability)	Although frontline chemotherapy with R-CHOP chemotherapy may cure 2/3rds of patients. Many patients either fail to respond to initial therapy or relapsed after having achieved an initial response. For patients that are younger and fitter, the aim of therapy is cure the disease. This may involve intensive chemotherapies with stem cell rescue or cellular therapies. Many patients with DLBCL are not fit enough for these approaches, or will have relapsed after initial intensive therapies. In this group the aim is to achieve a remission and long-term disease control. This keeps the patient well and symptom free and prolongs survival.
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)	Achieving a complete response to therapy followed by durable progression-free survival. Some reduction in tumour size, a partial response, will delay progression and so is of benefit. Incremental improvement in overall survival.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes. The efficacy of therapies for patients with relapsed or refractory DLBCL are disappointing, even for those treated with intensive therapies and with curative intent. We urgently need new therapies to improve the outcome for these patients as our therapies are currently palliative life extending.
11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of relapsed or refractory diffuse large B-cell lymphoma, 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.)	Patients may by broadly divided into those who are younger and fitter and those that are not fit for intensive therapies. Intensive pathway patients are treated in the second-line with non-cross reactive chemotherapy (R-GDP, R-ICE, R-DHAP). If they achieve a complete response or good partial response then they receive high-dose chemotherapy (HDT) with peripheral blood progenitor cell rescue. Those patients who relapse after HDT or do not achieve a sufficient response to second-line chemotherapy go onto receive CAR-T therapy in the third-line. These therapies are given with curative intent. If they fail to benefit from this approach, further therapies are either further lines of immunochemotherapy or clinical trials although the expectation of success is poor.

• What impact would tafasitamab with lenalidomide have on the current pathway of care?	Non-Intensive pathway: These patients are typically older and/or co-morbid. They would not tolerate the toxicity of the intensive regimens. Therapy is will disease modifying immunochemotherapy such as rituximab, gemcitabine and oxaliplatin (R-GemOx) and other local immunochemotherapy protocols. More recently the antibody-drug conjugate, polatuzumab, has been funded in combination with rituximab and bendamustine in this setting. It has rapidly gained traction in the NHS due to efficacy and tolerability (real world UK data: Northend et al. https://doi.org/10.1182/bloodadvances.2021005953). Expectation of success with these regimens is limited and many patients either fail to respond or relapse after a short time frame measured in months. Alternative chemotherapy regimens may be use, patients may be enrolled on clinical trials and palliative care provided. Some centres access lenalidomide through a compassionate access scheme run through Celgene. There is no doubt that this is an effective approach for some patients but lenalidomide is not commissioned by NHS-E. Other regimens that may be used in local sites included R-PMitCEBO, R-P/DECC, PEP-C and R-COCKLE. These are all variations on a simple theme. The approval of tafasitamab with lenalidomide (afa-len) would provide a new option with a distinct mechanism of action to chemotherapy and a favourable toxicity profile. This would no doubt provide benefit to patients who had been failed by intensive approaches and those who were not suitable for the non-intensive pathway. These agents are not currently commissioned in the NHS so the combination of targeting a novel B-cell associated antigen (CD19) on the surface of malignant B-cell cells with an augmented antibody and the immunomodulatory agent lenalidomide is highly attractive in those patients that have been failed by immunochemotherapy and other approaches.
12. Will tafasitamab with lenalidomide be used (or is it already used) in the same way as current care in NHS clinical practice?	Tafa-len will be delivered in secondary care. The mode of preparation and delivery in well within scope of any unit delivering SACT (systemic anti-cancer therapy). This includes cancer centres, cancer units, peripatetic chemotherapy delivery services and even homecare chemotherapy services.

• How does healthcare resource use differ between tafasitamab with lenalidomide and current care? • In what clinical setting should tafasitamab with lenalidomide be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce tafasitamab with lenalidomide? (for example, for facilities, equipment, or training)	As above, this would provide an alternative to immunochemotherapy which is currently being delivered in these settings. SACT delivery teams are well used to administering monoclonal antibodies in Haematology/Oncology. Some familiarisations with product will be required but training requirements will be minimal. Lenalidomide is already extensively used in haematological oncology.
13. Do you expect tafasitamab with lenalidomide to provide clinically meaningful benefits compared with current care? • Do you expect tafasitamab with lenalidomide to increase length of life more than current care? • Do you expect tafasitamab with lenalidomide to increase health-related quality of life more than current care?	Yes. In patients who have either relapsed after HDT or are ineligible the combination of tafa-len results in an overall response rate of 60% with 43% of patients achieving a complete response. This is clinically meaningful. These patients will have already demonstrated lack of response to immunochemotherapy Data published from the pivotal study demonstrated that the median overall survival had not been reached with a median follow-up of 19.6 months (Salles et al. https://doi.org/10.1016/S1470-2045(20)30225-4) with 74% of patients alive at 12 months and 64% at 18 months. This compares very favourably with historical data sets. The median duration of response was 21.7 months. For 72% of patients their response lasted more than 12 months. Median progression-free survival was 12.7 months. These are very favourable for patients with R/R DLBCL. The adverse event profile demonstrates that the combination of tafa-len is well tolerated. This means that an effective regimen can be delivered with limited toxicity. This will result in net QoL benefit

14. Are there any groups of people for whom tafasitamab with lenalidomide would be more or less effective (or appropriate) than the general population?	Yes This will be appropriate for patients who may be older and less fit. This group is significantly underserved by current regimens.
15. Will tafasitamab with lenalidomide 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)	Net the same. Treatment is until progression and after weekly loading (weekly for 12 weeks) treatment is every 12 weeks. The infusion time is 2 hours after a pre-med. There is however no chemotherapy component to deliver as lenalidomide is oral. In contrast, many immunochemotherapy regimens are of fixed duration (eg 6 cycles) Although this will require a 2-weekly infusion, in the main patients with R/R DLBCL are willing to accept this frequency to maintain disease control.
16. Will any rules (informal or formal) be used to start or stop treatment with tafasitamab with lenalidomide? Do these include any additional testing?	Progression of disease. Largely this will be clinically evident. Surveillance CT imaging may be performed during therapy. It is likely sites would adopt this 3 monthly, moving to 6 monthly after 1 year (recognising that median PFS is 12 months) Toxicity: Monitoring of clinical toxicity is in line with normal standard of care as are blood tests for laboratory adverse events.
17. Do you consider that the use of tafasitamab with lenalidomide 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 tafasitamab with	Yes, it is likely there are benefits that cannot be captured in the model

lenalidomide 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	
18. Do you consider tafasitamab with lenalidomide 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 tafasitamab with lenalidomide a 'step-change' in the management of relapsed or refractory diffuse large B-cell lymphoma? • Does the use of tafasitamab with lenalidomide address any particular unmet need of the patient population?	Yes. As above these two agents present a new mechanism of action. This is an incremental improvement rather than a step-change. This is how cancer care progresses trough taking significant but incremental beneficial steps forward. Step-changes in cancer care are rare. Tafa-len provides an efficacious low toxicity regimen that will be of clear benefit to older or frail patients with R/R DLBCL and those that have relapsed after more intensive therapies.
19. How do any side effects or adverse effects of tafasitamab with lenalidomide affect the management of relapsed or refractory diffuse large B-cell lymphoma and the patient's quality of life?	The modest haematological toxicity from tafa-len is we within that experience with other regimens for R/R DLBCL. Febrile neutropenia rates are low. Other adverse events such as diarrhoea, rash asthenia, anorexia and constipation are in the main grade 1/2 (mild) and readily managed. These compare favourably to immunochemotherapy.
20. Do the clinical trials on tafasitamab with lenalidomide 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?	The pivotal trial is single arm. It includes a patient profile that would reflect those that would be seen in UK practice. The inclusion/exclusion criteria are representative. The endpoints of response rate and then time to event (PFS, OS) and toxicity are entirely appropriate and objective. There have been no reports of emerging adverse events that were not reported in the trials

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 treatment(s) since the publication of NICE technology appraisal guidance [TA306; TA659]?	No
23. How do data on real-world experience compare with the trial data?	I am not award of a RWE data-set
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering relapsed or refractory diffuse large B-cell lymphoma and this treatment? Please explain if you think any groups of people with relapsed or refractory diffuse large B-cell lymphoma 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 appraisal 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	No

• 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.	

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 ERG report, 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 appraisal 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 ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Do you have any general comments on the key issues in the ERG report?	Well considered document. The ERG are concerned about a restricted search strategy to English and French. This will include all relevenet data sets
Key issue 1: To what extent are the following regimens used in NHS clinical practice for treating adults with relapsed/refractory DLBCL who are not eligible for ASCT?	All of the regimens below are generally infrequently used in the NHS. There may be some local preference, but absolute numbers of scripts will be modest for each regiment. It is entirely appropriate to pay minimal attention to these regimens as comparators. Those included in the company submission represent regimens delivered in practice and in guidelines. • R-Gem: This doublet is infrequently used. • R-P-MitCEBO: This may be used in a few centres. It has the advantage of a weekly alternating schedule and some new drugs but the absolute number of prescribed cycles will be low. • (R-)DECC. Some minimal local use.

• R-Gem • R-P-MitCEBO, • (R-)DECC • Pixantrone • Best supportive care	• Pixantrone: Although NICE approved, I am unaware of any prescriptions due to lack of efficacy (RWE Eyre et al.) The randomised confirmatory study demonstrated no advantage. • Best supportive care: For frail patients
Key issue 2: Are you aware of any other potentially relevant studies not included in the company submission for TAFA+LEN or any of the comparators?	No Could consider R-GemOx abstract Davies et al. presented at ICML 2021 (https://onlinelibrary.wiley.com/doi/10.1002/hon.11_2880?af=R) In considering comparator studies, the relative proportion of relapsed and refractory patients in any report should be reviewed.
Key issue 3: Which of the following indirect treatment comparisons do you consider to be more appropriate for decision making? • RE-MIND2 • Matching-adjusted indirect comparisons	RE-MIND provides a clear comparison to describe the additional efficacy of the tafa-len doublet. Lenalidomide is not routinely commissioned in the UK for R/R DLBCL so the comparison has limitations. Hence the MAIC has greater strength as represents UK practice.
Key issue 4: Which mean survival estimates from the	Longer follow-up of the pol-BR data would indicate that the Company estimates are more appropriate

economic model for pola-BR are most plausible? • Company (2.20 life years) • ERG (3.36 life years) Do you have any comments on the survival extrapolations for the other comparators?	
Key issue 5: The company's assumed reduced price for lenalidomide should not be used.	It is very difficult to understand the future lenalidomide market. I understand that it will come off patent in the UK in June 2022. Generics are readily available in other territories and mirroring the experience of other countries it is likely that that there will be a significant downward drive on the price in the very neat future. It seem wholly inappropriate to use current list price.
Key issue 6: To what extent are the NICE end-of-life criteria met for TAFA+LEN? The criteria are: • Patients face a short life expectancy, normally less than 24 months	I am comfortable that this meets the NICE end of life criteria. Data from the UK ARGO study of R-GemOx in a similar patient population shows a median OS of 52% at 12 moths and <20% at 24 months (Davies 2021).

• The treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatment	
Are there any important issues that have been missed in ERG report?	This is a comprehensive report.

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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.

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Clinical expert statement and technical engagement response form

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on tafasitamab with lenalidomide in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 ERG report that are likely to be discussed by the committee. The key issues in the ERG report 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 ERG report (section 1.1). 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) 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.

Clinical expert statement

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

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Deadline for comments by **5pm** on **Wednesday 6 April 2022.** 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 diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Kate Cwynarski
2. Name of organisation	UCLH
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? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☐ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or tafasitamab with lenalidomide? ☐ 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)	☒ 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 but I have repeated below for clarity

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 diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure relapsed or refractory diffuse large B-cell lymphoma, or prevent progression or disability)	Main aim: to delay progression. It may provide a durable response (so patients can be bridged to another form of consolidation) or potentially be curative in a cohort of patient The patient cohort 'for whom haematopoietic stem cell transplant is not suitable'. This encompasses 3 main groups of patients: 1. Patient who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant or CAR-T cell therapy 2. Patients who have already had a stem cell transplant or CAR-T cell therapy and have relapsed following it Patients who are young and fit enough for a stem cell transplant and CAR-T cell therapy but their disease is not in a good enough remission to proceed with this
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)	A clinically significant treatment response would be: reduction in tumour size (CR/PR/ORR) Possible sustained resolution of the tumour so it's not detectable (Complete Response (CR)). Partial responses in DLBCL are rarely sustainable. Prolongation of survival (PFS/OS measured in months)
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes – there is clearly an unmet need for patients as presently palliative approaches are adopted, or regimens with poor outcome or unacceptable toxicities.

11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of relapsed or refractory diffuse large B-cell lymphoma, 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 tafasitamab with lenalidomide have on the current pathway of care?	Patients who are not fit for transplant are offered low intensity chemotherapy regimens (sometimes with rituximab however there is no standard of care. The following comparators can be given with or without rituximab (depending on amount received by patient prior) • Rituximab Bendamustine and Polatuzumab (R-BP) • R-GemOx And less commonly: • R-Gem • R-P-MitCEBO • Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines) • (R-)DECC • PEP-C • R-COCKLE - For populations (2) and (3) above there is the option of CAR-T cells (recently introduced in UK in 2019). Benda+R+pola provides a bridging therapy to CAR T-cell therapy (presently only patients PS 0-1 are eligible for CAR-T therapy so this will be a small cohort) and this treatment modality may be used in a similar setting. The regimen may be used as part of a strategy to bridge to a potentially curative therapy such as allogeneic transplant – again this will be a small cohort.

	BCSH Guidelines 2013 (British Journal of Haematology): presently being revised. There are also ESMO guidelines and NCCN guidelines. It has not well defined as this cohort of patients are hard to treat as there have been poor clinical options. It is being redefined as there are a number of newer clinical options (CAR-T therapy, Rituximab Bendamustine and Polatuzumab (R-BP) etc) Since the introduction of CAR-T therapy in UK (potentially for cohort 2 and 3) in 2019 the national CAR-T panel has been set up and this is being reviewed as it evolves. It could dramatically change patient care as it would offer another therapeutic option for a cohort of patients where the options are poor and limited and durable remissions are uncommon.
12. Will tafasitamab with lenalidomide 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 tafasitamab with lenalidomide and current care? • In what clinical setting should tafasitamab with lenalidomide be used? (for example, primary or secondary care, specialist clinic)	Yes – in the same way. It involves immunotherapy and Lymphoma doctors and Haem-Onc departments have a wealth of experience in this field. Lenalidomide is an oral agent used widely in the UK for lymphoma patients (R/R Follicular lymphoma) The IV drug will be delivered in the chemotherapy day unit. Tafasitamab is a monoclonal antibody and would be a straightforward drug to administer as our units are used to delivering such therapies to our Lymphoma

• What investment is needed to introduce tafasitamab with lenalidomide? (for example, for facilities, equipment, or training)	patients. The sustained period of administration of tafasitamab to patients until disease progression if less common with present regimens. The lymphoma treating community have amended their approach to this group of patients. The introduction of Rituximab-Bendamustine -Polatuzumab (R-BP) and CAR-T cell therapy in the last 3 years has transformed the approach to treating this patient group. The patient treatment pathway has been revised accordingly. Patients generally remain under consultant haematology / oncology care as well as receiving active palliative care (possible use of palliative radiotherapy for symptoms, possible use of steroids Secondary care as outlined above Oral Lenalidamide is commonly prescribed across haematology units in the UK as it is a well accepted treatment for a different lymphoma: follicular lymphoma. Tafasitimab will be delivered in the chemotherapy day unit as are other monoclonal antibodies with monitoring of patients as is standard practice. In the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide for patients with relapsed or refractory diffuse large B-cell lymphoma patients received 28-day cycles of tafasitamab (12 mg/kg intravenously), once weekly during cycles 1-3, then every 2 weeks during cycles 4-12. Lenalidomide (25 mg orally) was administered on days 1-21 of cycles 1-12.

	After cycle 12, progression-free patients received tafasitamab every 2 weeks until disease progression. Although the prolonged nature of treatment duration for some patients would have an impact on our day units, the patient population is not common so we would expect the absolute impact to be modest.
13. Do you expect tafasitamab with lenalidomide to provide clinically meaningful benefits compared with current care? • Do you expect tafasitamab with lenalidomide to increase length of life more than current care? • Do you expect tafasitamab with lenalidomide to increase health-related quality of life more than current care?	Yes we would expect the technology to provide clinically meaningful benefits compared with current care. Antibody-drug conjugates have been applied successfully to high grade B-cell lymphomas. The data presented has shown impressive responses, durable in a group of patients. These 2 factors combined suggest this does have the potential to have a substantial impact on health-related benefits and is consistent with a step-change in the management of this condition. It is innovative in its potential in a population with a poor outcome and limited effective treatment options. Durable remissions are seen in a proportion of patients. Potentially it is another option to provide durable responses and provide prolonged PFS and OS in this subgroup of patients. The updated outcome published by Duell et al, in Haematologica in September 2021showed that after ≥35 months' follow-up. Yes – by improving lymphoma-related symptoms.

	Also an out-patient/day unit-delivered therapy
14. Are there any groups of people for whom tafasitamab with lenalidomide would be more or less effective (or appropriate) than the general population?	Overall response and CR rates were consistent regardless of refractoriness in patient subgroups. Although subgroup analyses did show differences in PFS and OS, the nature of such analysis is hypothesis generating and firm conclusions as to whether some groups benefit more or less are at present not possible to draw.
15. Will tafasitamab with lenalidomide 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)	No – the populations as defined above, `It has implications for patients (attending day unit as the tafasitamab is given intravenously continuously until progression whilst presently alternatives may be delivered orally or for shorter defined periods. However although the prolonged nature of treatment duration for some patients would have an impact on our day units, the patient population is not common so we would expect the absolute impact to be modest. Healthcare professionals will monitorside effects (cytopenias) and potential infective complications (but latter exists for oral therapies and other combinations). Lenalidamide/Tafasitamab has been associated with neutropenia and leukopenia and infectious complications so appropriate prophylaxis should be given(which is standard practice). Monitoring patients closely recommended when they have side effects

16. Will any rules (informal or formal) be used to start or stop treatment with tafasitamab with lenalidomide? Do these include any additional testing?	Stop treatment if progressive disease or unacceptable side effects
17. Do you consider that the use of tafasitamab with lenalidomide 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 tafasitamab with lenalidomide 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	Yes – we expect this technology will result in health-related benefits and some may not be included in the quality-adjusted life year (QALY) calculation
18. Do you consider tafasitamab with lenalidomide 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 tafasitamab with lenalidomide a 'step-change' in the management of relapsed or refractory diffuse large B-cell lymphoma? • Does the use of tafasitamab with lenalidomide address any particular unmet need of the patient population?	Yes we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and it will improve the way that current need is met. Patients have prolonged PFS and OS – especially if achieve CR or less prior treatments. A cohort of patients may be bridged to a curative line of therapy (CAR-T or allogeneic stem cell transplantation). Yes this is a another part of a 'step-change' in the management of the condition

	Yes – the unmet need of patients who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant or CAR-T cell therapy where other options are palliative. Also bridging therapy to potentially curative therapies as outlined above.
19. How do any side effects or adverse effects of tafasitamab with lenalidomide affect the management of relapsed or refractory diffuse large B-cell lymphoma and the patient's quality of life?	Infectious complications so appropriate prophylaxis should be given. Review need for thromboprophylaxis
20. Do the clinical trials on tafasitamab with lenalidomide 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?	Yes – as there is no standard comparator. The trial included patients with R/R DLBCL They had no more than 3 prior lines (although in reality patients with R/R DLBCL rarely receive > 3 lines of therapy due to the aggressive nature of the disease). N/A Yes – outcomes important to patients involve reduction in tumour size (and associated reduction/resolution of associated symptoms). Prolongation of survival (PFS/OS measured in months). These were measured N/A Not that I am aware of

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 treatment(s) since the publication of NICE technology appraisal guidance [TA306; TA659]?	No
23. How do data on real-world experience compare with the trial data?	I am not aware of real world experience in this setting
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering relapsed or refractory diffuse large B-cell lymphoma and this treatment? Please explain if you think any groups of people with relapsed or refractory diffuse large B-cell lymphoma 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 appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No equality issues

• 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.	

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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 ERG report, 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 appraisal 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 ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Do you have any general comments on the key issues in the ERG report?	
Key issue 1: To what extent are the following regimens used in NHS clinical practice for treating adults with relapsed/refractory DLBCL who are not eligible for ASCT?	The main treatments we use in this setting are: R-BP (Rituximab-Bendamustine and Polatuzumab) – the most common regimen. Less commonly we use R-GEM-OX (Gemcitabine and Oxiplatin) In contrast these agents are used far less often and are not considered good comparators. • R-Gem • R-P-MitCEBO,

Clinical expert statement

• R-Gem • R-P-MitCEBO, • (R-)DECC • Pixantrone • Best supportive care	• (R-)DECC • Pixantrone Best supportive care
Key issue 2: Are you aware of any other potentially relevant studies not included in the company submission for TAFA+LEN or any of the comparators?	I am not aware of any other relevant studies not included in the company submission for TAFA+LEN. For the comparators these have recently been published: Results of a UK real world study of **polatuzumab** vedotin, **bendamustine**, and **rituximab** for relapsed/refractory large B-cell lymphoma. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D, Phillips EH, Sim HW, Sadullah S, Shah N, Peng YY, Qureshi I, Addada J, Mora RF, Phillips N, Kuhnl A, Davies E, Wrench DJ, McKay P, Karpha I, Cowley A, Karim R, Challenor S, Singh V, Burton C, Auer R, Williams C, Cunningham J, Broom A, Arasaretnam A, Roddie C, Menne T, Townsend WM.Blood Adv. 2022 Jan 12:bloodadvances.2021005953. doi: 10.1182/bloodadvances.2021005953. **Polatuzumab** vedotin-based salvage immunochemotherapy as third-line or beyond treatment for patients with diffuse large B-cell lymphoma: a real-world experience. Wang YW, Tsai XC, Hou HA, Tien FM, Liu JH, Chou WC, Ko BS, Chen YW, Lin CC, Cheng CL, Lo MY, Lin YC, Lu LC, Wu SJ, Kuo SH, Hong RL, Huang TC, Yao M.Ann Hematol. 2022 Feb;101(2):349-358. doi: 10.1007/s00277-021-04711-9. Epub 2021 Nov 11. **Polatuzumab** vedotin plus **bendamustine** and **rituximab** in relapsed/refractory DLBCL: survival update and new extension cohort data. Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, Kim TM, McMillan A, Ozcan M, Safar V, Salles G, Ku G, Hirata J, Chang YM, Musick L, Matasar MJ.Blood Adv. 2022 Jan 25;6(2):533-543. doi: 10.1182/bloodadvances.2021005794. A phase 2 study of **polatuzumab** vedotin + **bendamustine** + **rituximab** in relapsed/refractory diffuse large B-cell lymphoma. Terui Y, Rai S, Izutsu K, Yamaguchi M, Takizawa J, Kuroda J, Ishikawa T, Kato K, Suehiro Y, Fukuhara N, Ohmine K, Goto H, Yamamoto K, Kanemura N, Ueda Y, Ishizawa K, Kumagai K, Kawasaki A, Saito T, Hashizume M, Shibayama H.Cancer Sci. 2021 Jul;112(7):2845-2854. doi: 10.1111/cas.14937. Epub 2021 Jun 4.

	Real-life experience with the combination of **polatuzumab** vedotin, **rituximab**, and **bendamustine** in aggressive B-cell lymphomas. Dimou M, Papageorgiou SG, Stavroyianni N, Katodritou E, Tsirogianni M, Kalpadakis C, Banti A, Arapaki M, Iliakis T, Bouzani M, Verrou E, Spanoudakis E, Giannouli S, Marinakis T, Mandala E, Mparmparousi D, Sachanas S, Dalekou-Tsolakou M, Hatzimichael E, Vadikolia C, Violaki V, Poziopoulos C, Tsirkinidis P, Chatzileontiadou S, Vervessou E, Ximeri M, Sioni A, Konstantinidou P, Kyrtsonis MC, Siakantaris MP, Angelopoulou MK, Pappa V, Konstantopoulos K, Panayiotidis P, Vassilakopoulos TP.Hematol Oncol. 2021 Aug;39(3):336-348. doi: 10.1002/hon.2842. Epub 2021 Mar 2.
Key issue 3: Which of the following indirect treatment comparisons do you consider to be more appropriate for decision making? • RE-MIND2 • Matching-adjusted indirect comparisons	Both have value. RE-MIND2 was a large, real-world, retrospective cohort study of patients with R/R DLBCL (N=3,454). The RE-MIND2 cohort included patients treated with the following regimens: BR, R-GemOx, pola-BR, rituximab (R)+lenalidomide (LEN), CAR-T therapies, and pixantrone; in the second, third, or fourth-line treatment settings. The “non- randomised cohorts were balanced with the L-MIND population on nine baseline covariates using estimated propensity score”, namely: 1. Age (as categorical variable with subgroups <70 vs. ≥70 years of age) 2. Ann Arbor stage (I/II vs. III/IV) 3. Refractoriness status to last therapy line (yes vs. no) 4. Number of prior lines of therapy (1 vs. 2/3) 5. History of primary refractoriness (yes vs. no) 6. Prior ASCT (yes vs. no) 7. Neutropenia (<1.5×109/l; conversion formula (g/dl×0.621=mmol/l); yes vs. no) 8. Anaemia (<10 g/dl [=6.21 mmol/l]; *) (yes vs. no) 9. Elevated lactate dehydrogenase (LDH>upper limit of normal [ULN]; yes vs. no)

	Two additional factors were used in sensitivity analyses, namely:[8] 10. History of early relapse (yes vs. no) and history of primary progressive disease (yes vs. no) 11. ECOG (0 to 1 vs. ≥2) However Lenalidamide is not commissioned for R/R DLBCL so that does limit the value of RE-MIND as a comparator. As outlined previously R GemOx and pola-BR are considered the most relevant comparators for patients with R/R DLBCL who are ineligible for ASCT in the UK and thus matching-adjusted indirect comparisons are probably most valid.
Key issue 4: Which mean survival estimates from the economic model for pola-BR are most plausible? • Company (2.20 life years) • ERG (3.36 life years) Do you have any comments on the survival extrapolations	Mean survival estimates from the economic model for pola-BR which is most plausible • Company (2.20 life years) 1. UK retrospective: 'Results of a UK real world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory large B-cell lymphoma' Northend et al, Blood Advances 2022: After median 7.7 months follow-up, median PFS and **OS** were 4.8 months and **8.2 months** respectively. 2. Polatuzumab vedotin-based salvage immunochemotherapy as third-line or beyond treatment for patients with diffuse large B-cell lymphoma: a real-world experience. Wang YW, et al Ann Hematol. 2022 With a median follow-up of 18.8 months, the median overall survival (OS) of the total cohort was **8.5 months.**

for the other comparators?	3. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Sehn LH, .Blood Adv. 2022 Trial population: Median overall survival **12.4 months**. In the extension cohort, the overall survival was **12.5 months.** 4. Real-life experience with the combination of polatuzumab vedotin, rituximab, and bendamustine in aggressive B-cell lymphomas. Dimou M, et al Hematol Oncol. 2021 Overall survival was **8.5 months** Use data from R-BP NICE appraisal for R-GEM-OX
Key issue 5: The company's assumed reduced price for lenalidomide should not be used.	We can not access Lenalidomide for R/R DLBCL in the NHS. I understand Lenalidomide patency will be lost soon and hence I think it's not unreasonable to assume the price will be reduced. I can not comment further.
Key issue 6: To what extent are the NICE end-of-life criteria met for TAFA+LEN? The criteria are: • Patients face a short life expectancy, normally less than 24 months • The treatment offers an extension to life of at least an	Yes they are met as the standard care is palliative. This therapy is for transplant ineligible patients and that situation will not change. • Patients face a short life expectancy, normally less than 24 months • The treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatment

additional 3 months, compared to current NHS treatment	
Are there any important issues that have been missed in ERG report?	No

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Improvement of tumour-associated symptoms
- Prolongation of progression-related survival
- prolongation of overall survival
- Well tolerated (low incidence of severe or persistent symptoms)
- A treatment approach for which there is no accepted standard of care

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.

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Technical engagement response form

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal 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 ERG report that are likely to be discussed by the committee. The key issues in the ERG report 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 ERG report.

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 ERG report 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 appraisal, 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.

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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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Wednesday 6 April 2022**. 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.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company's selection of comparators is narrower than the NICE final scope. R-Gem, R-P-MitCEBO, (R-)DECC, pixantrone and BSC were not included in the company submission.	No	The main treatments we use in this setting are: R-BP (Rituximab-Bendamustine and Polatuzumab) – the most common regimen. Less commonly we use R-GEM-OX (Gemcitabine and Oxiplatin) In contrast these agents are used far less often and are not considered good comparators. • R-Gem • R-P-MitCEBO, • (R-)DECC • Pixantrone Best supportive care
Key issue 2: The SLR of clinical effectiveness evidence was not conducted according to best recommended practice. Problems with the search	Yes	Our experts are not aware of any other relevant studies not included in the company submission for TAFA+LEN. For the comparators these have recently been published:

and study selection might mean that potentially relevant studies might have been missed. Furthermore, there were issues regarding data extraction and quality assessment.		Results of a UK real world study of **polatuzumab** vedotin, **bendamustine**, and **rituximab** for relapsed/refractory large B-cell lymphoma. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D, Phillips EH, Sim HW, Sadullah S, Shah N, Peng YY, Qureshi I, Addada J, Mora RF, Phillips N, Kuhnl A, Davies E, Wrench DJ, McKay P, Karpha I, Cowley A, Karim R, Challenor S, Singh V, Burton C, Auer R, Williams C, Cunningham J, Broom A, Arasaretnam A, Roddie C, Menne T, Townsend WM.Blood Adv. 2022 Jan 12:bloodadvances.2021005953. doi: 10.1182/bloodadvances.2021005953. **Polatuzumab** vedotin-based salvage immunochemotherapy as third-line or beyond treatment for patients with diffuse large B-cell lymphoma: a real-world experience. Wang YW, Tsai XC, Hou HA, Tien FM, Liu JH, Chou WC, Ko BS, Chen YW, Lin CC, Cheng CL, Lo MY, Lin YC, Lu LC, Wu SJ, Kuo SH, Hong RL, Huang TC, Yao M.Ann Hematol. 2022 Feb;101(2):349-358. doi: 10.1007/s00277-021-04711-9. Epub 2021 Nov 11. **Polatuzumab** vedotin plus **bendamustine** and **rituximab** in relapsed/refractory DLBCL: survival update and new extension cohort data. Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, Kim TM, McMillan A, Ozcan M, Safar V, Salles G, Ku G, Hirata J, Chang YM, Musick L, Matasar MJ.Blood Adv. 2022 Jan 25;6(2):533-543. doi: 10.1182/bloodadvances.2021005794. A phase 2 study of **polatuzumab** vedotin + **bendamustine** + **rituximab** in relapsed/refractory diffuse large B-cell lymphoma. Terui Y, Rai S, Izutsu K, Yamaguchi M, Takizawa J, Kuroda J, Ishikawa T, Kato K, Suehiro Y, Fukuhara N, Ohmine K, Goto H, Yamamoto K, Kanemura N, Ueda Y, Ishizawa K, Kumagai K, Kawasaki A, Saito T, Hashizume M, Shibayama H.Cancer Sci. 2021 Jul;112(7):2845-2854. doi: 10.1111/cas.14937. Epub 2021 Jun 4. Real-life experience with the combination of **polatuzumab** vedotin, **rituximab**, and **bendamustine** in aggressive B-cell lymphomas.

		Dimou M, Papageorgiou SG, Stavroyianni N, Katodritou E, Tsirogianni M, Kalpadakis C, Banti A, Arapaki M, Iliakis T, Bouzani M, Verrou E, Spanoudakis E, Giannouli S, Marinakis T, Mandala E, Mparmparousi D, Sachanas S, Dalekou-Tsolakou M, Hatzimichael E, Vadikolia C, Violaki V, Poziopoulos C, Tsirkinidis P, Chatzileontiadou S, Vervessou E, Ximeri M, Sioni A, Konstantinidou P, Kyrtsonis MC, Siakantaris MP, Angelopoulou MK, Pappa V, Konstantopoulos K, Panayiotidis P, Vassilakopoulos TP.Hematol Oncol. 2021 Aug;39(3):336-348. doi: 10.1002/hon.2842. Epub 2021 Mar 2.
Key issue 3: Questionable validity of ITCs and a number of potentially relevant analyses have not been provided.	No	As Lenalidamide is not commissioned for R/R DLBCL this does limit the value of RE-MIND as a comparator. As outlined previously R GemOx and Pola-BR are considered the most relevant comparators for patients with R/R DLBCL who are ineligible for ASCT in the UK and thus matching-adjusted indirect comparisons are helpful
Key issue 4: OS/PFS parametric extrapolations lack clinical validity, especially for pola-BR.	Yes	Mean survival estimates from the economic model for Pola-BR: 1. UK retrospective: 'Results of a UK real world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory large B-cell lymphoma' Northend et al, Blood Advances 2022: After median 7.7 months follow-up, median PFS and **OS** were 4.8 months and **8.2 months** respectively. 2. Polatuzumab vedotin-based salvage immunochemotherapy as third-line or beyond treatment for patients with diffuse large B-cell lymphoma: a real-world experience. Wang YW, et al Ann Hematol. 2022 With a median follow-up of 18.8 months, the median overall survival (OS) of the total cohort was **8.5 months.**

		3. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Sehn LH, .Blood Adv. 2022 Trial population: Median overall survival **12.4 months**. In the extension cohort, the overall survival was **12.5 months.** 4. Real-life experience with the combination of polatuzumab vedotin, rituximab, and bendamustine in aggressive B-cell lymphomas. Dimou M, et al Hematol Oncol. 2021 Overall survival was **8.5 months** Use data from R-BP NICE appraisal for R-GEM-OX
Key issue 5: The company's assumed reduced price for lenalidomide should not be used.	No	We cannot access Lenalidomide for R/R DLBCL in the NHS. Our experts believe Lenalidomide patency will be lost soon and hence think it's not unreasonable to assume the price will be reduced.
Key issue 6: The supporting literature for the company's claim for meeting the end-of-life criteria has limited relevance to the population in the submission.	No	Yes, they are met as the standard care is palliative. This therapy is for transplant ineligible patients and that situation will not change. • Patients face a short life expectancy, normally less than 24 months • The treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatment

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report N/A

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report 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)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Response to the technical engagement response form

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors

None.

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None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Abbreviations

ASCT	Autologous stem cell transplant
ATE	Average treatment effect
ATT	Average treatment effect on the treated
BR	Rituximab in combination with bendamustine
CAR-T	Chimeric antigen receptor T-cell therapy
CDF	Cancer Drugs Fund
CL	Clarification letter
CMU	Commercial Medicines Unit
CS	Company submission
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
eMIT	Electronic market information tool
EOL	End of life
ERG	Evidence Review Group
FAS	Full analysis set
FL	Follicular lymphoma
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
IPD	Individual participant data
IPI	International Prognostic Index
IPW	Inverse probability weighting
ITC	Indirect treatment comparison
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MI	Multiple imputation
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OS	Overall survival
PFS	Progression-free survival
PH	Proportional hazards
pola-BR	Polatuzumab vedotin with bendamustine and rituximab
QALY	Quality-adjusted life year
RA	Regression adjustment
R-CHOP	Rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone
RCT	Randomised controlled trial
R-Gem	Rituximab in combination with gemcitabine
R-GemOx	Rituximab in combination with gemcitabine and oxaliplatin
R/R	Relapsed or refractory
SAE	Serious adverse event
SCT	Stem cell transplant
SLR	Systematic literature review
SMD	Standardised mean differences
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology assessment
TAFA	Tafasitamab
TE	Technical engagement
TEAE	Treatment emergent adverse events
TSD	Technical support document
UK	United Kingdom

Introduction

This document is the Evidence Review Group's (ERG's) response to comments and additional data provided by the company as part of the technical engagement (TE) process for tafasitamab with lenalidomide (TAFA+LEN) for treating relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL).[1]

Key issue 1: The company's selection of comparators is narrower than the NICE final scope. R-Gem, R-P-MitCEBO, (R-)DECC, pixantrone and BSC were not included in the company submission.

The company provided some further comments in relation to their selection of comparators, together with cited literature intended to support the points made.[1]

ERG comment: The cited systematic literature review (SLR) supports some of the points made, namely that information from the literature provides limited insight into the choice of comparators because of a dearth of evidence from randomised controlled trials (RCTs) and considerable variation in treatment comparisons.[2] This said, the ERG's original comment still stands as explained in Table 1.2 and Section 2.3 of the ERG Report,[3] i.e., the company's selection of comparators is narrower than that shown in the NICE Final Scope.[4]

Key issue 2: The SLR of clinical effectiveness evidence was not conducted according to best recommended practice. Problems with the search and study selection might mean that potentially relevant studies might have been missed. Furthermore, there were issues regarding data extraction and quality assessment.

Search methods/Inclusion criteria (date ranges)

The company provided full search strategies for both the original SLR and update in their original format. Searches were re-run to account for terms not originally included in the strategies, and no additional relevant references were found. An Excel spreadsheet was provided to clarify which conference proceedings were covered by the Embase searches.[5]

ERG comment: Although some justification for the 2010+ date limit for the clinical effectiveness searches is provided, the ERG still believes that a longer date range might have been beneficial. The decision seems primarily based on the large number of records found by the clinical effectiveness searches compared with that found by the cost-effectiveness searches. The company also refer to '*recent and more relevant clinical treatment guidelines for this disease state*', but as these are uncited this cannot be verified.

Data extraction methods

The company provided further comments regarding the process of data extraction and the number of reviewers involved.[1]

ERG comment: This explanation appeared to amount to the same information as outlined in the company's response to question B.3 in the clarification letter (CL) albeit worded in a different way.[6] The ERG still considers that data extraction was not performed in line with best recommended practice[7] and as such, the outcome data and resulting estimates may be subject to error.

Inclusion criteria - language

The company outlined some further details concerning study eligibility on the basis of the language of publication.[1]

ERG comment: The new information essentially repeated the details presented by the company in their response to question B.2 of the CL.[6] The company now asserts that that no reports were excluded on the basis of language and that all exclusions were based on other PICOS criteria.[1] The ERG critique was based on information provided in the company submission (CS)[8, 9] and the company's response to the CL.[6]

Key issue 3: Questionable validity of ITCs and a number of potentially relevant analyses have not been provided.

The company have provided the following responses:

1) In Appendix TE2. Overview of indirect treatment comparison (ITC) analyses the company have provided three figures of the adjustment analyses (using individual participant data [IPD] in the form of RE-MIND2 or matching-adjusted indirect comparisons [MAICs]) conducted, one for each of the comparisons with polatuzumab vedotin with bendamustine and rituximab (pola-BR), bendamustine in combination with rituximab (BR) and rituximab in combination with gemcitabine and oxaliplatin (RGemOx).
2) As requested by the ERG, the company have provided tables comparing the baseline characteristics used for the RE-MIND2 adjustment between TAFA+LEN and each of those comparators with the associated standardised mean differences (SMDs).
3) The company present forests plots of the hazard ratios (HRs) for all analyses described in those three figures.
4) The company represents the rationale for the use of time varying overall survival (OS) HRs for the comparison with pola-BR, including baseline characteristics by whether died/progressed <= 4 months or > 4 months in Appendix TE3.

Each of these responses is addressed by the ERG in the ERG comment below.

ERG comment:

1) These figures confirm the ERG's conclusions in the ERG report that matching using the propensity score based on nine covariates was used in the base-case for comparison using RE-MIND2 for comparison with BR and RGemOx, although the company claim that this was to estimate the average treatment effect on the treated (ATT), which was not the impression of the ERG as expressed in the ERG report, Section 3.4. This is because, although the differences in baseline characteristics were small, and sample size only varied by 1, the fact that an "*adjustment factor*" was considered if the Kaplan-Meier (KM) plots suggested that the original and matched TAFA+LEN patients were different in terms of OS or progression free survival (PFS), indicates a more substantial difference between the matched and unmatched TAFA + LEN data. It is therefore unlikely that the ATT was estimated, but unclear what the nature of the treatment effect was. Therefore, although not explicitly stated, the ERG postulated in the ERG report Section 3.4 that if TAFA + LEN data were adjusted to better match the comparator characteristics then this might be regarded as the average treatment effect on those treated with the comparator. In contrast to the figures for BR and RGemOx, the figure for Pola-BR suggests that it was not the ATT

that was estimated because "*less comparator patients were recruited compared to treated patients*" and that instead what was estimated was the "*average treatment effect on the treated patients for whom a comparator patients could be found*". Notwithstanding the grammatical error, this appears to be consistent with the speculation expressed in the ERG report that the "average treatment effect on those treated with the comparator" was estimated. Matching of 6 or 9 covariates was used for Pola-BR.

The figures also confirm the ERG report conclusion that inverse probability weighting (IPW) to estimate the ATT was also used for pola-BR and overlap weights to estimate the average treatment effect (ATE) for R-GemOx and BR. However, the figure for Pola-BR suggests that overlap weights were used and a reference is cited (MorphoSysAG. Data on File. MOR208C213_REMIND2_Statistical Report_posthoc_August 2021.pdf. TLFs), but the ERG cannot locate this in the original CS or the technical engagement reference pack. The figures for BR and RGemOx state that IPW was not applied because "*ATT could be estimated from 1:1 matching using 9 covariates*".

The figures also indicate that regression adjustment (RA) was performed at technical engagement and the company also state that "*…we have evaluated the feasibility of conducting regression analyses with the RE-MIND2 data through Cox regression models. Results of these analyses were aligned with results obtained with other methodologies and are presented in Appendix TE2b below.*" However, the ERG cannot locate Appendix TE2b. The company do state that the results of the RA should be regarded with caution given the questionable proportional hazards (PH) assumption, but the results of testing for this have not been presented.

2) The following is a summary of the SMDs:
    a. For Pola-BR, all SMDs are below 0.2 except where not defined due to missing data with matching (on 9 or 6 covariates) and there seems to be reasonable similarity of characteristics. With IPW, there are bigger differences in some characteristics as indicated by SMDs for age, Ann Arbor stage, prior autologous stem cell transplant (ASCT) and elevated lactate dehydrogenase (LDH) being above 0.2 without multiple imputation (MI): with MI, very few characteristic are similar. No results were presented for the overlap weight analysis.
    b. For BR, all SMDs are below 0.2 with matching, whether on 9 or 11 covariates. No results were presented for the overlap weight analysis.
    c. For RGemOx, all SMDs are below 0.2 with matching, whether on 9 or 11 covariates. No results were presented for the overlap weight analysis.
3) The following is a summary of the HRs:
    a. For comparison with Pola-BR, the HRs (OS and PFS) using the MAIC (including the base case) are generally higher than using RE-MIND2 regardless of method of adjustment (including RA).
    b. For comparison with BR, the second lowest HRs are using the base case MAIC (pooled for PFS), only RA using RE-MIND2 being slightly lower.
    c. For comparison with RGemOx, the HRs for the MAIC are higher than using RE-MIND2 regardless of method of adjustment (including RA), although not by much for OS.

As stated in the ERG report and discussed in Key issue 4, the validity of the ITCs has been judged ultimately by the ERG in the context of their implications on life expectancy as estimated in the economic model. The only new analyses presented at technical engagement, as requested by the ERG, are those using RA, which appear to produce results similar to those based on the other RE-MIND2 analyses, the only exception being for BR. As described in Key issue 4, life expectancy for BR using the lowest OS HR from the MAIC might be too high, if compared to TA649, but it was validated by clinical experts: if the RA value were used it would probably go down, but probably not by much and this would probably reduce the incremental cost-effectiveness ratio (ICER).

4) As acknowledged in the ERG report section 4.2.6.5, the company had provided a rationale for rejecting the PH assumption, which included the crossing of log-cumulative hazard plots and the [redacted]. The baseline characteristics presented by the company do suggest that patients who die or progress had characteristics that suggested a poor prognosis, but that is self-evidently true. As the company argue, there might be a plausible explanation for the non-proportionality, but the ERG did not question that there was evidence of non-proportional hazards. However, the main problem identified by the ERG was the questionable alignment of the company base case extrapolation with the results of TA649, as discussed further in Key Issue 4 below.

Key issue 4: OS/PFS parametric extrapolations lack clinical validity, especially for pola-BR.

The company requested the ERG to further clarify its general concerns around the clinical or external validity of the extrapolations for each comparator, and their perspective on the UK clinical expert feedback collected for the RE-MIND2 study during the appraisal process for BR and R-GemOx. In addition, the company discussed the following points:

Terminology: The company suggested that since the ERG's concerns about extrapolations appear to be primarily based on comparisons to the extrapolations and results from NICE TA649, it may be more appropriate to classify these concerns as "*external validity*" rather than "*clinical validity*". The company also asked the ERG to provide further confirmation on whether there were other clinical validity considerations involved in their decision-making process.

Company's approach to modelling pola-BR: The company reiterate in their response to TE that, the MAIC-based extrapolations were selected instead of RE MIND2-based extrapolations based on clinical expert feedback. They also reiterate that time-varying HRs were chosen for the company base-case analysis over a constant HR on the basis of a clear violation of the PH assumption. Furthermore, as highlighted in response to Key Issue 3, the company also state that differences were also observed in the patient characteristics for TAFA+LEN patients in L-MIND who died or progressed within the first 4 months compared to after 4 months, as well as differences between TAFA+LEN and pola-BR in treatment administration schedules (already mentioned in the company submission), timing of responses and inclusion of chemotherapy within the dosing regimen. These factors provide, according to the company, a strong clinical and statistical rationale for use of a time-varying HR with 4-month piecewise split to capture a differential effect of TAFA+LEN compared with pola-BR.

Comparison with available data: Table 1.1 is a copy of a table provided by the company in their response and provides a summary of the MAIC-based extrapolation results in comparison two recent pola-BR studies. The company noted the UK real-world evidence Northend et al. 2022,[10] and the Japanese study Terui et al. 2022.[11] It can be seen that the available median OS data for the stand-alone treatment cohort from Northend 2022[10] was lower than the MAIC constant HR extrapolation (10.2 months vs 18.7 months) and closer to, but still lower than, the median estimate from the time-varying HR extrapolation (14.8 months). Median PFS data from both Northend 2022 (5.4 months)[10] and Terui 2022 (5.2 months)[11] were also lower than the median PFS estimate produced by the constant HR extrapolation (15.3 months), and the time-varying HR estimate (10.8 months). This was also the case for the 1-year PFS estimate from Terui 2022 (~38%),[11] which was well aligned with the time-varying HR PFS estimate at 1 year (39.4%) and lower than the constant HR value (51.7%).

Table 1.1: Comparison of MAIC-based extrapolations against recently published data for pola-BR

Outcome	Pola-BR efficacy data source				
	MAIC-time-varying HR (Company base-case)	**MAIC-constant HR (ERG base-case)**	**Northend 2022 - stand-alone treatment cohort (N=76)**	**Northend 2022 - all patients (N=131)**	**Terui 2022 (N=35)**
Median (95% CI) OS, months	14.8	18.7	10.2 (5.2-14.3)	8.2 (5.9-14.3)	Not reached (8.4-NE)
OS at 1 year	57.9%	60.9%	NA	~43%	~59%
Median (95% CI) PFS, months	10.8	15.3	5.4 (3.0-10.8)	4.8 (3.7-9.3)	5.2
PFS at 1 year	39.4%	51.7%	NA	~28%	~38%

Based on first table from company's queries on Key Issue 4[1] with data derived from Northend et al. 2022[10] and Terui et al. 2022[11]
CI = confidence interval; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; NA = not available; OS = overall survival; PFS = progression-free survival; pola-BR = Polatuzumab vedotin with bendamustine and rituximab

ERG comment: The ERG acknowledges that using the right terminology is crucial to properly explain and to understand the ERG's concerns regarding the validity of the pola-BR results presented by the company in this appraisal. The company is correct that the ERG's main concerns are related to the comparison with the results from NICE TA649, specifically economic model results in terms of life-years and quality-adjusted life years (QALYs) for Pola-BR. Using the terminology and definitions in Vemer et al. 2016,[12] the most appropriate type of validation regarding the comparison between results produced by different models would be cross validation. External validation, as we understand it, is related to the comparison between the model results and empirical data that were not used to build the model (also called independent validation). An example of an external validation exercise was provided by the company in Table 1.1 and was discussed by the ERG below. It also needs to be made clear that the results of the TA649 economic model are based to large extent on the use of a polaBR trial,[13] the OS and PFS results of which were used for validation in the CS, but not represented in the TE response. Therefore, we would like to clarify that the use of TA649 for validation by the ERG was based on the assumption that results from NICE TA649 were validated by clinical experts and accepted by the TA649 Appraisal Committee. Based on that assumption, and terminology aside, the ERG considers that the company should clarify why their analyses resulted in substantially different results for pola-BR compared to TA649, when in TA649 and in this appraisal the underlying condition and populations are the same. Therefore, the ERG still considers it appropriate and reasonable to assume that if results in TA649 were deemed as valid (in any relevant aspect), then the results in this appraisal should be similar, and in the opinion of the ERG, this is not the case.

As already stated in the ERG report, the ERG agrees with the company in the selection of MAIC-based extrapolations to model pola-BR. Extrapolations based on RE-MIND2 data overly underestimated OS and PFS for pola-BR as acknowledged by the experts consulted by the company. The ERG considers that one of the most straightforward validation exercises would be a comparison with NICE TA649, a previous appraisal on the same condition and population. However, it seems that this was not done. The ERG also acknowledged in the ERG report (Section 4.2.6.5) that the PH assumption was violated in the MAIC, and, for that reason, a time-varying HR would have been preferred. However, again, based on the comparison against TA649, the results obtained assuming a time-varying HR with 4-month piecewise split were not in line to those in TA649. Furthermore, the ERG has no reasons to disagree with the company in that differences were observed in L-MIND before and after 4 months or that there are differences between TAFA+LEN and pola-BR in treatment administration schedules, timing of responses and inclusion of chemotherapy within the dosing regimen. However, the ERG is not convinced that this alone provided a strong clinical and statistical rationale for use of a time-varying HR with 4-month piecewise split to capture a differential effect of TAFA+LEN compared with pola-BR. To make such a statement, the ERG considers that the validity of the assumed model (the time-varying HR) should be assessed. The ERG did this by comparing their results against TA649, and it was concluded that the time-varying model did not provide valid enough results (as explained in Sections 4.2.6.4, 4.2.6.9 and 5.1 of the ERG Report).

The company presented in Table 1.1 a comparison between the median OS/PFS and the OS/PFS at year 1 predicted by the company's and ERG's base-case analyses and data observed in two recent studies.[10, 11] The company concluded that while these naïve comparisons against

available published data should be interpreted with some caution, these indicated that the observed survival for pola-BR from real-world evidence may be much lower than produced by the extrapolations produced by the constant HRs for OS and PFS generated from the MAIC and were closer to the time-varying HR values (although these also appeared to potentially overpredict OS and PFS for pola-BR). The ERG agrees with the company that the comparisons in Table 1.1 should be interpreted with caution: for example, it is not shown whether the populations in the studies are comparable. Moreover, the interpretation of the company tends to be subjective and biased. While it is true that the values from the two studies in Table 1.1 were closer to the time-varying HR values (the company's base-case), the two studies presented resulted in OS/PFS predictions considerably lower than those in the company's base-case as well. The study from Sehn et al. 2022,[13] (data from GO29365, used in TA649) reported a median OS of 12.4 months in the trial population and 12.5 months in the extension cohort, still lower than in the company's and ERG's scenarios but higher than those presented by the company in Table 1.1. Finally, note that the median OS/PFS and OS/PFS at 1 year do not capture the complete picture of this issue. As shown in the comparison with the TA649 life years (or life expectancy), this is an "*area under the curve*" problem, and it is well-known that most differences occur in the long-term extrapolations, so most likely after the median or after 1 year. Figures 1.1 to 1.5 below can be used for illustration purposes. To improve clarity, the ERG would like to explain precisely how the TA649 model results were used:

- We used the passage from TA649 in which it is mentioned that "*the ERG base-case showed a total 2.08 life years gain between two interventions*",[14] the interventions here being pola-BR and BR and the gain in life years for pola-BR compared to BR.
- We used the results in Table 7.4 of the ERG report in TA649 (ERG preferred base-case scenario), where the total life years gained for BR were 1.00.[14] Thus, it can be inferred that the total life years gained for pola-BR in TA649 were 3.08.
- In summary, based on TA649, we expected that the total life years accrued in the pola-BR arm should be around 3 years, and in the BR arm around 1 year.
- Furthermore, Table 7.4 of the ERG report in TA649 (ERG preferred base-case scenario) shows that for BR 1.00 LYG "*results*" in 0.68 QALYs (so approximately a 0.7 factor).[14] Using the same approximation for pola-BR, we expected approximately 2.10 QALYs.

The ERG also has provided a summary of the company and ERG base cases, as well as three further scenarios to show how they compare when validated using the TA649 model results. These scenarios are defined in Table 1.2. In all scenarios, it was assumed that TAFA+LEN would be unchanged, and therefore, a lognormal distribution from L-MIND data was used all the time. Then, in one scenario it was assumed that all comparators were sourced from the MAIC, in another scenario all comparators were sourced from RE-MIND2 and in the last scenario the company's base-case was modified assuming a different time-varying HR for pola-BR. For each scenario total life years, QALYs and a plot of the OS curves are shown. It should be noted that we have prioritised the consideration of OS over PFS, but for sake of completeness, similar scenarios should be run for PFS too, even though the impact of PFS on the model results is less than the impact of OS.

Table 1.2: Scenarios used to illustrate the validity of the pola-BR OS extrapolations

Treatment arm	Scenarios OS efficacy data source				
	Company's base-case	**ERG's base-case**	**All comparators MAIC**	**All comparators RE-MIND2 (Best scenario for pola-BR)**	**Company's base-case (alt. time-varying HR pola-BR)**
TAFA+LEN	Lognormal (L-MIND)	Lognormal (L-MIND)	Lognormal (L-MIND)	Lognormal (L-MIND)	Lognormal (L-MIND)
Pola-BR	Time-varying HR, 4 months (MAIC)	Constant HR (MAIC)	Constant HR (MAIC)	Constant HR (RE-MIND2)	Time-varying HR, 11 months (MAIC)
BR	PH (RE-MIND2)	Constant HR (MAIC)	Constant HR (MAIC)	PH (RE-MIND2)	PH (RE-MIND2)
R-GemOx	Lognormal (RE-MIND2)	Lognormal (RE-MIND2)	Constant HR (MAIC)	Lognormal (RE-MIND2)	Lognormal (RE-MIND2)

BR = rituximab in combination with bendamustine; ERG = Evidence Review Group; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PH = proportional hazards; pola-BR = Polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

Table 1.3 shows the life years and QALYs accrued for all comparators in all five scenarios, while the OS curves for all scenarios are shown in Figures 1.1 to 1.5. It can be seen in Table 1.3 that only the ERG base-case scenario provided results that resemble those obtained in TA649. Regarding the OS curves, it is clear that different shapes are obtained depending on the underlying assumptions made for OS and that these can explain, to a great extent, the results observed in Table 1.3. Figure 1.1 and Figure 1.2 show the OS curves assumed in the company's and the ERG's base-case, respectively. Even though the company and the ERG selected a different curve for BR, these resulted in similar outcomes, and therefore, the main difference was due to pola-BR. The company assumed a time-varying HR with a change in hazards at 4 months.

[redacted]. It is unclear to the ERG whether this scenario represents a plausible situation or not. The ERG's base-case (Figure 1.2) represents a scenario [redacted]. Even though the ERG considers this scenario more plausible than the company's base-case, as it matches better the results in TA649,

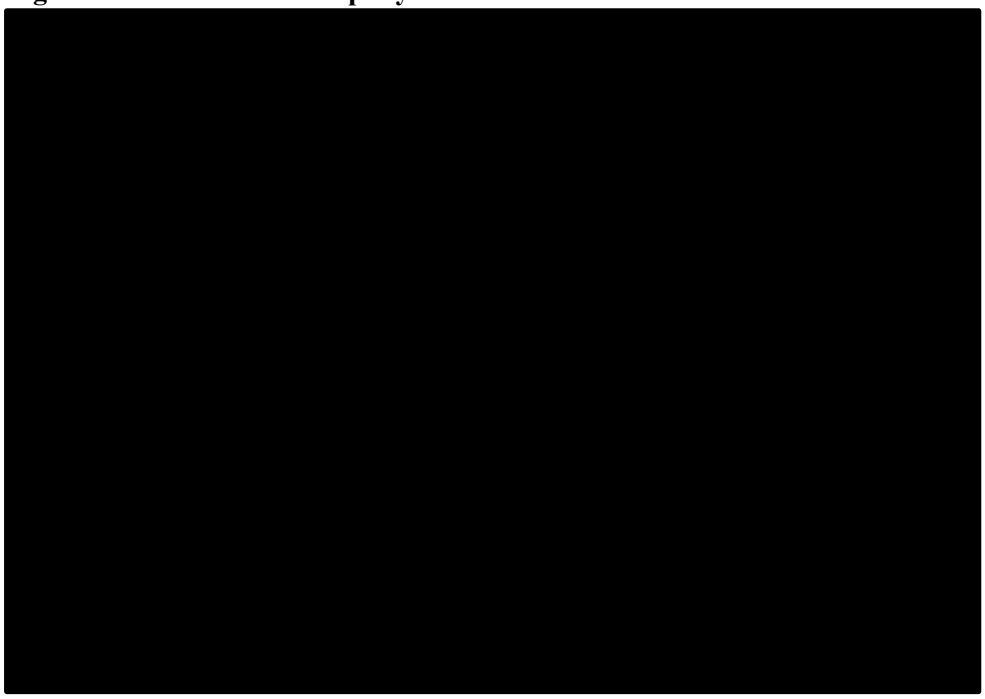
it should be further validated by clinical experts. The scenarios represented in Figures 1.3 and 1.4 were deemed as implausible by the ERG because they seem to overly overestimate OS for R-GemOx and underestimate OS for pola-BR, respectively. Finally, Figure 1.5 depicts OS in a modified company's base-case scenario in which a time-varying HR for pola-BR with a change in hazards at 11 months, was assumed. [redacted]. Again, it is unclear to the ERG whether this scenario represents a plausible situation or not, and why it is substantially different to the company's base-case, when the only difference was the time where the hazards change.

Table 1.3: Results (life years and QALYs) of the OS scenarios presented by the ERG

	TAFA+LEN	Pola-BR	BR	R-GemOx
Company's base-case				
Life years	5.08	2.20	1.76	1.82
QALYs	[redacted]	1.45	1.13	1.16
ERG's base-case				
Life years	5.08	3.36	1.60	1.82
QALYs	[redacted]	2.20	1.02	1.16
All comparators MAIC				
Life years	5.08	3.36	1.60	2.56
QALYs	[redacted]	2.20	1.02	1.65
All comparators RE-MIND2 (best scenario for pola-BR out of possible extrapolations)				
Life years	5.08	1.77	1.76	1.82
QALYs	[redacted]	1.11	1.13	1.16
Company's base-case (alt. time-varying HR pola-BR)				
Life years	5.08	2.04	1.76	1.82
QALYs	[redacted]	1.33	1.13	1.16

BR = rituximab in combination with bendamustine; ERG = Evidence Review Group; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA+LEN = tafasitamab + lenalidomide

Figure 1.1: OS curves: company's base-case

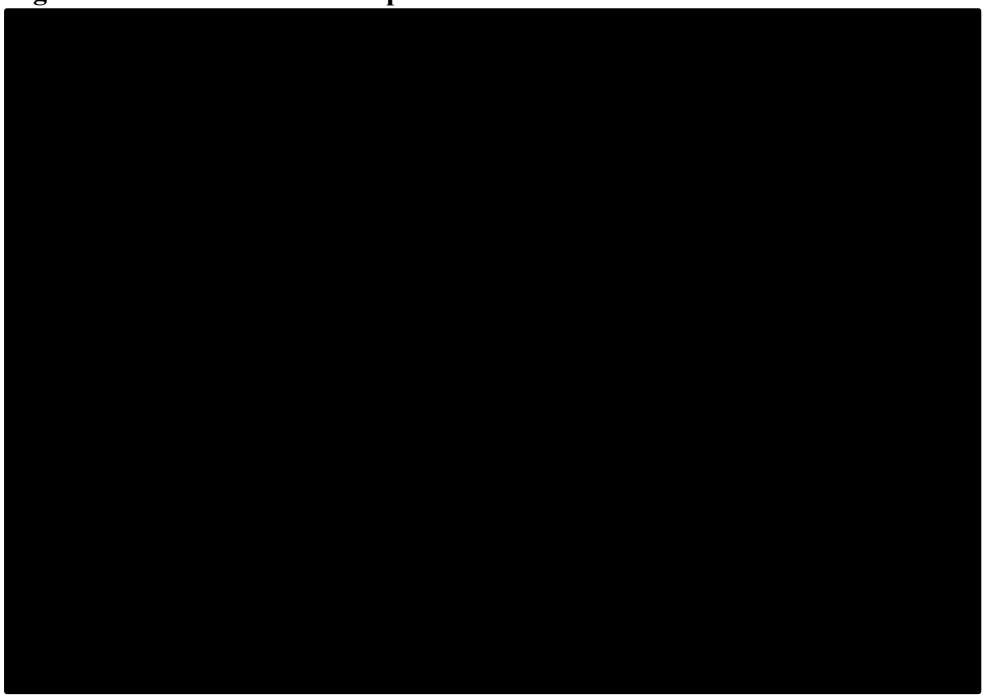


Source: electronic model.
KM = Kaplan-Meier; OS = overall survival

Figure 1.2: OS curves: ERG's base-case

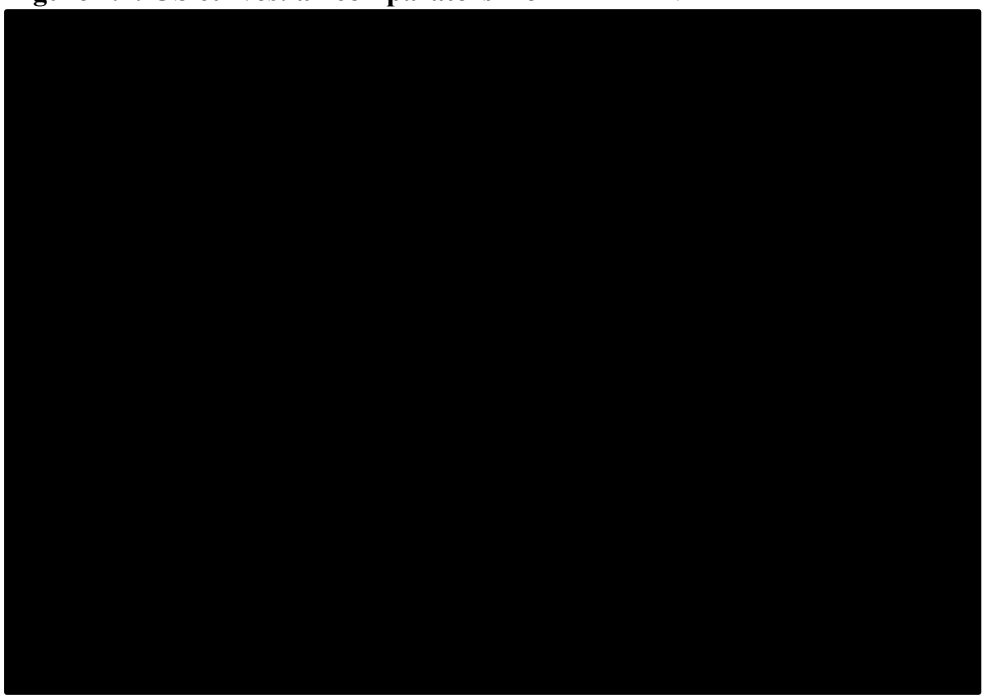
Source: electronic model.
ERG = Evidence Review Group; KM = Kaplan-Meier; OS = overall survival

Figure 1.3: OS curves: all comparators from MAIC



Source: electronic model.
MAIC = matching-adjusted indirect comparison; KM = Kaplan-Meier; OS = overall survival

Figure 1.4: OS curves: all comparators from RE-MIND2



Source: electronic model.
KM = Kaplan-Meier; OS = overall survival

Figure 1.5: OS curves: company' s base-case with alternative time varying HR for pola-BR

Source: electronic model.
HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; pola-BR = polatuzumab + bendamustine + rituximab

In summary, according to the ERG, the following can be concluded:

- For all comparators in general, the ERG preferred patient-level data (RE-MIND2) over the MAIC. However, this resulted in implausible results for pola-BR, as shown for example in Figure 1.4 (the pola-BR OS curve was nearly identical to the BR OS curve, that is why it can barely be seen in the plot) and in Table 1.3 (*All comparators RE-MIND2 (best scenario for pola-BR)*). Note that the scenario presented by the ERG represents the best-case scenario for pola-BR amongst all possible choices based on RE-MIND2 extrapolations; any other choice would result in less survival for pola-BR. Therefore, for pola-BR, the MAIC seems to be the only meaningful option to model OS.
- Since with the available data pola-BR must be sourced from the MAIC, the ERG initially considered to source all comparators from the MAIC, to reduce to some extent structural uncertainty. However, in that scenario (*All comparators MAIC*), R-GemOx was substantially better than BR in terms of OS, as can be seen in Figure 1.3 and in Table 1.3. The ERG considers that there is no evidence to support these results and worked under the assumption that R-GemOx and BR are approximately equivalent in terms of effectiveness, even though this assumption should be validated by clinical experts.
- As mentioned above, our rationale was that based on TA649, total life years and QALYs accrued for pola-BR should be around 3 and 2.1, respectively. The only scenario in which this happened, is the one assuming a constant HR from the MAIC, as in the ERG base-case. Even though it could be argued that the ERG base-case might overestimate pola-BR benefits compared to TA649, this could be seen as a conservative

approach for TAFA+LEN. The other scenarios, on the other hand, underestimate pola-BR benefits vs. BR compared to TA649.

- For BR, as mentioned above, our rationale was that, based on TA649, total life years and QALYs accrued for BR should be around 1 and 0.68, respectively. Note that all scenarios overestimate BR benefits compared to TA649. However, since BR results were validated by clinical experts, according to the company, we worked under the assumption that BR results were valid. The ERG has no strong preference for one approach in particular (RE-MIND2 or MAIC), since as shown in Table 1.3, both assumptions provided fairly similar results, but those with the MAIC were closer to TA649. Uncertainty should be assessed with scenario analyses.

Finally, a summary of the ERG's assessment of the validity of the scenarios presented above is shown in Table 1.4. In conclusion, despite the issues described above, and extensively discussed in the ERG report, the ERG still considers that the ERG base-case represents the most plausible scenario for pola-BR in comparison to TA649.

Table 1.4: ERG's assessment of the validity of the scenarios

ERG criterion	Company's base-case	ERG's base-case	All comparators MAIC	All comparators RE-MIND2 (Best scenario for pola-BR out of possible extrapolations)	Company's base-case (alt. time-varying HR pola-BR)
LYG pola-BR vs. BR ~ 2	☹ (0.44)	☺ (1.76)	☺ (1.76)	☹ (0.01)	☹ (0.28)
LYs pola-BR ~ 3	☹ (2.20)	☺ (3.36)	☺ (3.36)	☹ (1.77)	☹ (2.04)
LYs BR ~ 1	😐 (1.76)	😐 (1.60)	😐 (1.60)	😐 (1.76)	☹ (1.76)
QALYs pola-BR ~ 2.1	☹ (1.45)	☺ (2.20)	☹ (2.20)	☺ (1.11)	☹ (1.33)
QALYs BR ~ 0.68	😐 (1.13)	😐 (1.02)	😐 (1.02)	😐 (1.13)	😐 (1.13)

BR = rituximab in combination with bendamustine; ERG = Evidence Review Group; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin

Key issue 5: The company's assumed reduced price for lenalidomide should not be used.

The company acknowledged that generic lenalidomide was not available at the time of writing the ERG report. The company included an estimation of the price of generic lenalidomide based on the expected date of patent exclusivity of lenalidomide (due to expire in Q1 2022) and the reduction to the list price for lenalidomide observed in countries like Italy, Spain, France, and Ireland. The company also indicated that in [redacted]. Therefore, the company asked the ERG to reconsider its position regarding applying the list price of lenalidomide in its analyses.

ERG comment: The ERG would like to reiterate that cost effectiveness analyses should be conducted with the current available evidence. Therefore, the ERG considers that lenalidomide list price should be used in the analyses presented by the company and the ERG (in the ERG report), and that it is inaccurate to assume a discount price based on the company's expectations. To assess the impact of lenalidomide's price on the cost effectiveness results, the ERG refers to the confidential addendum to the ERG report which shows the results of the cost effectiveness analyses based on the lowest nationally available prices of the drugs against which tafasitamab is compared, lenalidomide, co-medications and subsequent treatments included in the economic model.[15] These prices were provided by the Commercial Medicines Unit (CMU) and the prices of generic drugs in equivalent formulations were derived from the electronic market information tool (eMIT).

Key issue 6: The supporting literature for the company's claim for meeting the end-of-life criteria has limited relevance to the population in the submission.

The ERG acknowledges the additional comments provided by the company regarding the possibility of TAFA+LEN meeting the NICE end-of-life (EOL) criteria.[1]

ERG comment: The ERG agrees that the SLR by Thuresson et al. 2020 supports the statement that the median OS across 11 studies with different treatment comparisons ranged from 5.0 to 22.2 months in patients with R/R DLBCL.[2] However, the ERG also notes that the median OS for pola-BR exceeded 24 months in TA649 (2.08 life years gain for pola-BR when compared with BR).[14] Furthermore, the use of pola-BR was associated with 2.20 life years gain in the company's base-case analysis (presented in Table 1.3 above). The ERG concludes that depending on the comparator being considered, TAFA+LEN may not meet criterion 1 of the NICE EOL criteria.

Additional issue 1: Consideration of tafasitamab inclusion in the Cancer Drugs Fund

The ERG acknowledges the company's outline of information about consideration of inclusion of tafasitamab in the Cancer Drugs Fund (CDF)[1] however, cannot comment further as this issue is beyond the ERG's remit.

Additional issue 2: Generalisability of L-MIND to the UK population with R/R DLBCL who are not eligible for transplant

The ERG notes the company's comments in relation to the generalisability of the international L-MIND study to the UK population with R/R DLBCL who are not eligible for stem cell transplant (SCT).[1] As part of their argument, the company cited a recently-published UK-based study by Northend et al. 2022 recruiting patients with R/R DLBCL (n = 78) treated with pola-BR as '*stand-alone*' therapy (i.e., not

used as preparation for chimeric antigen receptor T-cell therapy [CAR-T] or SCT).[10] The company asserted that the reported baseline characteristics were similar between L-MIND[16] and Northend et al. 2022,[10] highlighting the similarity in median age and the number of patients: receiving second-line treatment, refractory to first-line treatment and who had bulky disease. The company concluded that the baseline data from Northend et al. 2022[10] supported the notion of generalisability of L-MIND to the UK population with R/R DLBCL who are not eligible for SCT.

ERG comment: After scrutinising the baseline characteristics of Northend et al. 2022[10] and L-MIND,[16] the ERG agrees that the baseline data on age appear broadly similar between the two studies. However, the ERG noted potential between-study differences in the following baseline variables with values for Northend et al. 2022[10] and L-MIND[16] presented respectively below:

- proportion of males 69.2% versus 54.0%
- presence of bulky disease 28.2% versus 19.0%
- International Prognostic Index (IPI) score 0 to 2 26.9% versus 49.0%
- IPI score ≥3 71.8% versus score 3 to 5 51.0%
- Median (range) lines of prior therapy 1 (1 to 6) versus 2 (1 to 4)
- One line of prior therapy 55.1% versus 50.0%
- Two lines of prior therapy 16.7% versus 43.0%
- ≥3 lines of prior therapy 25.6% versus 3 or 4 lines of prior therapy 7.0%
- refractory to last line of treatment 57.7% to 44.0%

Of note, it appears that the company misread the information on the proportion of patients receiving second-line therapy in both papers.[10, 16]

Overall, the ERG is still uncertain about the generalisability of L-MIND to the UK population with R/R DLBCL who are not eligible for SCT.

Additional issue 3: Serious adverse event (SAE) data for the L-MIND and MOR208C201 studies

Sections 3.2.1.2 and 3.2.2.2 of the ERG report highlighted concerns surrounding the paucity of evidence on the serious adverse events (SAEs) experienced by patients in the L-MIND and MOR208C201 study.[3] In response, the company provided information on treatment-emergent severe adverse events (TEAEs) for the L-MIND and MOR208C201 studies in Tables 16 and 17 of the Technical Engagement Response form.[1]

In the MOR208C201 study, the incidence of TEAEs was higher in the DLBCL cohort when compared to other non-Hodgkin's lymphoma (NHL) subtypes, particularly for follicular lymphoma (FL) which was of a similar sample size. Neutropenia was the most frequently occurring serious haematological TEAE whilst disease progression was the most frequently occurring non-haematological serious TEAE.

In the L-MIND study which only included patients with DLBCL, the most frequently reported serious TEAEs were febrile neutropenia (haematological) and pneumonia (non-haematological). It is unclear if these results are for the full analysis set (FAS) or safety population which consisted of all patients who received at least dose of either tafasitamab or lenalidomide.

Additional issue 4: Assessment of proportional hazards between TAFA+LEN and BR OS for RE-MIND2

The company requested the ERG report to re-assess its interpretation regarding the PH assumption between TAFA+LEN and BR for the OS extrapolation using the RE-MIND2 data.

ERG comment: The ERG understands the company's position in this point and since in the ERG's view this is a matter of judgement, we think that we do not have to agree in this aspect. In any case, the ERG considers this a minor technical issue and would like to refer to what was mentioned above in the response to Key Issue 4: the ERG has no strong preference for one approach in particular (RE-MIND2 PH or MAIC constant HR), since as shown in Table 1.3, both assumptions provided fairly similar results. Those with the MAIC were closer to TA649, and that was the main reason why the ERG chose it for its base-case.

Appendix TE4

The ERG noted Table 15 in Appendix TE4 which provided a summary of ongoing studies of tafasitamab.[1] It was apparent from this that the next relevant point for emergence of new data would be November 2022 as the next follow-up point for L-MIND (MOR208C203, NCT02399085) (n = 81 participants).[17] The ERG also noted the largest evaluation, FRONT-MIND (comparing TAFA+LEN combined with rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin and prednisolone [R-CHOP] versus R-CHOP) in patients with DLBCL in n = 880 participants; recruitment is ongoing (MOR208C310, NCT04824092).[18]

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1. COMPANY'S BASE-CASE RESULTS BASED ON TAFASITAMAB PAS PRICE AND LENALIDOMIDE LIST PRICE

The results presented by the company were based on the model provided alongside their response to the Technical Engagement questions. Table 1.1 shows the deterministic results of the company's base-case analysis using the PAS price for Tafasitamab and the list price for lenalidomide. All results are discounted. Given that there are three comparators included in the analyses, results are reported in a full incremental way. Pairwise incremental cost effectiveness ratios (ICERs) of TAFA+LEN vs. each of the comparators are also reported for completeness. Results indicated that [redacted]

Table 1.1: Company base-case cost effectiveness results (tafasitamab PAS price, lenalidomide list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
R-GemOx	[redacted]	1.82	1.16					[redacted]
BR	[redacted]	1.60	1.04	[redacted]				[redacted]
Pola-BR	[redacted]	2.20	1.45	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	2.88	[redacted]	[redacted]	

* All pairwise ICERs are calculated vs. TAFA+LEN

BR = bendamustine + rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

2. EVIDENCE REVIEW GROUP'S BASE-CASE RESULTS BASED ON TAFASITAMAB PAS PRICE AND LENALIDOMIDE LIST PRICE

Table 2.1 shows the deterministic results of the ERG preferred base-case analysis. All results are discounted.

[redacted]

Table 2.1: ERG preferred base-case deterministic cost effectiveness results (tafasitamab PAS price, lenalidomide list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
R-GemOx	[redacted]	1.82	1.16					[redacted]
BR	[redacted]	1.60	1.02	[redacted]				[redacted]
Pola-BR	[redacted]	3.36	2.20	[redacted]	1.53	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	1.73	[redacted]	[redacted]	

* All pairwise ICERs are calculated vs. TAFA+LEN

BR = bendamustine + rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

3. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES BASED ON TAFASITAMAB PAS PRICE AND LENALIDOMIDE LIST PRICE

Table 3.1 shows the results of the ERG's additional scenario analyses. All results are discounted.

Table 3.1: ERG scenario analyses results (tafasitamab PAS price, lenalidomide list price)

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
ERG base-case	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: Pola-BR											
MAIC time-varying HR (4 months)	[redacted]	[redacted]	[redacted]	1.47	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
MAIC time-varying HR (11 months)	[redacted]	[redacted]	[redacted]	1.36	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
RE-MIND2 constant HR	[redacted]	[redacted]	[redacted]	1.11	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: BR											
Exponential (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	0.88	[redacted]	[redacted]	1.16	[redacted]
Weibull (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	0.93	[redacted]	[redacted]	1.16	[redacted]
Lognormal (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.11	[redacted]	[redacted]	1.16	[redacted]
Log-logistic (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.16	[redacted]	[redacted]	1.16	[redacted]
Gompertz (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.47	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.36	[redacted]	[redacted]	1.16	[redacted]

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
Constant HR (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.13	[redacted]	[redacted]	1.16	[redacted]
Alternative PFS: Pola-BR											
MAIC time-varying HR (4 months)	[redacted]	[redacted]	[redacted]	2.10	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
MAIC time-varying HR (11 months)	[redacted]	[redacted]	[redacted]	2.09	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.16	[redacted]
Alternative PFS: BR											
Exponential (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.10	[redacted]	[redacted]	1.16	[redacted]
Weibull (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.10	[redacted]	[redacted]	1.16	[redacted]
Lognormal (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.11	[redacted]	[redacted]	1.16	[redacted]
Log-logistic (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.12	[redacted]	[redacted]	1.16	[redacted]
Gompertz (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.10	[redacted]	[redacted]	1.16	[redacted]
Generalised Gamma (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.10	[redacted]	[redacted]	1.16	[redacted]
Constant HR (RE-MIND2)	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.14	[redacted]	[redacted]	1.16	[redacted]
Alternative OS: Constant HR from MAIC for Pola-BR, BR and R-GemOx											
All comparators MAIC	[redacted]	[redacted]	[redacted]	2.20	[redacted]	[redacted]	1.02	[redacted]	[redacted]	1.65	[redacted]
Alternative OS: Pola-BR (Constant HR), BR (PH) and R-GemOx (Lognormal) based on RE-MIND-2											

Scenarios	TAFA+LEN		Pola-BR			BR			R-GemOx		
	Total costs (£)	Total QALY	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)	Total costs (£)	Total QALY	ICER (£/QALY)
All comparators RE-MIND2 (Best scenario for Pola-BR)	[redacted]	[redacted]	[redacted]	1.11	[redacted]	[redacted]	1.13	[redacted]	[redacted]	1.16	[redacted]

CS = company submission; BR = bendamustine and rituximab; CAR-T = chimeric antigen receptor T-cell therapy; ERG = Evidence Review Group; FAD = Final Appraisal Determination; HR = hazard ratio; ICER = incremental cost effectiveness ratio; KM =Kaplan-Meier; LEN = lenalidomide; MAIC = matching-adjusted indirect comparison; OS = overall survival; PD = progressed disease, PFS = progression-free survival; PH = proportional hazards; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab; TTD = time to treatment discontinuation