Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic treatments [ID3943]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

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

1. **Company submission from Swedish Orphan Biovitrum:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

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. **External Assessment Report** prepared by Warwick Evidence

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from Swedish Orphan Biovitrum**

7. **Technical engagement responses and statements from experts:**
   a. Dr Andrea Kuhnl – clinical expert, nominated by National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
   b. Dr Cathy Burton – clinical expert, nominated by National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

8. **External Assessment Report critique of company response to technical engagement** prepared by Warwick Evidence

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Document B

Company evidence submission

17 March 2023

File name	Version	Contains confidential information	Date
ID3943- Loncastuximab tesirine-RR-DLBCL-DocumentB-Redacted	1	Redacted	17 March 2023

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Abbreviations

ABC	Activated B-cell
ABW	Adjusted body weight
ADA	Antidrug antibody
ADC	Antibody-drug conjugate
AE	Adverse events
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
Allo-SCT	Allogenic stem cell transplantation
BIC	Bayesian Information Criterion
BNF	British National Formulary
BMI	Body mass index
BOR	Best overall response
BR	Bendamustine plus rituximab
BSA	Body surface area
BSH	British Society for Haematology
CAR T-cell	Chimeric antigen receptor T cells
CCU	Critical care unit
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CEP	Cost-effectiveness plane
CI	Confidence interval
CNS	Central nervous system
COO	Cell-of-origin
CR	Complete response
CRR	Complete response rate
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
BCL	B-cell lymphoma gene
DECC	Dexamethasone, etoposide, chlorambucil, lomustine
DH	Double hit
DHAP	Cisplatin, cytarabine, dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSA	Deterministic sensitivity analysis

ABC	Activated B-cell
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic marketing information tool
EMR	Electronic medical record
EOT	End of treatment
EQ-5D	EuroQol five dimension
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EWB	Emotional well-being
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FACT-G	Functional Assessment of Cancer Therapy – General
FL	Follicular lymphoma
FWB	Functional well-being
GCB	Germinal centre B-cell
GDP	Cisplatin, gemcitabine, dexamethasone
GGT	Gamma-glutamyl transferase
HGBL	High-grade B-cell lymphoma
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility value
HTA	Health technology assessment
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient data
IPI	International Prognostic Index
IQR	Interquartile range
IV	intravenous
IVE	Ifosfamide, epirubicin and etoposide
IWG	International Working Group
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
Lonca	Loncastuximab tesirine
LY	Life year
LymS	Lymphoma subscale
MAIC	Matching adjusted indirect comparison
MID	Minimally important difference

ABC	Activated B-cell
MMAE	Monomethyl auristatin
MYC	Myelocytomatosis
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOS	Not otherwise specified
NR	Not reported
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PartSA	Partitioned survival analysis
PBD	Pyrrolobenzodiazepine
PD	Progressed disease
PEPC	Prednisone, etoposide, cyclophosphamide and procarbazine
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazardsa
PK	Pharmacokinetic
PMBCL	Primary mediastinal B-cell lymphoma
Pola+BR	Polatuzumab plus bendamustine plus rituximab
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partition survival model
PT	Preferred term
PWB	Physical well-being
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
R	Rituximab
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CHP	Rituximab, cyclophosphamide, doxorubicin and prednisolone
RDI	Relative dose intensity
RFS	Relapse-free survival
R-GemOx	Rituximab with gemcitabine and oxaliplatin
R/R	Relapsed or refractory
RWE	Real-world evidence

ABC	Activated B-cell
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
STA	Single technology appraisal
SWB	Social/family well-being
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TH	Triple hit
TiNHL	Transformed indolent non-Hodgkin's lymphoma
TOI	Trial Outcome Index
TSD	Technical Support Document
TTD	Time-to-treatment discontinuation
TTO	Time trade-off
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual Analog Scale
vs	versus
WHO	World Health Organization
WTP	Willingness-to-pay
2L	Second-line
3L	Third-line

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

Summary of the health condition

- Diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), with and without myelocytomatosis (MYC) and B-cell lymphoma 2 (BCL2) and/or BCL6 rearrangements, are classified by the World Health Organization (WHO) as mature large B-cell lymphomas are an aggressive form of non-Hodgkin's lymphoma (1), primarily affecting the elderly population, with a median age at diagnosis of 70 years (2)
- Up to 40% of patients relapse or become refractory to initial treatment (3)
- Relapse/refractory (R/R) DLBCL is difficult to treat, and prognosis is particularly poor for patients with R/R DLBCL after two or more lines of systemic treatment, with a median overall survival (OS) ranging from only four to 10 months (4-6)

Summary of the treatment pathway and the position of loncastuximab tesirine

- The current recommendation for first-line therapy is chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (7-10). Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) has recently been recommended by NICE for untreated DLBCL in adults if they have an International Prognostic Index (IPI) score of 2 to 5 (11).
- Treatment for patients with R/R DLBCL involves an intensive second-line chemoimmunotherapy regimen and patients who demonstrate chemosensitivity and respond to second-line chemoimmunotherapy may proceed to autologous stem cell transplant (ASCT) (12, 13)
- These is no clear standard of care (SoC) for patients with R/R DLBCL who are ineligible for intensive second-line therapy followed by ASCT. Patients who are transplant ineligible may receive polatuzumab vedotin combined with bendamustine + rituximab (Pola+BR) in the second-line setting (9, 14)
- CAR T-cell therapies are currently recommended in the third-line setting (15), which have shown high response and extended OS in patients; however, only 17.2% of DLBCL patients who received ≥3 prior lines of treatment were treated with CAR T-cell therapies and these are associated with life-threatening CRS and neurologic toxicity (16)
- Pixantrone monotherapy is currently recommended by NICE in the third- and fourth-line settings (17), and it has not been considered a comparator in prior TAs (11, 15, 18) (19). There are limited data in the real world to support the efficacy (median OS 3.4 months) (20) and clinical experts in the UK did not consider pixantrone a suitable treatment option for patients with R/R DLBCL
- Pola+BR has been shown to be more effective than chemotherapy, with experts indicating they would use Pola+BR in all patients, provided they were willing to accept the additional toxicity. A UK RWE study suggests that the majority of use is in third-line-plus patients (21). As such, the primary comparison in this analysis is with Pola+BR. A proportion of patients are still treated with chemotherapy and so a comparison with chemotherapy has also been included.

- Loncastuximab tesirine is a monotherapy which is less invasive and time consuming compared with recently approved treatments and traditional chemotherapies, potentially offering a new therapeutic option for heavily pre-treated R/R DLBCL patients
- Loncastuximab tesirine is being positioned according to the licensed indication as a treatment for adults with R/R DLBCL and HGBL, after two or more lines of systemic therapy. Although other treatments are available at third-line Pola+BR is considered the main comparator

B.1.1. Decision problem

The submission focuses on the technology's full marketing authorisation to evaluate the clinical and cost-effectiveness of loncastuximab tesirine for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy (23-25).

The decision problem addressed by the submission is outlined in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma who have had two or more systemic therapies	Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.	Aligned with marketing authorisation the submission addresses adults with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy.
Intervention	Loncastuximab tesirine	Aligned with scope	Not applicable
Comparator**(s)**	Established clinical management which may include: • Chemotherapy, such as: – DHAP (cisplatin, cytarabine, dexamethasone) – GDP (cisplatin, gemcitabine, dexamethasone) – ICE (ifosfamide, carboplatin, etoposide) – IVE (ifosfamide, epirubicin and etoposide) – R-GemOx (rituximab, gemcitabine oxaliplatin) – BR (bendamustine, rituximab) • polatuzumab vedotin with rituximab and bendamustine (if haematopoietic stem cell transplantation is not possible) • pixantrone • axicabtagene ciloleucel (subject to NICE evaluation) • tafasitamab with lenalidomide (if haematopoietic stem cell transplantation is not possible, subject to NICE evaluation)	Established clinical management which may include: • Chemotherapy, such as: – DHAP (cisplatin, cytarabine, dexamethasone) – GDP (cisplatin, gemcitabine, dexamethasone) – ICE (ifosfamide, carboplatin, etoposide) – IVE (ifosfamide, epirubicin and etoposide) – R-GemOx (rituximab + gemcitabine + oxaliplatin – BR (bendamustine and rituximab) • polatuzumab vedotin with rituximab and bendamustine (if haematopoietic stem cell transplantation is not possible)	Clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients who are not eligible for HSCT or CAR-T therapy. In the third-line setting, Pola+BR would be the main treatment option for patients. It is recognised that chemotherapy is also an option within this position in the treatment pathway, albeit less utilised due to its lower efficacy. The Company sought clinical opinion on which chemotherapy regimens were most widely used at third-line in R/R DLBCL. The clinicians stated that DHAP, ICE and IVE would not be used at this line as they are considered too toxic. The most commonly mentioned regimen was RGemOX, whereas (R)GDP, DECC, PEPC, gemcitabine monotherapy and R+lenalidomide were also considered as options at third-line-plus. While additional therapies are recommended by NICE in the third-line setting including a CAR T-cell therapy (axicabtagene ciloleucel) (26) and pixantrone monotherapy (17), they have not been included as comparators in the model. Approximately 17.2% of DLBCL patients who receive ≥3 prior lines of treatment are treated with CAR T-cell therapy due to its severe treatment burden and most patients have a rapid clinical disease course rendering them unsuitable for the treatment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			(16). Clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients that are not eligible for transplant or CAR-T therapy (22). As such, CAR-T therapies are not considered as comparators in the submission. Pixantrone has not been included as a comparator. Previous appraisals of interventions for R/R DLBCL including TA559 (15), TA567 (18), TA649 (11) and GID-TA10645 (19) removed pixantrone as a comparator either at the scoping stage or through the committee process. The respective committees were informed by clinical experts that pixantrone is rarely used in the UK; therefore, they concluded in each case that it was not a relevant comparator. The clinicians interviewed to inform this submission further confirmed that pixantrone is not used in clinical practice (22), and also noted the exclusion of pixantrone as a treatment option for patients with R/R DLBCL in the BSH guidelines (14). At the time of submission, tafasitamab with lenalidomide (if haematopoietic stem cell transplantation is not possible) is still subject to NICE evaluation with the final outcome pending).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered in the submission include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	The listed outcome measures are as per final scope issued by NICE

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		Other outcomes collected in the trial included and these data are also presented in the submission (see Section B.2.3.6).	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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.	As per the NICE reference case the cost-effectiveness of loncastuximab tesirine is expressed in terms of incremental costs per QALY, and costs have been considered from the perspective of the NHS and PSS.	In line with final scope.
Subgroups to be considered	Not applicable. No subgroups specified in scope.	Subgroup data are provided in Section B.2.7.	Not applicable; no subgroups specified in final scope
Special considerations including issues related to equity or equality	Not applicable. No special considerations specified in scope.	No equality issues related to the use of loncastuximab tesirine in patients with R/R DLBCL have been identified.	Not applicable; no special considerations noted in final scope

Source: NICE Final Scope (27)
Abbreviations: CAR-T, chimeric antigen receptor T-cell; DECC, dexamethasone, etoposide, chlorambucil, lomustine; DHAP, cisplatin, cytarabine, dexamethasone; DLBCL, diffuse large B-cell lymphoma; GDP, cisplatin, gemcitabine, dexamethasone; HGBL, high-grade B-cell lymphoma; HSCT, haematopoietic stem cell transplantation; ICE, ifosfamide, carboplatin, etoposide; IVE, ifosfamide, epirubicin and etoposide; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; Pola+BR, polatuzumab plus bendamustine plus rituximab ; PSS, personal social services; QALY, quality-adjusted life year; R, rituximab; RGemOX, rituximab with gemcitabine and oxaliplatin; TA, technology appraisal.

B.1.2. Description of the technology being evaluated

The summary of product characteristics or information for use, and the UK public assessment report, scientific discussion or drafts are provided in Appendix C.

A description of loncastuximab tesirine is provided in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	Loncastuximab tesirine (ZYNLONTA™)
Mechanism of action	Loncastuximab tesirine is an antibody-drug conjugate targeting CD19. The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is SG3199, a pyrrolobenzodiazepine dimer and alkylating agent. Upon binding to CD19, lonca is internalised followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death.
Marketing authorisation/CE mark status	Loncastuximab tesirine was granted conditional approval by the EC on December 20th 2022. The marketing authorisation was approved in the UK in February 2023 via the EC MHRA reliance route procedure.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Loncastuximab tesirine as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy.
Method of administration and dosage	Loncastuximab tesirine is an intravenous infusion given over 30 minutes on Day 1 of each cycle (every three weeks). The recommended dosage is: • 0.15 mg/kg every three weeks for two cycles • 0.075 mg/kg every three weeks for subsequent cycles Patients with a body-mass index of 35 kg/m² or more were dosed on the basis of adjusted body weight (35 kg/m² × [height in m]²): dose (mg) = dosage (µg/kg) × adjusted bodyweight/1,000
Additional tests or investigations	No additional test or investigations are required.
List price and average cost of a course of treatment	Loncastuximab tesirine list price: £15,200 per vial

	Average cost of a course of treatment (list price): £85,561.74
Patient access scheme (if applicable)	Loncastuximab tesirine PAS price: [redacted] per vial Average cost of a course of treatment (PAS price): [redacted]

Abbreviations: CD19, cluster of differentiation 19; CHMP, Committee for Medicinal Products for Human Use; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribonucleic acid; EC, European Commission; HGBL, high-grade B-cell lymphoma; IFU, information for use; IgG1, immunoglobulin G1; lonca, loncastuximab tesirine; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, Patient Access Scheme; SmPC, summary of product characteristics; UK, United Kingdom

B.1.3. Health condition and position of the technology

B.1.3.1. Disease overview

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignant neoplasms originating in the lymphocyte cells of the immune system (1). There are over 40 subtypes of NHL that originate from three distinct cell lines: B-cells (accounting for 85–90% of cases), T-cells (10–15% of cases), and natural killer cells (very rare cases) (1, 28). NHL represents a biologically and clinically heterogeneous group of lymphoproliferative malignancies which in 90% of cases are derived from B-cells with DLBCL with distinctive prognostic profiles including cell of origin: germinal centre B-cell (GCB) type or activated B-cell (ABC) type (24). DLBCL is the most common form of NHL (29). High-grade B-cell lymphoma (HGBL) is also a category of B-cell NHL (separate diagnostic entity per 2016 World Health Organization [WHO] classification) (1). This type of lymphoma can be grouped in two subtypes: (1) HGBL not otherwise specified and (2) HGBL with myelocytomatosis (MYC) and B-cell lymphoma (BCL)2 and/or BCL6 rearrangements (HGBL-double hit [DH]/triple hit [TH]) (1). The proportion of HGBL-DH/TH among tumours with DLBCL morphology is estimated to be 1% to 12% (30). DLBCL and HGBL are aggressive (fast growing), high-grade lymphomas (31).

In general, these large B-cell lymphomas are curable with first-line chemoimmunotherapy in most patients (8). However, up to 40% of patients relapse or become refractory to initial treatment, and the prognosis for patients with relapse/refractory (R/R) DLBCL remain poor (3). Despite subsequent therapy, prognosis is particularly poor for patients with R/R DLBCL after two or more lines of systemic treatment, due to the progressive nature of the disease and the cumulative adverse effects of intensive therapy, with a median overall survival (OS) ranging from only four to 10 months (4-6).

The staging system currently recommended is the Lugano-modified Ann Arbor system which classifies the stage and spread of DLBCL based on the number and location of nodes involved, in addition to extra nodal involvement (9, 32).

Table 3: Lugano modification of Ann Arbor Staging System for lymphomas

Stage	Involvement	Extranodal status
Limited		
Stage I	Single node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky[†]	Stage II as above with "bulky" disease	NA
Advanced		
Stage III	Nodes on both sides of the diaphragm with spleen involvement	NA
Stage IV	Additional noncontiguous extralymphatic involvement	NA

Source: Cheson 2014 (32).
[†]Defined as any tumour ≥10 cm in longest dimension. Whether it is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.
Abbreviations: NA, not applicable.

B.1.3.2. Epidemiology

DLBCL is the most common B-cell NHL and historically has accounted for up to 40% of B-cell NHL cases (29). In the United Kingdom (UK), the Haematological Malignancy Research Network (HMRN) estimates that there will be approximately 5,510 new cases of DLBCL each year (33). Age is an important prognostic indicator as DLBCL is more prevalent in the elderly population, with a median age at diagnosis of 70 years and a slightly higher incidence in men (2).

HGBL, not otherwise specified (NOS), and HGBL with MYC and BCL2 and/or BCL6 rearrangements (termed double-hit [2 genetic rearrangements] or triple-hit [3 genetic rearrangements]) are very aggressive B-cell NHLs (1). As these categories are newly recognised by the WHO, there are no Surveillance, Epidemiology, and End Results (SEER) data specific to their incidence. However, patients with HGBLs have a poor prognosis, with a median OS of only 0.2 to 1.5 years (34, 35). Studies show that up to 50% of patients become

refractory or relapse after treatment and the outcomes are worsened further for those who are refractory at the first-line treatment stage, with a median OS of 6.3 months and only 22% of patients survive at two years (3).

B.1.3.3. Disease burden

B.1.3.3.1. Patient burden

DLBCL is an aggressive, high-grade lymphoma that is fatal without treatment. Untreated DLBCL patients have an estimated life expectancy of less than one year. Symptom presentation in DLBCL is variable and dependent on the site of disease involvement. Patients with DLBCL typically present with a rapidly enlarging mass, most commonly nodal enlargement in the neck or abdomen, but may also present as a mass lesion anywhere in the body. The most common extranodal sites are gastrointestinal tract, head and neck, and skin and soft tissue. Bone marrow is involved in 10-15% of cases.(36) Systemic B-symptoms, such as fever, unintentional weight loss, and recurrent night sweats, are observed in approximately 30% of patients and the serum lactate dehydrogenase (LDH) is elevated in over 50% of patients. As noted in Section B.1.3.1, despite subsequent therapy, prognosis is particularly poor for patients with R/R DLBCL after two or more lines of systemic treatment with a median overall survival (OS) ranging from only four to 10 months (4-6).

There are limited data on the impact of first-line DLBCL on patients' quality of life (QoL).(37-39) However, studies have shown that the QoL burden was higher and more impaired in patients who did not respond well to first-line treatments (primary refractory), patients with an aggressive form of NHL, and in younger DLBCL patients.

Due to poor prognosis and the need for additional and intensive therapy, patients with R/R DLBCL demonstrated a lower health-related quality of life (HRQoL) compared with patients with low-grade NHL, including physical, social, emotional and functional well-being (38). In a systematic literature review (SLR) evaluating HRQoL of patients with R/R DLBCL or R/R NHL receiving standard of care therapy such as rituximab, platinum-containing chemotherapy regimens, and hematopoietic stem cell transplant (HSCT), it was also found that HRQoL of patients decreased during treatment (40).

B.1.3.3.2. Economic burden

DLBCL is the most costly lymphoma to treat in Europe compared with Hodgkin's lymphoma and follicular lymphoma. The main cost drivers were hospitalisation costs, cancer-related drugs, outpatient medication and productivity loss (41). Costs for patients with DLBCL increased as treatment advanced from early to later lines which involve multiple sites of care and treatment types (42).

Chimeric antigen receptor T-cell (CAR T-cell) therapy is a major advance in third-line treatment; however, it comes with a high treatment cost associated with its costly administration and management of adverse events including cytokine release syndrome (CRS) and neurologic events (43, 44). These result in a significant healthcare and economic burden.

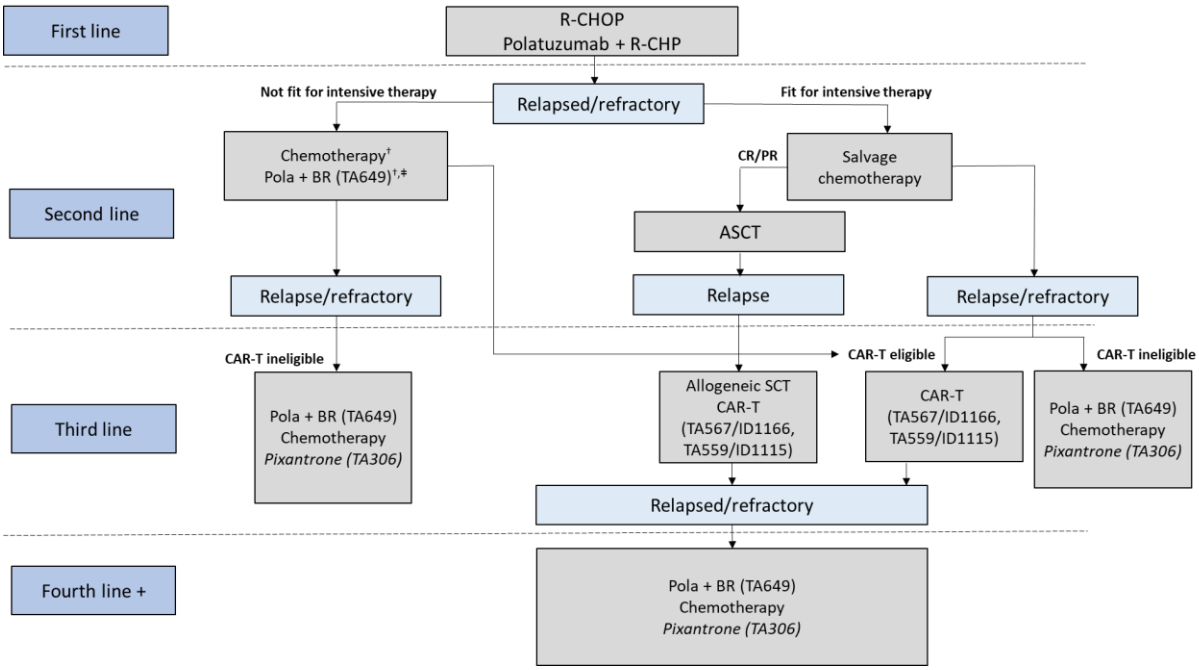
A cost modelling study in a representative population-based patient cohort in the UK estimated that the total cost associated with treating new patients with DLBCL over a one-year period was approximately £88 to £92 million (45). However, there are currently limited cost studies completed for treatments used in later lines.

B.1.3.4. Clinical pathway of care

The treatment pathway for patients with DLBCL is provided by NICE 2016 guidance NG52, the British Society for Haematology (BSH), the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) (9-11, 15, 17, 18). An overview of the current treatment pathway in the UK is summarised in Figure 1 which includes new treatments that become available after the publication of these guidelines.

As outlined in Section B.1.1, UK clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients that are not eligible for HSCT or CAR-T therapy after two or more lines of systemic therapy. In the third-line setting, clinical experts stated that polatuzumab vedotin with bendamustine and rituximab (Pola+BR) would be the main treatment option for patients as it is more effective than chemotherapy, provided they were willing to accept the additional toxicity (22). Clinicians also noted that they would look for a trial or compassionate access to bispecifics rather than chemotherapy (22). While Pola+BR can be used at second-line as well as third-line plus, data from a UK real-world evidence (RWE) study suggests that the majority of use is in third-line plus patients (21). As such, Pola+BR is considered the primary comparator of loncastuximab tesirine.

Figure 1: Current NICE recommended treatment pathways for R/R DLBCL



Source: NICENG52(10); NICE TA649(11); NICE TA567(18); NICE TA559(15); NICE TA306(17); Tilly 2015(9).
Pixantrone is rarely used in UK clinical practice.
†Clinicians indicated that some patients not previously fit for intensive therapy may respond to first-line treatment to a degree such that some may be considered eligible for CAR T-cell therapy.
‡If polatuzumab is given in first-line setting, it would not be given in the second-line setting
Abbreviations: ASCT, autologous stem cell transplant; BR, bendamustine with rituximab; CAR-T, chimeric antigen receptor T-cell; CR, complete response; Pola, polatuzumab vedotin; PR, partial response; R, rituximab; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP; rituximab, cyclophosphamide, doxorubicin and prednisone; R/R, relapsed/refractory; SCT, stem cell transplant; TA, technology appraisal.

B.1.3.4.1. First-line therapy for DLBCL

Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy has been the mainstay for the initial treatment of DLBCL after various more intensive chemotherapy combinations failed to show additional benefit (46, 47). The addition of rituximab, a chimeric monoclonal antibody targeting CD20, improved 10-year progression-free survival (PFS) and OS rates in elderly patients aged 60 to 80 years, with an overall increase of 16% vs CHOP alone. This makes chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) the current recommendation for first-line therapy (7-10).

Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) has recently been recommended by NICE for untreated DLBCL in adults if they have an International Prognostic Index (IPI) score of 2 to 5 (11).

B.1.3.4.2. Second-line therapy for DLBCL (primary refractory or initial relapse)

Approximately 30% to 40% of patients with DLBCL who receive first-line chemoimmunotherapy do not have long-term disease control. Of these patients, 10% to 15% exhibit primary refractory disease, with no response to initial treatment or relapse within three months of initial treatment (12). Another 20% to 25% of patients experience relapse following a response to initial treatment, the majority of which occurs within the first two to three years after first-line chemoimmunotherapy (8, 12).

Treatment for patients with R/R DLBCL depends on relative fitness of the patient. Patients who are not fit for intensive therapy may receive Pola+BR or chemotherapy. Patients who are fit for intensive may receive intensive salvage chemotherapy followed by autologous stem cell transplant (ASCT) (12). However, approximately half of the patients who are candidates for this intensive approach do not respond to second-line chemoimmunotherapy and therefore are unable to proceed to ASCT (48). Patients are ineligible for intensive second-line therapy followed by ASCT primarily due to comorbidities, significant organ dysfunction, poor performance status, chemotherapy-refractory disease, and advanced age (7, 49).

Patients eligible for intensive second-line therapy followed by ASCT

Intensive, non-cross-resistant chemoimmunotherapy regimens, most commonly containing rituximab and platinum, are generally administered as second-line therapy in patients with R/R DLBCL who are transplant-eligible (13). Randomised trials have reported no significant differences in response rates or survival outcomes between the most commonly used intensive second-line chemoimmunotherapy regimens (rituximab, ifosfamide, etoposide, and carboplatin [R-ICE]; rituximab, dexamethasone, high-dose cytarabine, and cisplatin [R-DHAP]; and gemcitabine, dexamethasone, and cisplatin ± rituximab [R-GDP]) (50, 51).

Patients who demonstrate chemosensitivity and respond to second-line chemoimmunotherapy may proceed to ASCT or allogeneic SCT (allo-SCT) (12, 13), receive anti-CD19 CAR T-cell therapy, or enrol in a clinical trial. Patients who have no response or progressive disease should proceed to third-line treatment.

Patients ineligible for intensive second-line therapy followed by ASCT

These is no clear standard of care (SoC) for patients with R/R DLBCL who are ineligible for intensive second-line therapy followed by ASCT; therefore, clinical management has historically

been palliative care or clinical studies with novel drugs. However, newer targeted therapies including Pola+BR and CAR T-cell therapies have recently become available. Clinical opinion received to inform this evidence submission suggested that a proportion of patients with good response may subsequently become eligible for CAR-T therapy (22).

Polatuzumab vedotin combined with bendamustine + rituximab (Pola+BR)

Patients who are transplant ineligible may receive Pola+BR in the second-line setting, which has been recommended by NICE, the ESMO and BSH (9, 14).

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate delivering monomethyl auristatin E (MMAE), a microtubule inhibitor. CD79b is a signalling component of the B-cell receptor located on normal B cells and most mature B-cell lymphomas, including >95% of DLBCL (52). However, complete response (CR) rates are low (0-15%) with polatuzumab vedotin, prompting the combination with additional agents such as bendamustine + rituximab (BR), which could also avoid the risk of overlapping neurotoxicity with platinum-based regimens (52).

A randomised Phase 1b/2 trial comparing Pola+BR against BR was carried out in patients (N=80) with transplant-ineligible R/R DLBCL or failed prior ASCT after ≥1 prior line of therapy. Pola+BR demonstrated an overall response rate (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 (95% CI: 9.0, not estimated). In the Pola+BR treatment arm, 33.3% of patients discontinued treatment due to adverse events (AE). 43.6% of patients experienced peripheral neuropathy (all grades 1 to 2) including peripheral motor neuropathy, peripheral sensory neuropathy, decreased vibratory sense, hypaesthesia and paraesthesias, resulting in treatment delay in one patient (52).

However, it is notable that this trial included a significant proportion of second-line patients (27%), in whom the expected outcomes of the treatments used in more heavily pre-treated patients remain uncertain (52). Further, there is a lack of convincing RWE and these therapies are associated with major toxicities, with 57% of patients receiving Pola+BR experiencing at least one serious adverse event (SAE) (Section B.1.3.4.4) (53).

B.1.3.4.3. Third-line and subsequent therapy for DLBCL (chemotherapy-refractory or second and subsequent relapses)

In the third-line setting, Pola+BR would be the main treatment option for patients (22). However, it is recognised that chemotherapy is also an option within this position in the treatment pathway, albeit less utilised due to its lower efficacy, therefore a comparative analysis of loncastuximab tesirine vs chemotherapies is also provided. Other alternative treatments are also accessed at third-line through clinical trials, early access schemes and compassionate use programmes but are not routinely commissioned.

Additional therapies recommended by NICE in the third-line setting include CAR T-cell therapies and pixantrone monotherapy (15). However, prognosis is particularly poor for patients with R/R DLBCL after ≥2 or more lines of systemic therapy, with a median OS ranging from only four to 7.7 months for non-cell therapies (6). CAR T-cell therapies have shown high response and extended OS in patients. However, only 17.2% of DLBCL patients who received ≥3 prior lines of treatment were treated with CAR T-cell therapy as most patients have a rapid clinical disease course rendering them unsuitable for the treatment (16).

Pixantrone monotherapy is currently recommended by NICE in the third- and fourth-line settings (17). However, there are limited data in the real world to support the efficacy (median OS 3.4 months) (20) and its use in clinical practice is restricted. In addition, clinical experts in the UK did not consider pixantrone a suitable treatment option for patients with R/R DLBCL and it was excluded as a treatment option in the BSH guidelines (14). It has been confirmed in an advisory board meeting with clinical experts in the UK that pixantrone is no longer used in clinical practice (22).

CAR T-cell therapies are gene-modified autologous cellular therapies including axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. CAR T-cell therapies have demonstrated ORRs between 52% and 83% among patients with R/R large B-cell lymphomas (54-56). However, CAR T-cell therapies are associated with life-threatening CRS and neurologic toxicity, which require intense monitoring after administration. This together with the complex manufacturing and distribution have limited this treatment option only to specialised healthcare facilities, precluding patients who are not fit for intensive therapy.

Two CAR T-cell therapies are currently available (15, 18). Axicabtagene ciloleucel (TA559) has recently been recommended by NICE for patients with R/R DLBCL or primary mediastinal large

B-cell lymphoma who have had ≥2 lines of prior systemic therapy (15). Tisagenlecleucel is also recommended for use via the Cancer Drugs Fund (CDF) if patients are healthy enough to undergo the treatment and have previously received two or more systemic therapies (18).

B.1.3.4.4. Unmet need

The treatment landscape continues to evolve as several new treatments have been approved for R/R DLBCL, all of which have demonstrated potential in improving patient outcomes. However, none are considered to have transformed life expectancy in the third-line and subsequent treatment setting, and the overall survival for this large group of R/R DLBCL patients is poor with limited treatment options.

With no established SoC for patients with R/R DLBCL after ≥2 or more lines of systemic therapy, there is a significant unmet need for new and more effective treatments that extend survival with better CRR and tolerability profiles which would improve the prospect of a long-term remission for more patients. Moreover, there is a lack of simpler dosing regimens and monotherapies that do not require a chemotherapeutic element.

CAR T-cell therapies are considered as a major advance in DLBCL with some patients achieving durable responses. However, patients with no supportive family and living on their own have difficulties accessing these intensive therapies at specific healthcare centres due to severe treatment burden and geographical location. Patients often have progressive disease and therefore require a bridging therapy while waiting for CAR-T treatments (22). In addition, eligible patients need to meet specific health requirements e.g. a reasonable count for leukapheresis and relevant cardiopulmonary status. CAR T-cell therapies also require central national approval and access to speciality services such as neurological expertise, intensive care unit (ICU)/critical care unit (CCU) during treatment. Due to these limitations, CAR T-cell therapies are only used in a small minority of patients (17.2%). For patients who received CAR T-cell therapies, only half of them achieved CRs and the rest required subsequent treatments after failure of the therapies (16). Recently approved pharmacologic therapies including Pola+BR showed good responses in R/R DLBCL patients in their trials. Nevertheless, there is a lack of convincing RWE and these therapies are associated with major toxicities, with 57% of patients receiving Pola+BR experiencing at least one serious adverse event (SAE) (53). Furthermore, these trials did not consistently include patients with at least two prior lines of therapies, who have poor prognosis and are more challenging to manage. It remains unknown if

these recently approved agents are effective in heavily pre-treated patients. Clinicians consulted for this submission noted that all these new drugs have side effects, and particularly frail and older patients need to have alternative treatment options with better toxicity profiles. Loncastuximab tesirine is available 'off the shelf' and thus is more accessible for patients including older and frailer patients. Clinical experts in the UK also emphasised the major advantage of it being effective quickly (after two to four cycles) in patients that respond and relatively well tolerated (22). As a treatment option, loncastuximab tesirine may particularly favour patients with fast progressing disease that urgently require a short time to response.

B.1.3.5. Proposed position of loncastuximab tesirine in the treatment pathway

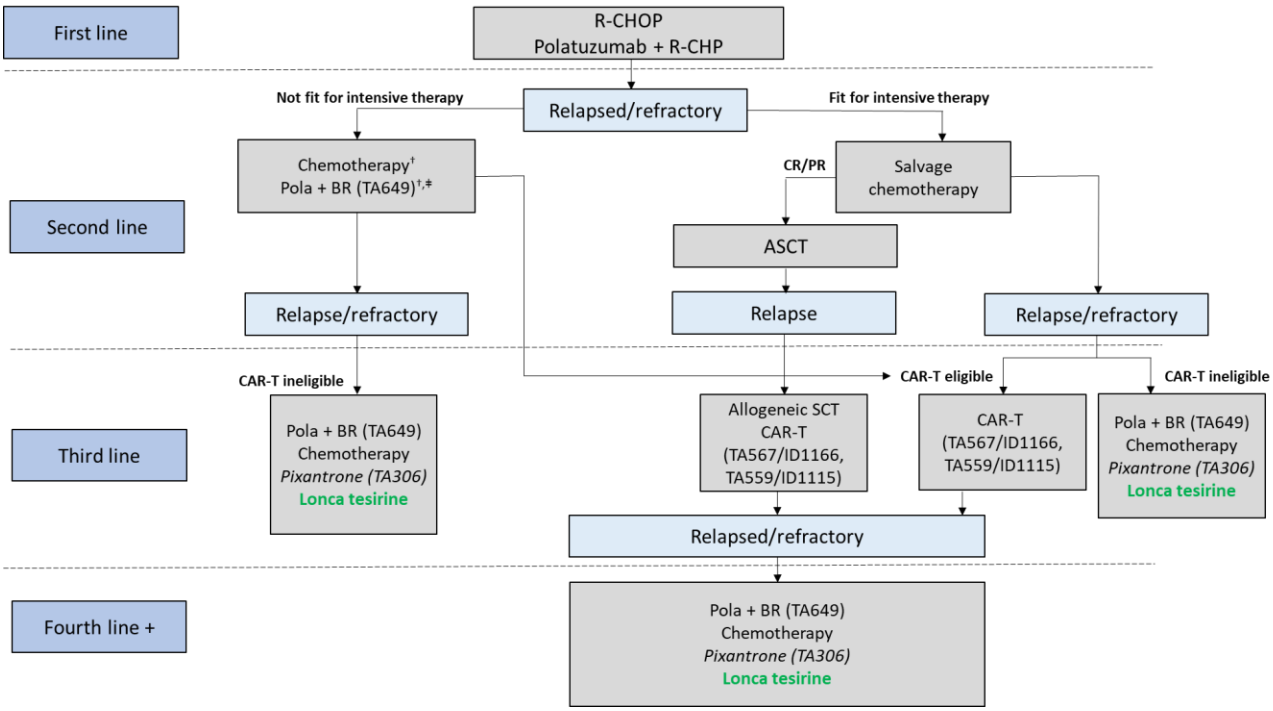
The proposed treatment pathway and position of loncastuximab tesirine is summarised in Figure 2. Although other treatments are available at third-line, Pola+BR is considered the main comparator and SoC within this submission, which is informed by clinical opinion received (22). The company recognises that chemotherapy is also an option within this position in the treatment pathway, albeit less utilised, therefore comparative analysis for loncastuximab tesirine is also provided with chemotherapies.

Loncastuximab tesirine is a highly selective CD-19-targeted antibody drug conjugate (ADC), delivering a potent and mechanistically novel and stable linker and cytotoxin which is different from other traditional therapies (22, 57). It is internalised following binding to the CD19 molecule on target tumour cells; the dimer cytotoxin is released and binds to target cell deoxyribonucleic acid (DNA) forming highly cytotoxic DNA inter-strand crosslinks and induces cell death (58).

Loncastuximab tesirine is a monotherapy which is more easily accessible with a less burdensome dosing regimen compared with traditional chemotherapies and recently approved treatments (59). Given the benefits of its mechanism of action, it is fast acting with quick response, potentially offering a new therapeutic option for heavily pre-treated R/R DLBCL patients. Data also indicate that [redacted] following the use of loncastuximab tesirine with no further treatment (60).

The evidence to support the use of loncastuximab tesirine is based on the Phase 2 trial LOTIS-2 (NCT03589469) (Section B.2). Loncastuximab tesirine is anticipated to be used as a third-line treatment for CAR-T ineligible patients with R/R DLBCL, and as a fourth-line treatment for patients relapsing after CAR-T therapy.

Figure 2: Current NICE recommended treatment pathways for R/R DLBCL including loncastuximab tesirine



Source: NICENG52(10); NICE TA649(11); NICE TA567(18); NICE TA559(15); NICE TA306(17); Tilly 2015(9).
Pixantrone is rarely used in UK clinical practice.
†Clinicians indicated that some patients not previously fit for intensive therapy may respond to firstline treatment to a degree such that some may be considered eligible for CAR T-cell therapy.
‡If polatuzumab is given in firstline setting, it would not be given in the secondline setting
Abbreviations: ASCT, autologous stem cell transplant; BR, bendamustine with rituximab; CAR-T, chimeric antigen receptor T-cell; CR, complete response; Pola, polatuzumab vedotin; PR, partial response; R, rituximab; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP; rituximab, cyclophosphamide, doxorubicin and prednisone; R/R, relapsed/refractory; SCT, stem cell transplant; TA, technology appraisal.

B.1.4. Equality considerations

No equality issues related to the use of loncastuximab tesirine in patients with R/R DLBCL have been identified.

B.2. Clinical effectiveness

- LOTIS-2 was a Phase 2 clinical trial which investigated the efficacy and safety of loncastuximab tesirine as monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
- Loncastuximab tesirine was effective and well-tolerated, producing durable responses in heavily pre-treated patients with DLBCL after two or more multiagent systemic treatments. The overall response rate (ORR) was 48% with a complete response rate (CRR) of 25%, including patients with high-risk disease [redacted] data cut)
- The median duration of response (DOR) was 13.4 months (95% CI: 6.9 to not estimable) in participants who achieved complete response (CR) or partial response (PR) ([redacted] data cut)
- The median time to first response (CR or PR) was 41.0 days (range: 35 to 247 days) and the mean time was 51.5 days (1 March 2021 data cut)
- As of the final data cut ([redacted]), the median progression-free survival (PFS) was [redacted] and the median overall survival (OS) was [redacted]
- Loncastuximab tesirine produced durable responses in patients with double hit/triple hit genetics, advanced stage disease (Stage III/IV), transformed disease, primary refractory disease, and disease which was refractory to all prior therapies; and was also effective in elderly patients and in patients who had previous CD19-directed chimeric antigen receptor T cells (CAR-T) therapy
- EQ-5D-5L and Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) questionnaires demonstrated improvement in quality of life (QoL) for patients who responded to treatment
- Overall loncastuximab tesirine was well-tolerated with low level of neuropathy and infections. Toxicities were generally reversible and manageable in most patients with dose delays/reductions
- Due to LOTIS-2 being a single-armed study, MAICs (matching-adjusted indirect comparisons) were conducted to evaluate outcomes for loncastuximab tesirine versus polatuzumab plus bendamustine and rituximab (Pola+BR) and versus chemotherapy. Limited data were available to inform these comparisons confirming clinical feedback on the lack of a consistent treatment approach at third- or later-line for these patients
- Due to LOTIS-2 being a single-armed study, MAICs (matching-adjusted indirect comparisons) were conducted to evaluate outcomes for loncastuximab tesirine versus polatuzumab plus bendamustine and rituximab (Pola+BR) and versus chemotherapy. Limited data were available to inform these comparisons confirming clinical feedback on the lack of a consistent treatment approach at third- or later-line for these patients
  - versus Pola+BR:
    - OS was similar or improved for loncastuximab tesirine, and when compared with COTA database evidence and using a bootstrap estimate for the 95% confidence interval (CI), loncastuximab tesirine offered significantly longer survival than Pola+BR

- Loncastuximab tesirine was also similar or significantly favoured over Pola+BR in terms of PFS benefit
- Loncastuximab tesirine demonstrates similar odds of an overall response (ORR) when compared with Pola+BR
- Loncastuximab tesirine demonstrates a favourable safety profile compared with Pola+BR, [redacted] patients experiencing Grade 3-4 infections and infestations; and [redacted] experiencing SAEs [redacted]
- Other safety outcomes considered included discontinuations due to AEs; fatal AEs; and Grade 3-4 AEs with frequent occurrence, for which the point estimate for the odds ratio was in favour of loncastuximab tesirine (<1.0), however the 95% CI crosses 1.0

– versus chemotherapy:

- OS was significantly improved for patients receiving loncastuximab tesirine compared with those receiving chemotherapy (HR < 1.0), across all comparisons
- Loncastuximab tesirine demonstrates improved odds of response when compared with chemotherapy
- No safety comparisons were possible to compare loncastuximab tesirine and chemotherapy

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies. In total, the SLR identified 59 records reporting on 45 unique studies. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

Of the total included studies, a total of six publications reporting two studies (LOTIS-1 and LOTIS-2 pooled analysis and LOTIS-2) were identified that evaluated loncastuximab tesirine for the treatment of patients with DLBCL who have received two or more prior therapies, a summary of identified studies is provided in Table 4.

Table 4. Identified clinical effectiveness evidence

Study name, trial number, phase	Intervention	Comparator	Author, year/source
RCTs and single arm trials			
LOTIS-1 + LOTIS-2, NCT02669017; NCT03589469, phase 1-2, pooled analysis	Loncastuximab tesirine	-	Solh 2021 (61)
LOTIS-2, NCT03589469, phase 2 single-arm trial	Loncastuximab tesirine	-	Alderuccio 2021 (62)
			Caimi 2021 (59)
			Caimi 2022 (63)
			Zinzani 2021a (64)
			Zinzani 2021c (65)

B.2.2. List of relevant clinical effectiveness evidence

The clinical evidence used to support the marketing authorisation and reimbursement of loncastuximab tesirine for the treatment of DLBCL comes from the LOTIS-2 (NCT03589469) (Table 5).

Table 5. Clinical effectiveness evidence

Study	LOTIS-2 (NCT03589469)
Study design	Phase 2, multicentre, open-label, single-arm
Population	Adult patients with relapsed or refractory DLBCL (including HGBL) who do not respond to or who have progressive disease after salvage therapies have a poor prognosis
Intervention(s)	Loncastuximab tesirine
Comparator(s)	NA
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	• ORR (primary endpoint) • DOR • CRR • PFS • OS • Frequency and severity of AEs and SAEs • HRQoL outcomes (EQ-5D-5L and FACT-Lym)

All other reported outcomes	• RFS • Concentrations and PK parameters • Immunogenicity • Relation between exposure and selected efficacy and safety endpoints • Relation between tumour and/or blood biomarkers and selected efficacy and safety endpoints

Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: AE, adverse events; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; DOR, documentation of tumour response; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HGBL, high-grade B-cell lymphoma; HRQoL, health-related quality of life; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progressive-free survival; PK, pharmacokinetic; RFS, relapse-free survival; SAE, serious adverse event.

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

The key LOTIS-2 data considered in this submission are from four different data cut-off dates:

Data cut-off:	Unpublished source	Published sources
6 April 2020 (snapshot date 15 May 2020)	CSR	Caimi 2021(59)
Data cut-off: March 2021	CSR Appendix (TFL)	Alderuccio 2021 (subgroup HGBL-DH/TH)(62); Alderuccio 2022‡ (subgroup HGBL-DH/TH)(67) Caimi 2022 (subgroup post CAR-T) (63) Zinzani 2021(64, 65)
Data cut-off: March 2022	CSR Appendix (TFL)	--
Data cut-off: September 2022	Not yet available†	Caimi 2023(60)‡ (provided as academic in confidence)

†Not available for submission, CSR available Q3/Q4 2023.‡Note that Alderuccio 2022 (subgroup HGBL-DH/TH) was not included in the CSR as it did not meet PICO criteria and Caimi 2023 (provided as academic in confidence) was outside of the date parameters of the search
Abbreviations: CAR-T, chimeric antigen receptor T cells; CSR, clinical study report; DH, double hit; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; NA, not applicable; TFL, tables, figures, listings; TH, triple hit

For data cut 6 April 2020, data were available for all outcomes. There are two subsequent data cuts (1 March 2021 and 1 March 2022), but data were not available for all outcomes as outlined in Table 6. Analysis for these data cuts was conducted as per the conditions of a conditional European Medicines Agency (EMA) marketing authorisation. Limited data from the final data cut [redacted] are available as outlined in Table 6: note data from this data cut are currently

only available as a conference abstract (provided as academic in confidence) with the clinical study report (CSR) anticipated in Q3/Q4 2023.

Table 6. Outcome data available for each data cut

Data cut-off:	6 April 2020	1 March 2021	1 March 2022	September 2022†
ORR independent review	✓	✓	✓	[redacted]
ORR investigator assessed	✓	NA	NA	[redacted]
CRR	✓	✓	✓	[redacted]
DoR	✓	✓	✓	[redacted]
RFS	✓	Not reached	NA	[redacted]
PFS	✓	✓	✓¶	[redacted]
OS	✓	✓	✓¶	[redacted]
PRO/HRQoL	✓	NA	NA	[redacted]
Safety	✓	✓	NA	[redacted]
Subgroup analyses	✓	✓‡	NA	[redacted]

†Limited data available for submission (abstract level detail), CSR available Q3/Q4 2023; ‡Subgroup data for some outcomes refer to Appendix E; ¶Individual patient data only available for these outcomes.
Abbreviations: CRR, complete response rate; DoR, duration of response; HRQoL, health-related quality of life; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PRO, patient reported outcome; RFS, relapse free survival

Data from the 6 April 2020 are presented within the tables. In addition, data from the 1 March 2021, 1 March 2022, and [redacted] data cuts are presented within the data tables where available. The indirect treatment comparison (outcomes OS, PFS and ORR) and the cost-effectiveness analysis (OS and PFS) are based on the 1 March 2022 data cut. Note that aggregate data were not available for OS and PFS outcomes for the 1 March 2022 data cut, and as such data are not included in text or tables and Kaplan-Meier curves are not presented in Section B.2.6.2.4 and Section B.2.6.2.5. Individual patient data from the 1 March 2022 data cut were used in the MAIC.

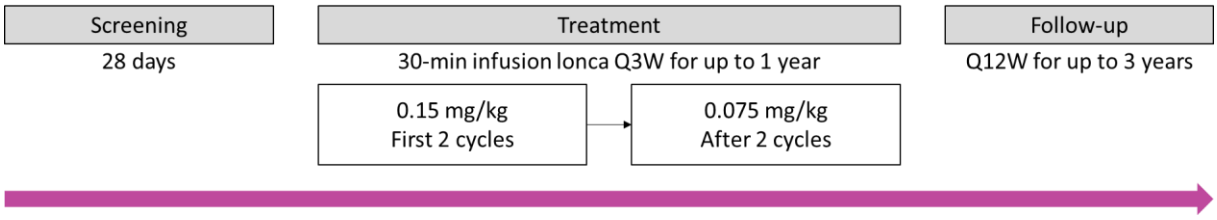
B.2.3.1. Study design

LOTIS-2 is a Phase 2, multicentre, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine used as monotherapy in patients with relapsed or refractory DLBCL. A total of 184 patients were assessed for eligibility and 145 (79%) were enrolled (59). To enhance patient safety, a two-stage design was used, with an interim analysis for futility using the data on the first 52 patients. If ≥10 patients responded (complete response [CR] + partial response [PR]), the study was to proceed to complete full enrolment. Enrolment was to continue during

the interim analysis; however, further enrolment was to be halted if futility was confirmed to minimise exposure of patients in this study. In this study, the futility analysis was performed on the first 52 patients. The duration of the study participation for each patient was defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, lost to follow-up, or death, whichever occurred first. The study included a screening period (up to 28 days), a treatment period (cycles of three weeks) up to one year, and a follow-up period (visits approximately every 12 weeks for up to three years after treatment discontinuation).

The study design of LOTIS-2 is shown in Figure 3.

Figure 3. Schematic of LOTIS-2 design



Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: Q3W every three weeks; Q12W, every 12 weeks.

B.2.3.2. Eligibility criteria

Key inclusion criteria are listed in Table 7.

Table 7. Key inclusion and exclusion criteria

Key inclusion criteria
• Male or female patient aged 18 years or older • Pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to include: DLBCL NOS; primary mediastinal large B-cell lymphoma; and high grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements† • Relapsed or refractory disease following two or more multi-agent systemic treatment regimens • Patients who received previous CD19-directed therapy were required to have a biopsy that showed CD19 protein expression after completion of the CD19-directed therapy. • Measurable disease as defined by the 2014 Lugano classification (Appendix 2 of the protocol) • Availability of formalin-fixed paraffin-embedded tumor tissue block (or minimum 10 freshly cut unstained slides if block was not available)† • ECOG performance status 0 to 2

Key inclusion criteria
• Adequate organ function as defined by screening laboratory values within the following parameters‡: • Absolute neutrophil count ≥1.0×103/μL (off growth factors at least 72 hours) • Platelet count ≥75×103/μL without transfusion in the prior 7 days • ALT, AST, and GGT ≤2.5×the ULN • Total bilirubin ≤1.5×ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3×ULN) • Blood creatinine ≤1.5×ULN or calculated creatinine clearance ≥60 mL/min by the Cockcroft and Gault equation • Negative β-HCG pregnancy test within 7 days prior to start of study drug (Cycle 1, Day 1) for women of childbearing potential • Women of childbearing potential were required to agree to use a highly effective method of contraception¶ from the time of giving informed consent until at least 16 weeks after the last dose of lonca. Men with female partners who were of childbearing potential were required to agree that they would use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient received his last dose of lonca
Key exclusion criteria
• Previous treatment with lonca • Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody • Pathologic diagnosis of Burkitt's lymphoma • Bulky disease, defined as any tumour ≥10 cm in longest dimension • Active second primary malignancy other than nonmelanoma skin cancers, nonmetastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agreed and document should not be exclusionary • Autologous SCT within 30 days prior to start of study drug (Cycle 1, Day 1) • Allogeneic SCT within 60 days prior to start of study drug (Cycle 1, Day 1) • Active graft-versus-host disease • Posttransplant lymphoproliferative disorders • Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other CNS autoimmune disease • Known seropositive and requiring antiviral therapy for human immunodeficiency virus, HBV, or hepatitis C virus§ • History of Stevens-Johnson syndrome or toxic epidermal necrolysis • Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease • Clinically significant third space fluid accumulation (ie, ascites requiring drainage or pleural effusion that either required drainage or was associated with shortness of breath) • Breastfeeding or pregnant • Significant medical comorbidities, including but not limited to uncontrolled hypertension (blood pressure ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure

Key inclusion criteria
(greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty, or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease • Major surgery, radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days prior to start of study drug (Cycle 1, Day 1), except shorter if approved by the Sponsor • Use of any other experimental medication within 14 days prior to start of study drug (Cycle 1, Day 1) • Planned live vaccine administration after starting study drug (Cycle 1, Day 1) • Failure to recover to Grade ≤1 (CTCAE version 4.0) from acute nonhematologic toxicity (Grade ≤2 neuropathy or alopecia) due to previous therapy prior to screening • Congenital long QT syndrome or a QTc using QTcF interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block) • Any other significant medical illness, abnormality, or condition that would have, in the Investigator's judgment, made the patient inappropriate for trial participation or put the patient at risk

Source: Sobi 2020 LOTIS-2 CSR (66).
[†]Any biopsy since initial diagnosis was acceptable, but if several samples were available, the most recent sample was preferred; [‡]A laboratory assessment could be repeated a maximum of two times during the screening period to confirm eligibility; [¶]Women of childbearing potential were defined as sexually mature women who had not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who had not been postmenopausal (ie, who had not menstruated at all) for at least 1 year. Highly effective forms of birth control were methods that achieved a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control included: hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this was the preferred and usual lifestyle of the patient. The double-barrier method (eg, synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, postovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only were not acceptable as highly effective methods of contraception; [§]Testing was not mandatory to be eligible.
Abbreviations: ADA, antidrug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCL2, B-cell lymphoma 2 apoptosis regulator; BCL6, B-cell lymphoma 6 transcription repressor; β-HCG, beta-human chorionic gonadotropin; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; lonca, loncastuximab tesirine; NOS, not otherwise specified; QTc, corrected QT; QTcF, Fridericia's correction; SCT, stem cell transplant; ULN, upper limit of normal; WHO, World Health Organization.

B.2.3.3. Data collection: Settings and locations

LOTIS-2 was a single-arm trial enrolled participants from 28 hospital sites in the USA ([redacted] sites), UK ([redacted] sites), Italy ([redacted] sites), and Switzerland ([redacted] site).

In total, [redacted]% (n=[redacted]) of study patients were enrolled at UK sites, [redacted]% (n=[redacted]) were enrolled at USA sites, [redacted]% (n=[redacted]) were enrolled at Italy sites, and [redacted]% (n=[redacted]) were enrolled in Switzerland.

B.2.3.4. Treatments administered

Loncastuximab tesirine was administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle every three weeks (Q3W) at a dose of 150 µg/kg for two cycles and then 75 µg/kg for subsequent cycles. Patients received premedication with dexamethasone unless otherwise contraindicated.

Patients with a body mass index (BMI) ≥35 kg/m^2 had their dose calculated based on an adjusted body weight (ABW) as follows:

- ABW in kg=35 kg/m^2×(height in metres)^2
- Dose to administer (mg)=dosage (µg/kg)×ABW/1000.

Loncastuximab tesirine solution at a concentration of 5 mg/mL was the basis for the preparation of the infusion solution. The amount of the product to be diluted depended on the dose level, weight, and the BMI of the patient. Patients with a BMI ≥35 kg/m^2 had their dose calculated based on an ABW.

Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines were not considered a protocol deviation.

B.2.3.5. Trial drugs and concomitant medications

Permitted and prohibited concomitant medications are detailed in Table 8

Table 8. Permitted and prohibited concomitant medications in LOTIS-2

Permitted	Prohibited
• All medications or procedures for the clinical care of the patient, including management of AEs, were permitted during the study • Hematopoietic growth factors were to be permitted as per American Society of Clinical Oncology guidelines (Smith 2006)	• Other anticancer therapy with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer • Other investigational agents • Live vaccines

Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: AE, adverse event.

B.2.3.6. Outcomes

B.2.3.6.1. Primary endpoints

- ORR according to the 2014 Lugano classification (32) as determined by central review in all-treated patients; ORR was defined as the proportion of patients with a best overall response (BOR) of CR or PR.

B.2.3.6.2. Secondary endpoints

- Duration of response (DOR) defined as the time from first documentation of tumour response to disease progression or death.
- CR rate (CRR) defined as the percentage of treated patients with a BOR of CR.
- Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death.
- PFS defined as the time between start of treatment and the first documentation of recurrence, progression, or death.
- OS defined as the time between the start of treatment and death from any cause.
- Frequency and severity of AEs and SAEs.
- Changes from baseline of safety laboratory variables, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs).

B.2.3.6.3. Other secondary endpoints

- Concentrations and pharmacokinetic (PK) parameters of loncastuximab tesirine total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated warhead SG3199 (these data will be analysed and reported separately).
- Antidrug antibody (ADA) titers and, if applicable, neutralising activity to loncastuximab tesirine after treatment with loncastuximab tesirine (these data will be analysed and reported separately).
- Change from baseline in HRQoL as measured by EuroQol 5 Dimensions-5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym).

EuroIQol-5 Dimensions-5 Levels

The EQ-5D-5L is an international, standardized, generic instrument for describing and QoL. The EQ-5D-5L consists of two parts:

The Descriptive System: QoL is classified according to 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises five levels of perceived problems (eg, none, slight, moderate, severe, and extreme).

The Visual Analog Scale (VAS): patients were asked to indicate their health state today on a VAS with the endpoints labelled “the best health you can imagine” (score 100), and “the worst health you can imagine” (score 0). Patients were asked to mark an “X” on the VAS to indicate their own health and to then report the score in the text box.

Functional Assessment of Cancer Therapy-Lymphoma

The FACT-Lym is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire (Hlubocky, 2013). It consists of 15 specific items that are used together with the core 27-item questionnaire; the Functional Assessment of Cancer Therapy-General (FACT-G). The patient was asked to respond to each item with a score of 0 to 4, where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a lot, and 4=very much.

The FACT-Lym questionnaire includes subscales for physical well-being (PWB) (7 items), social/family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), functional well-being (FWB, 7 items), and additional concerns (Lymphoma Subscale, LymS, 15 items).

B.2.3.6.4. Exploratory endpoints

- Relation between exposure (loncastuximab tesirine dose, PK metrics) and selected efficacy and safety endpoints (these data will be analysed and reported separately).
- Relation between tumour and/or blood biomarkers and selected efficacy and safety endpoints (these data will be analysed and reported separately).

B.2.3.7. Baseline characteristics

Overall, 145 participants were enrolled in the total study population and received a mean of 4.3 cycles of loncastuximab tesirine (range 1, 15) as of 6 April 2020. The median participant age was 66 years (Interquartile range [IQR] 56, 71). Three types of DLBCL from the 2016 WHO

classification of lymphoid neoplasms were recruited: DLBCL NOS, HGBL, and primary mediastinal B-cell lymphoma (PMBCL) (1). Eighty-eight percent (n=127) of participants had DLBCL NOS, 8% (n=11) had HGBL and 5% (n=7) had PMBCL. Of the 127 participants with DLBCL NOS, 29 (20%) had transformed from follicular lymphoma (FL), and 15 participants (10%) had double-hit or triple-hit disease (investigator reported). There were 112 participants (77%) with advanced (Stage III/IV) disease. At baseline, 24 participants (16%) had received any prior stem cell transplantation (SCT) and 13 participants (9%) had prior CART-cell therapy. A summary of the baseline characteristics of study participants in LOTIS-2 is provided in Table 9.

Table 9. Baseline demographic and clinical characteristics (all-treated population)

	All-treated population (N=145)
Sex	
Female	60 (41%)
Male	85 (59%)
Age, years	
Median (IQR)	66 (56–71)
<65	65 (45%)
≥65 to <75	59 (41%)
≥75	21 (14%)
Histology	
DLBCL, not otherwise specified	127 (88%)
HGBL	11 (8%)
PMBCL	7 (5%)
Cell of Origin, GCB or ABC DLBCL†	
GCB	48 (33%)
ABC	23 (16%)
Unknown	74 (51%)
Double-hit or triple-hit DLBCL‡	15 (10%)
Double-expressor or triple-expressor DLBCL	20 (14%)
Bulky disease	
Yes	8 (6%)
No	137 (94%)
Transformed DLBCL	29 (20%)
Disease stage¶	
I–II	33 (23%)
III–IV	112 (77%)

	All-treated population (N=145)
Previous systemic therapies[§]	
Median (IQR)	3.0 (2.0–4.0)
Two lines	63 (43%)
Three lines	35 (24%)
More than three lines	47 (32%)
Response to first-line systemic therapy	
Relapse	99 (68%)
Refractory[††]	29 (20%)
Other[‡‡]	17 (12%)
Response to most recent line of systemic therapy[¶¶]	
Relapse	43 (30%)
Refractory[††]	84 (58%)
Other[‡‡]	18 (12%)
Refractory to all previous therapies[††]	
Yes	25 (17%)
No	115 (79%)
Other[‡‡]	5 (3%)
Relapse within 3 months of first-line therapy[§§]	
Yes	35 (24%)
No	110 (76%)
Relapse within 6 months of first-line therapy[§§]	
Yes	57 (39%)
No	88 (61%)
Previous HSCT	
Allogeneic	2 (1%)
Autologous	21 (14%)
Both	1 (1%)
Previous CAR T-cell therapy	
Yes	13 (9%)
No	132 (91%)

Source: Caimi 2021 (59).
Data are n (%) unless otherwise stated. Percentages might not total 100% due to rounding.
[†]ABC and GCB were investigator-reported without independent testing; [‡]Some patients had a diagnosis of double-hit or triple-hit lymphoma based on institutional pathology before the WHO classification of HGBL with *MYC* and *BCL2* or *BCL6* rearrangements, or with *MYC* and *BCL2* and *BCL6* rearrangements; [¶]Disease stage at study entry; [§]Previous HSCT is included; for patients who received an autologous transplant, the mobilisation regimen was considered a line of therapy if it was chemotherapy-based and distinct from the other previous lines of treatment; [††]Refractory disease defined as no response to therapy; [‡‡]Other defined as unknown, not evaluable, or missing; [¶¶]If HSCT was the most recent line of systemic therapy, response to therapy was defined as response to the therapy immediately preceding HSCT; [§§]Only includes patients with complete response or partial response, and whose disease progression was 1–

182 days after the end of first-line systemic therapy with missing imputation rule; when the progression date was missing, start date of the next line of treatment was used to input the disease progression data.
Abbreviations: ABC, activated B-cell; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell; HGBL, high-grade B-cell lymphoma with *MYC* and *BCL2* or *BCL6* rearrangements, or with *MYC* and *BCL2* and *BCL6* rearrangements; HSCT, haematopoietic stem cell transplantation; IQR, interquartile range; PMBCL, primary mediastinal B-cell lymphoma.

B.2.3.8. Expert elicitation or expert opinion

An exercise was conducted to elicit opinion from health economists and clinicians, comprising of a series of interviews (with health economists and clinicians) and a survey of five clinicians. Three of the five clinicians had personal experience in prescribing loncastuximab tesirine.

The first stage included the interviewing of two health economists with the following objectives:

- Raising key questions to clinicians, to establish the decision problem/appropriate methodologies for data analysis and economic modelling.
- Receiving opinions on the appropriateness of the proposed data/evidence use, analysis methodology, and assumptions.

The second stage included the surveying and interviewing of five clinicians with experience in the treatment of lymphoma. Initially, four clinicians working in large cancer centres (Oxford, Newcastle, London) were surveyed, one centre being a dedicated CAR-T referral centre. The objectives of the survey and interviews were to establish the following:

- Patient profiles and treatment heterogeneity
- The treatment pathway and relevant comparators for loncastuximab tesirine in the UK
- The DLBCL clinical evidence base, especially related to loncastuximab tesirine, and the most appropriate clinical and modelling assumptions.

A final interview was conducted with a clinician with experience in loncastuximab tesirine. The interview included presentation of the prior clinical opinion collected, with the additional objective of characterising/explaining the variation in opinion.

Clinicians were followed up to confirm the accuracy of the report and with some final questions.

A summary of the output of the exercise in presented in the clinician interview summary report (22).

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

A summary of statistical analysis methods for LOTIS-2 is provided in Table 12.

Details of the numbers of participants eligible to enter the study and participant flow are provided in Appendix D.

B.2.4.1. Analysis populations

The sets of analysis populations defined in the trial are presented in Table 10.

Table 10: Definition of analysis populations

Analysis populations	Definition	Reported in submission
All-treated population	All patients who received at least one dose of lonca. This population was used in the primary analyses of efficacy and safety	Yes
Per-protocol population	All patients in the all-treated population who met the inclusion/exclusion criteria, did not take a prohibited concomitant treatment, and did not have other protocol deviation that could have had a major impact on efficacy results	Reported in Appendix M
SCT population	All patients who responded to lonca and underwent SCT (either autologous or allogeneic) after permanent discontinuation of lonca treatment without any intervening anticancer therapy. (This population was introduced in the SAP and was not specified in the protocol)	No
PK population	All patients who received at least one dose of lonca with evaluable and sufficient concentration-time data to permit reliable estimation of lonca exposure. (This population was used for PK analyses which will be described in a separate PK/pharmacodynamic analysis plan and report)	No
Immunogenicity analysis population	All patients who received at least one dose of lonca with evaluable pre-dose immunogenicity data to permit reliable evaluation of lonca ADA effect. (This population was used for ADA analyses which will be described in a separate PK/pharmacodynamic analysis plan and report)	No
Pharmacodynamics population	Patients for which archival tumour tissue or pretreatment biopsies were available who received at least one dose of lonca and who had at least one value for a pharmacodynamic/biomarker assessment. (This population was used for pharmacodynamic analyses which will be described in a separate K/pharmacodynamic analysis plan and report)	No
PRO analysis population	All patients in the all-treated population with baseline score (at least one instrument) and at least one postbaseline score	No

Analysis populations	Definition	Reported in submission
	(in at least one instrument). (This population was introduced in the SAP and was not specified in the protocol)	

Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: ADA, anti-drug antibody; lonca, loncastuximab tesirine; PK, pharmacokinetic; PRO, patient reported outcomes; SAP, Statistical Analysis Plan; SCT, stem cell transplantation.

Overall, 145 patients were treated and included in the all-treated population and 121 patients (83.4%) were included in the per-protocol population (Table 11).

Table 11: Patient analysis sets (all-enrolled patients)

	All-treated population 150 (N=145)
Patients enrolled [n]	145
Patients treated, all-treated population [n(%)†]	145 (100)
Patients enrolled but not treated [n(%)†]	0
Per-protocol population	121 (83.4)
Patient-reported outcomes population [n(%)†]	130 (89.7)
Stem cell transplant population [n(%)†]	10 (6.9)

Source: Sobi 2020 LOTIS-2 CSR (66).
†Percent is based on all-enrolled patients.

B.2.4.2. Sample size

Patients with relapsed or refractory DLBCL generally have a poor prognosis, with response to second-line salvage therapy ranging from 14% to 26% and with a median survival of 6.1 months (3, 68). A treatment with a response rate of >20% would be considered clinically meaningful in this population.

The sample size was determined based on the assumption that an ORR of 20% would be clinically meaningful in this patient population. The primary hypothesis was that the ORR based on central review for patients treated with loncastuximab tesirine was significantly greater than 20% (ie, null hypothesis: $p \leq 0.2$ versus alternative hypothesis: $p > 0.2$). This hypothesis was tested at type I error of 0.05 (2-sided).

Using nQuery exact test for single proportion, a sample size of 140 patients had >99% power to achieve a 1-sided significance level of 0.025 (2-sided significance level of 0.05). This sample size provided adequate precision for observed ORR in the expected range and a robust population for safety evaluation.

B.2.4.3. General methodology

All available data were used in the analyses, and important data were included in data listings, sorted by patient, and by visit within patient. Missing data were not imputed, except via censoring in survival analyses and as otherwise specified. Unless otherwise noted, categorical data were presented using counts and percentages, with the number of patients in the analysis population as the denominator for percentages. Percentages were rounded to one decimal place, except 100% which was displayed without any decimal places, and percentages were not displayed for zero counts. Continuous data, unless otherwise noted, were summarized using the number of observations (n), mean, standard deviation (sd), median, minimum, and maximum. Minima and maxima were rounded to the precision of the original value, and means, medians, and 95% confidence intervals (CIs) if presented were rounded to one decimal place greater than the precision of the original value. The standard deviation was rounded to two decimal places greater than the precision of the original value, up to a maximum of three decimal places.

B.2.4.4. Interim analyses

An interim analysis was performed when the first 52 patients dosed had two tumour assessments (approximately 12 weeks after start of loncastuximab tesirine). The ORR and the corresponding 95% CI were reported. Enrolment continued during the interim analysis. If <10 patients responded the study enrolment was to be halted. Other analyses such as DOR, PFS, CR rate, RFS, OS, and safety analyses may have been performed if necessary.

B.2.4.5. Subsequent analyses

For primary and key secondary endpoints analyses, a database snapshot was taken when all patients who achieved a response had a minimum of six months follow-up after initial documented response. All efficacy and safety endpoints were analysed and reported.

The exact binomial test was used in the subsequent analyses for the primary endpoint because of the practical consideration that accrual could not be limited to exactly 140 patients and because patients included in the interim analysis as non-responding may have been included in the subsequent analysis as responding if they experienced a late response.

Two further data cuts are presented in the submission (1 March 2021 and 1 March 2022). The final CSR will be based on the final data cut from September 2022 and will be available in

Q3/Q4 2023 (limited data available for this final data cut in a conference abstract are provided as academic in confidence). Table 6 outlines the data available for each of the data cuts.

B.2.4.6. Efficacy analyses

The efficacy analyses used the independent reviewer's evaluation according to the 2014 Lugano Classification criteria before the start of subsequent anticancer therapy or procedure.

Lesion assessment data (target lesions, non-target lesions, and new lesions) and tumour response were listed. A separate listing contains derived data for DOR, RFS, PFS, and OS. Primary analyses of efficacy were performed in the all-treated population.

Table 12. Summary of statistical analyses

Outcome	Statistical analysis	Data management, patient withdrawals	Analysis set
ORR (primary efficacy analysis)	The ORR and the corresponding 95% two-sided exact CI were presented. Subgroup analysis was provided for disease subtype, disease stage, double/triple hit (yes/no), bulky disease (yes/no), germinal centre B-cell/activated B-cell, transformed (yes/no), age group, sex, country, response to the first line and/or most recent line of prior systematic therapy (relapse: CR+PR versus refractory: SD+PD versus other: NE + missing), and other relevant variables. Percentage change from baseline in SPD for target lesions was presented for available data in the all- treated population. These data were also displayed as a waterfall plot, with vertical bars representing the sorted values of best percent reduction for each patient.	ORR was defined as the proportion of patients who achieved either CR or PR as BOR as assessed by central review using the Lugano classification criteria before the start of subsequent anticancer therapy or procedure. For the primary ORR analysis in the all-treated population, patients with a CR or PR were counted as successes and all other patients (including those with missing response information) were counted as failures. The order of overall response category was: CR, PR, SD, NE, PD (including disease recurrence/relapse). The overall response category was derived based on response assessment performed on or before the start of subsequent anticancer therapy/procedure. Patients without documented subsequent anticancer therapy and/or with missing start date of anticancer therapy were considered as not having received subsequent anticancer therapy. A BOR of SD could only be made after the patient was on study for a minimum of 35 days after the first dose of lonca. Any tumour assessment indicating SD before this time period was considered as NE for BOR if no assessment after this time period was available.	All-treated population

Outcome	Statistical analysis	Data management, patient withdrawals	Analysis set
DOR	DOR was estimated and displayed for the all-treated population using Kaplan-Meier (KM) methods. A KM plot was presented. A sensitivity analysis of DOR was conducted in which the DOR for patients who underwent SCT were not censored at SCT. A sensitivity analysis of DOR per Investigator assessments was also conducted.	DOR was defined for patients with CR or PR only as the interval between the date of initial documentation of a response and the date of the first documented evidence of PD based on independent radiographic assessment or death, whichever occurred first. Clinical progression at EOT/EOS without radiographic assessment could have been considered as an event in a sensitivity analysis.	All-treated population
CRR	CRR was defined as the proportion of patients with a BOR of CR. The percentage of CRR with its 95% CI was presented.		
RFS	RFS was estimated and displayed for the all-treated population using KM methods. A KM plot was presented. A sensitivity analysis of RFS was conducted in which RFS for patients who underwent SCT were not censored at SCT. A sensitivity analysis of RFS per Investigator assessments was also conducted.	RFS was defined among CR patients as the time from the date of first CR until the date of the first disease relapse based on independent radiographic assessment, or death, whichever occurred first. The date of PD was defined as the earliest date of PD based on central review. Clinical progression at EOT/EOS without radiographic assessment could be considered as an event in a sensitivity analysis.	All-treated population
PFS	PFS was estimated and displayed for the all-treated population using KM methods. A KM plot was presented. A sensitivity analysis of PFS was conducted in which the PFS for patients who underwent SCT was not censored at SCT. A sensitivity analysis of PFS per Investigator assessments was also conducted.	PFS was defined as the interval between the date of first dose of lonca and the date of the first PD based on independent radiographic assessment, or death, whichever occurred first. The date of PD was defined as the earliest date of PD based on central review. For patients who had the event after the start of subsequent anticancer therapy/procedure, or were progression-free and alive at the time of clinical cut-off, or had unknown status, censoring was performed using the date of the last valid disease assessment on or before the start of subsequent anticancer therapy/procedure or clinical cut-off time. When a subsequent anticancer therapy was used and PD (based on radiographic or clinical progression at EOT/EOS) was observed within 6 days, the	All-treated population

Outcome	Statistical analysis	Data management, patient withdrawals	Analysis set
		events were to have occurred as the same visit (within the protocol specified ±6 days window) and the patient was counted as having an event.	
OS	OS was estimated and displayed for the all-treated population using KM methods. A KM plot was presented.	OS was defined as the interval between the date of the first dose and the date of death from any cause. Patients who were known to be alive as of their last known status were censored at their date of last contact. Patients who were lost to follow-up were censored at the date the patient was last known to have been alive. The last confirmed alive date was the latest of the following: study visit date, telephone contact date, EOS last confirmed alive date, follow-up systemic (anticancer) therapy end date or start date (if ongoing or end date is missing), local or central radiologist scan date, or other date in the clinical database.	All-treated population

Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; CRR, complete response rate; DOR, duration of response; EOS, end of study; EOT, end of treatment; KM, Kaplan-Meier; lonca, loncastuximab tesirine; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progressive-free survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; SPD, the sum of product of the perpendicular diameters; SCT, stem cell transplant.

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

A complete quality assessment for each study is provided in Appendix D.

B.2.6. Clinical effectiveness results of the relevant studies

The results presented are from four different data cut-off dates, data sources are summarised in Table 5

B.2.6.1. Primary endpoint

B.2.6.1.1. Overall response rate

Overall response rate by independent reviewer

In the all-treated population, the ORR was 48.3% (70/145 patients; 95% CI: 39.9% to 56.7%). BORs included 35 patients (24.1%) with CR and 35 patients (24.1%) with PR. There were 22 patients (15.2%) with a BOR of stable disease (SD) (Table 13) (6 April 2020 data cut).

In both the 1 March 2021 and the 1 March 2022 data cut, in the all-treated population, the ORR was 48.3% (70/145 patients; 95% CI: 39.9% to 56.7%) (Table 13). BORs included 36 patients (24.8%) with CR and 34 patients (23.4%) with PR. There were 22 patients (15.2%) with a BOR of stable disease (SD).

As of the final data cut off [redacted]; median follow-up: [redacted], the ORR was [redacted]% ([redacted] of 145 participants) (Table 13) (60).

The median time to first response (CR or PR) by independent reviewers in the all-treated population was [redacted]days (range [redacted] to [redacted] days) (6 April 2020 and 1 March 2021 data cuts).

Overall response rate by investigator assessment (sensitivity analysis)

In the all-treated population, the ORR using the investigator assessment was 49.7% (72/145 patients; 95% CI: 41.3% to 58.1%). Best overall responses included 36 patients (24.8%) with CR and 36 patients (24.8%) with PR. There were 20 patients (13.8%) with a BOR of SD (6 April 2020 data cut) (Table 13).

No data were reported for ORR by investigator assessment in the later data cuts.

Table 13: Overall response rate (all-treated population)[†]

		Best overall response							
	Data cut date	Complete response	Partial response	Stable disease	Not evaluable	Progressive disease	ORR (CR + PR)	95% CI for ORR	95% CI for CR
Independent review committee									
All-treated population (N=145)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-treated population (N=145)	**01-Mar-22**	36 (24.8)	34 (23.4)	22 (15.2)	23 (15.9)	30 (20.7)	70 (48.3)	(39.9, 56.7)	(18.0, 32.7)
All-treated population (N=145)	**01-Mar-21**	36 (24.8)	34 (23.4)	22 (15.2)	23 (15.9)	30 (20.7)	70 (48.3)	(39.9, 56.7)	NR
All-treated population (N=145)	**06-Apr-20**	35 (24.1)	35 (24.1)	22 (15.2)	23 (15.9)	30 (20.7)	70 (48.3)	(39.9, 56.7)	(17.4, 31.9)
Investigator assessment									
All-treated population (N=145)	**06-Apr-20**	36 (24.8)	36 (24.8)	20 (13.8)	4 (2.8)	49 (33.8)	72 (49.7)	(41.3, 58.1)	(18.0, 32.7)

Source: Sobi 2020 LOTIS-2 CSR (66); Sobi Clinical overview 2021 (69); Sobi CSR Appendix (TLF) 2022 (70); Caimi 2023 (60).
[†]Best overall response by independent reviewer. Not evaluable included patients without any scan to the independent reviewer (even clinical progressive disease) or patients whose scan was determined to be not evaluable by the independent reviewer.
Abbreviations: CI, confidence interval; CR, complete response; NR, not reported; ORR, overall response rate; PR, partial response.

B.2.6.2. Key secondary endpoints

B.2.6.2.1. Complete response rate

The efficacy of single agent loncastuximab tesirine measured by CRR and assessed by independent reviewer is presented in Table 13 in the all-treated population.

In the all-treated population, there were:

- 35 participants with CR by independent reviewer. The CRR was 24.1% (95% CI: 17.4, 31.9) (6 April 2020 data cut);
- 36 participants with CR by independent reviewer. The CRR was 24.8% (95% CI: NR) (1 March 2021 data cut);
- 36 participants with CR by independent reviewer. The CRR was 24.8% (95% CI: 18.0, 32.7) (1 March 2022 data cut).

As of the final data cut off [redacted], [redacted] participants achieved CR; [redacted] of the [redacted] participants who achieved CR were [redacted]. Median numbers of doses were [redacted] and [redacted] for participants with CR who were[redacted]. All [redacted] participants with CR who were [redacted] were censored at study end (60).

B.2.6.2.2. Duration of response

Duration of response (DOR) was defined for patients with CR or PR as the interval between the date of initial documentation of a response and the date of the first documented evidence of PD based on independent radiographic assessment or death, whichever occurred first. If PD or death was not observed, the DOR was censored at the last valid disease assessment.

- 6 April 2020 data cut: Of the 70 participants who achieved CR or PR by independent reviewer, the median DOR was 10.25 months (95% CI: 6.87 to not estimable). The probability of maintaining response was 68.1% at six months, 63.8% at nine months, and 38.3% at 12 months (Table 14). Figure 4 presents DOR assessed by independent reviewer as a Kaplan-Meier (KM) curve in the all-treated population (6 April 2020 data cut).
- 1 March 2021 data cut: Of the 70 participants who achieved CR or PR by independent reviewers, the median DOR was 13.37 months (95% CI: 6.87 to not estimable). The probability of maintaining response was 67.3% at six months, 64.4% at nine months, and

54.7% at 12 months (Table 14). Figure 5 presents DOR assessed by independent reviewer as a KM curve in the all-treated population.

- 1 March 2022 data cut: Of the 70 participants who achieved CR or PR by independent reviewers, the median DOR was 13.37 months (95% CI: 6.87 to not estimable. Figure 6 presents DOR assessed by independent reviewer as a KM curve in the all-treated population.

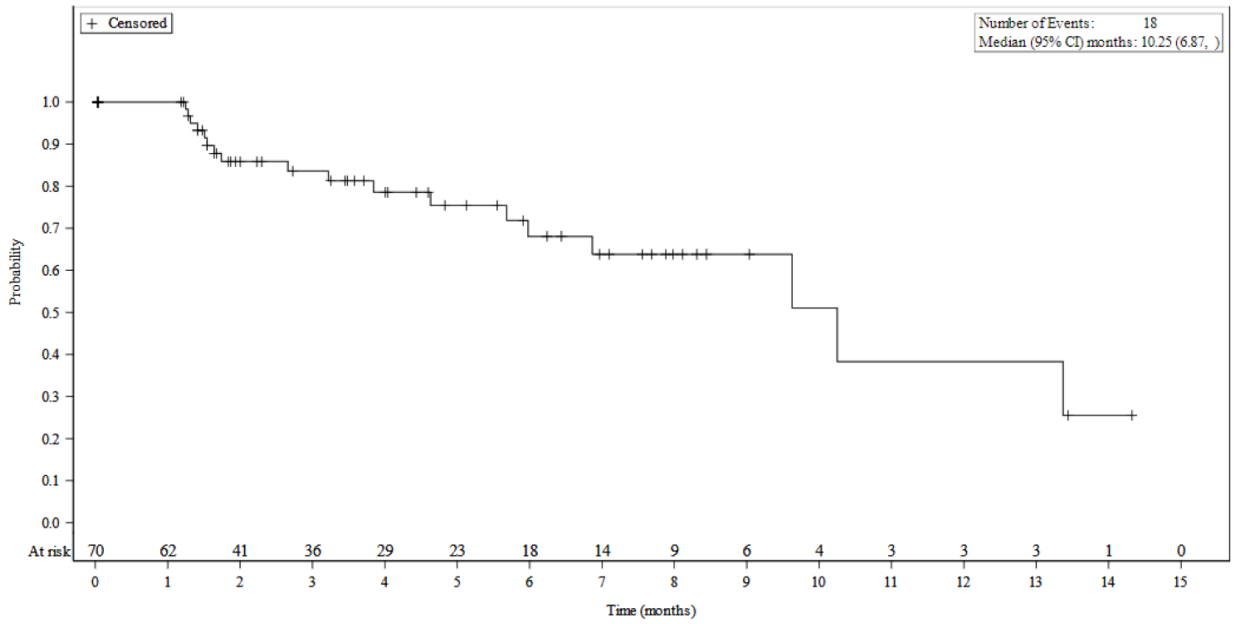
As of final data cut off [redacted], median DOR was [redacted] months (95% CI: [redacted]).

Table 14: Summary of DOR† by independent reviewer (all-treated population)

	All-treated population (N=145)			
Data cut	**6 Apr 2020**	**1 Mar 2021**	**1 Mar 2022**	[redacted]
Total number of responders	70	70	70	[redacted]
Number of events	18	23	23	[redacted]
Number of censored	52	47	47	[redacted]
25 percentile of DOR (95% CI) (month)	5.68 (1.74, 9.63)	5.26 (1.64, 9.26)	NR	[redacted]
50 percentile of DOR (95% CI) (month)	10.25 (6.87, -)	13.37 (6.87, -)	13.37 (6.87, -)	[redacted]
75 percentile of DOR (95% CI) (month)	not reached	Not reached	NR	[redacted]
Probability to maintain the response for 6 months (95% CI)	68.1 (50.6, 80.5)	67.3 (51.6, 78.9)	NR	[redacted]
Probability to maintain the response for 9 months (95% CI)	63.8 (45.4, 77.4)	64.4 (48.3, 76.6)	NR	[redacted]
Probability to maintain the response for 12 months (95% CI)	38.3 (12.0, 64.7)	54.7 (37.9, 68.8)	NR	[redacted]

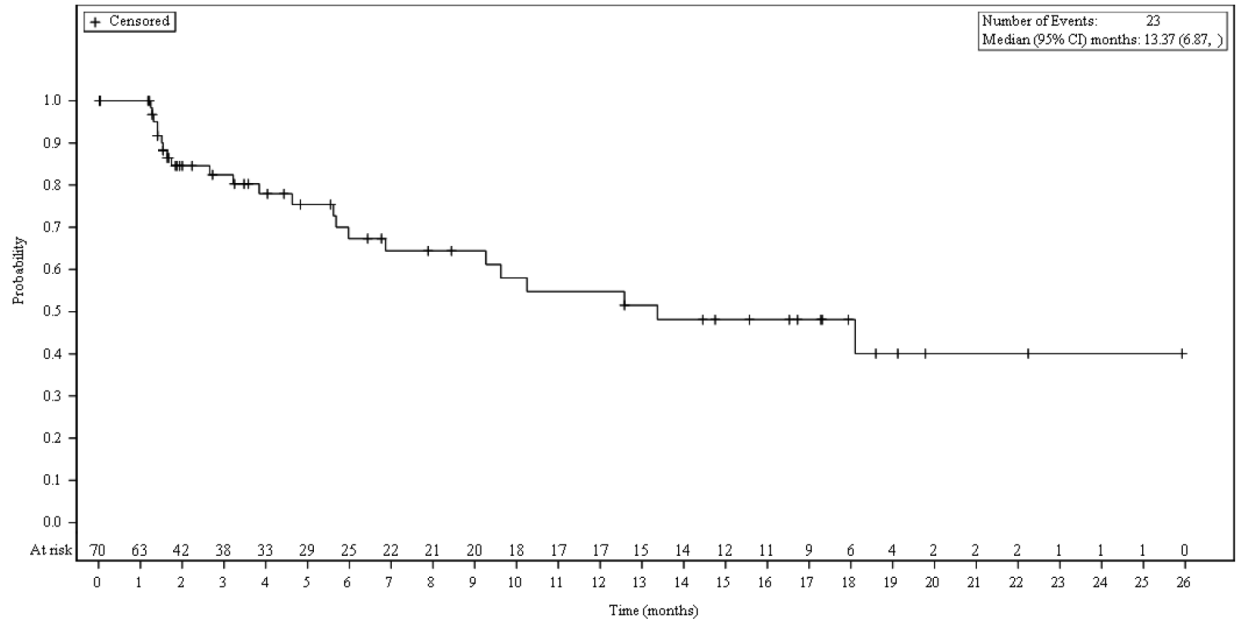
Source: Sobi 2020 LOTIS-2 CSR (66); Sobi Clinical overview 2021 (69); Caimi 2023 (60).
†Point estimates not reported for 1April 2022 data cut, data only reported in K-M curve
Source: Sobi 'Summary of clinical efficacy' 2021, Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: CI, confidence interval; DOR, duration of response, NR, not reported.

Figure 4: Kaplan-Meier plot of DOR by independent reviewer (all-treated population)† (6 April 2020 data cut)



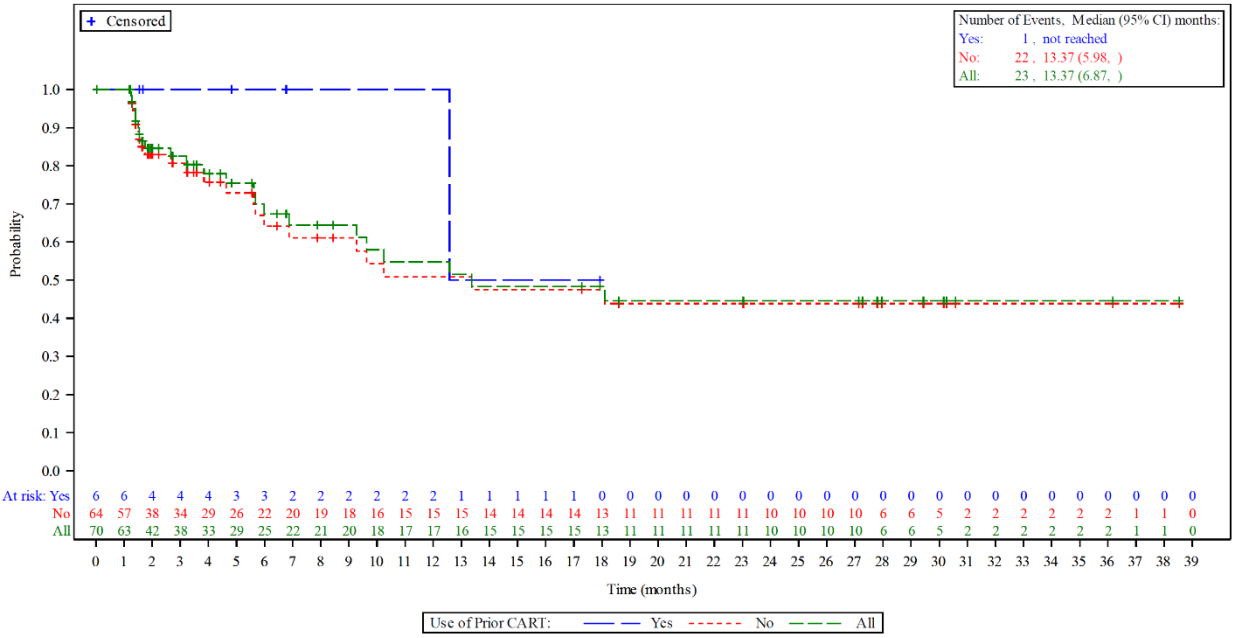
Source: Sobi 2020 LOTIS-2 CSR (66).
†Based on independent reviewer, including death as event.
Abbreviations: DOR, duration of response.

Figure 5: Kaplan-Meier plot of DOR by independent reviewer (all-treated population)† (1 March 2021 data cut)



Source: Sobi Clinical overview 2021 (69).
†Based on independent reviewer, including death as event.
Abbreviations: DOR, duration of response.

Figure 6: Kaplan-Meier plot of DOR by independent reviewer (all-treated population)† (1 March 2022 data cut)



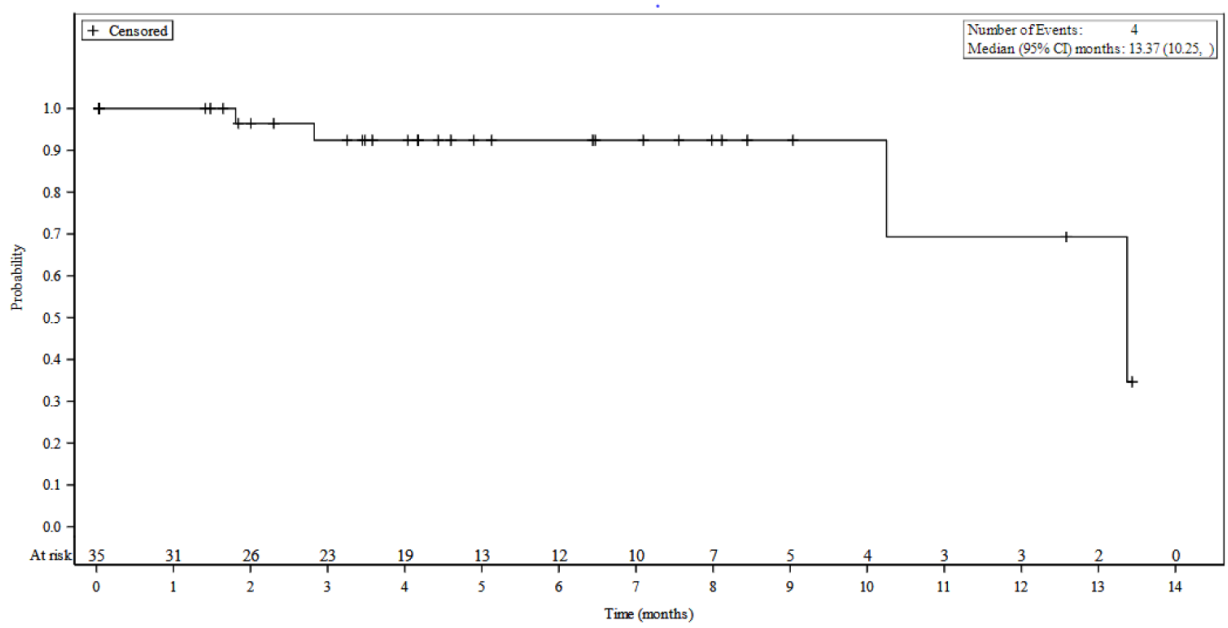
Source: Sobi CSR Appendix (TLF) 2022 (70).
†Based on independent reviewer, including death as event.
Abbreviations: DOR, duration of response.

B.2.6.2.3. Relapse-free survival

Figure 7 presents the clinical activity of loncastuximab tesirine measured by RFS by independent reviewer and presented as a KM curve in the all-treated population who achieved CR (6 April 2020 data cut).

RFS was defined among participants with CR as the time from the date of first CR until the date of the first disease relapse based on independent radiographic assessment, or death, whichever occurred first. Of the 35 participants who achieved CR, the median RFS was 13.37 months (95% CI: 10.25, to not estimable) (6 April 2020 data cut).

Figure 7: Kaplan-Meier plot of RFS by independent reviewer (all-treated population)† (6 April 2020)

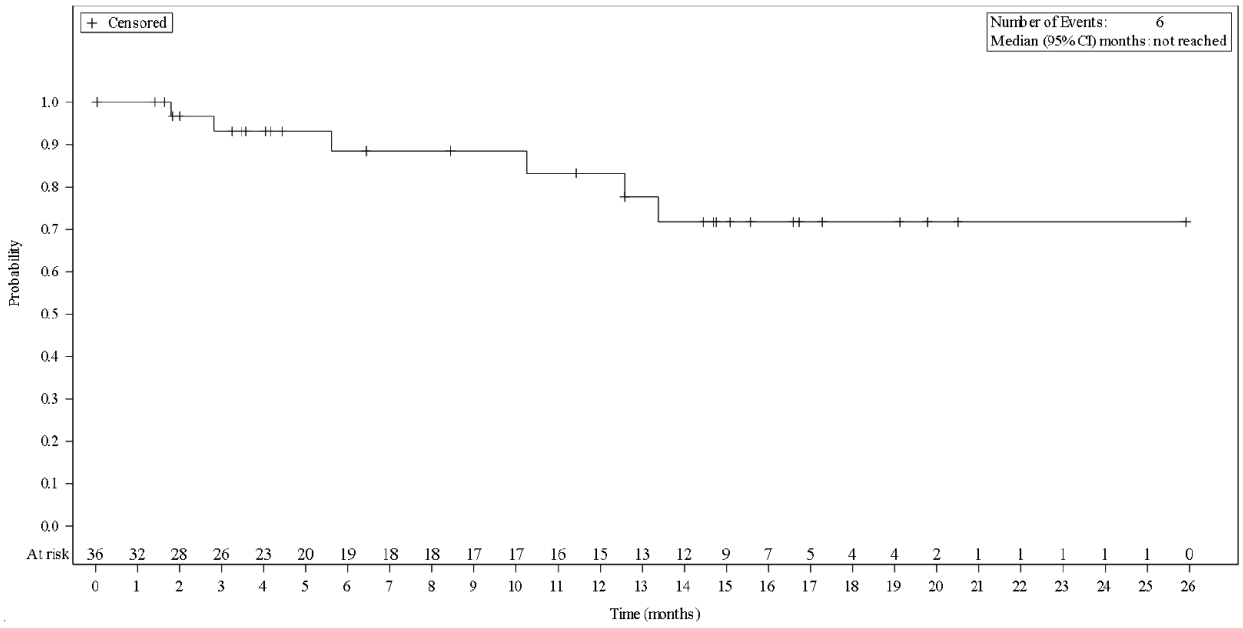


Source: Sobi 2020 LOTIS-2 CSR (66).
†Based on independent reviewer data including death as event.
Abbreviations: CI, confidence interval; RFS, relapse-free survival.

RFS from 1 March 2021 data cut is presented as a KM curve in Figure 8. The median RFS was not reached.

No data for RFS were available for the 1 March 2022 data cut or the final data cut ([redacted]).

Figure 8: Kaplan-Meier plot of RFS by independent reviewer (all-treated population)† (1 March 2021)



Source: Sobi Clinical overview 2021 (69).
†Based on independent reviewer data including death as event.
Abbreviations: CI, confidence interval; RFS, relapse-free survival.

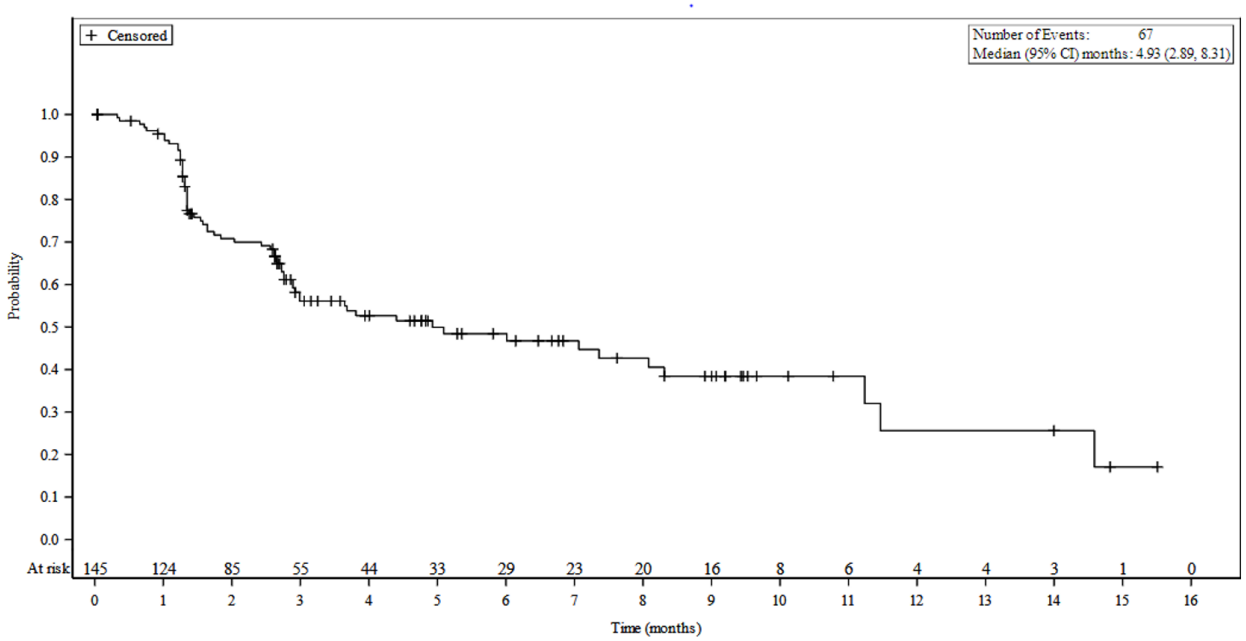
B.2.6.2.4. Progression-free survival

Figure 9 (6 April 2020 data cut) and Figure 10 (1 March 2021 data cut) present the clinical activity of loncastuximab tesirine measured by PFS as assessed by independent reviewer and presented as a KM curve in the all-treated population.

PFS was defined as the interval between the date of first dose of loncastuximab tesirine and the date of first PD based on independent radiographic assessment or death, whichever occurred first. There were 145 patients at risk in this analysis. The median PFS was 4.93 months (95% CI: 2.89, 8.31) (data cuts 6 April 2020, 1 March 2021). No data were available for the 1 March 2022 data (IPD were used in the MAIC).

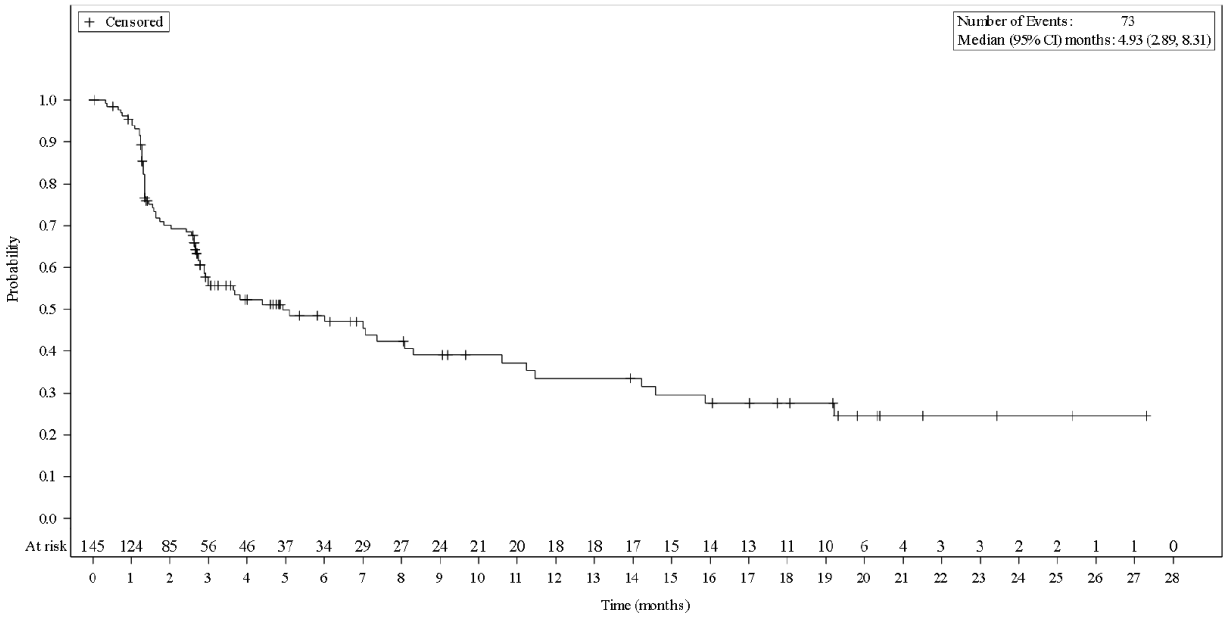
As of final data cut off ([redacted]), median OFS was [redacted] months (95% CI: [redacted]).

Figure 9: Kaplan-Meier plot of PFS by independent reviewer (all-treated population) (6 April 2020 data cut)



Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: CI, confidence interval; PFS, progression-free survival.

Figure 10: Kaplan-Meier plot of PFS by independent reviewer (all-treated population) (1 March 2021 data cut)



Source: Sobi Clinical overview 2021 (69).
Abbreviations: CI, confidence interval; PFS, progression-free survival.

B.2.6.2.5. Overall survival

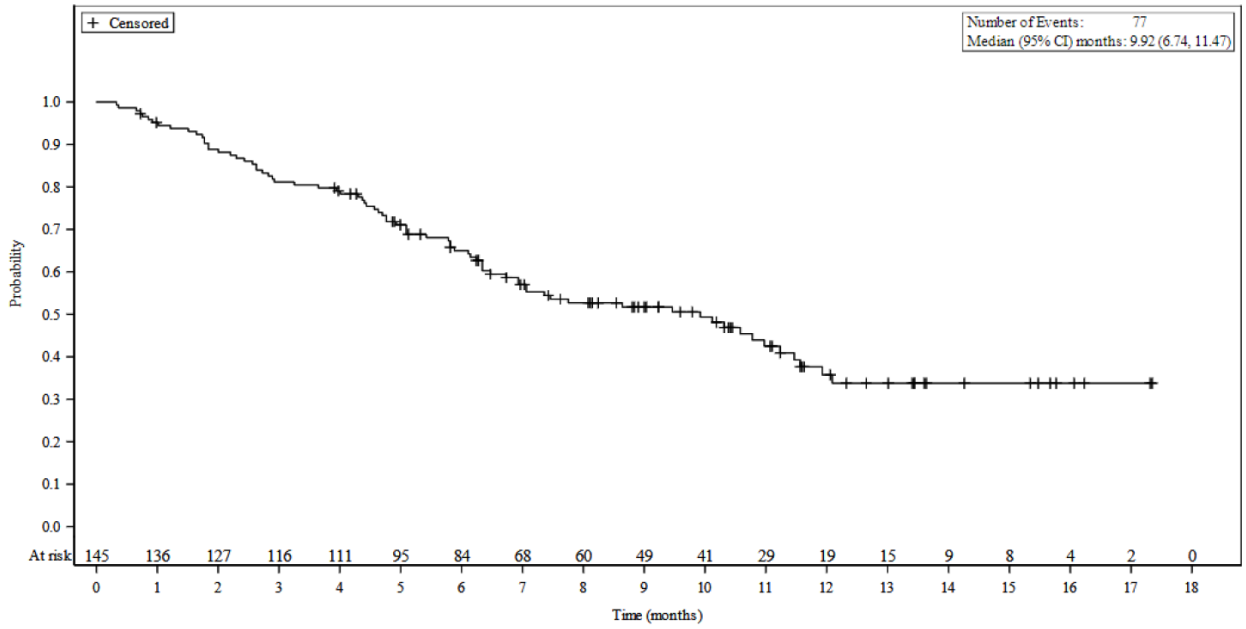
Figure 11 (6 April 2020 data cut) and Figure 12 (1 March 2021 data cut) present the clinical activity of loncastuximab tesirine measured by OS as a KM curve in the all-treated population.

OS was defined as the interval between the date of the first dose and the date of death from any cause. Of the 145 patients in the all-treated population, the median OS was 9.92 months (95% CI: 6.74, 11.47) (6 April 2020 data cut).

The median OS was 9.53 months (95% CI: 6.93, 11.47) (1 March 2021 data cut). No OS data were available for the 1 March 2022 data cut (IPD were used in the MAIC).

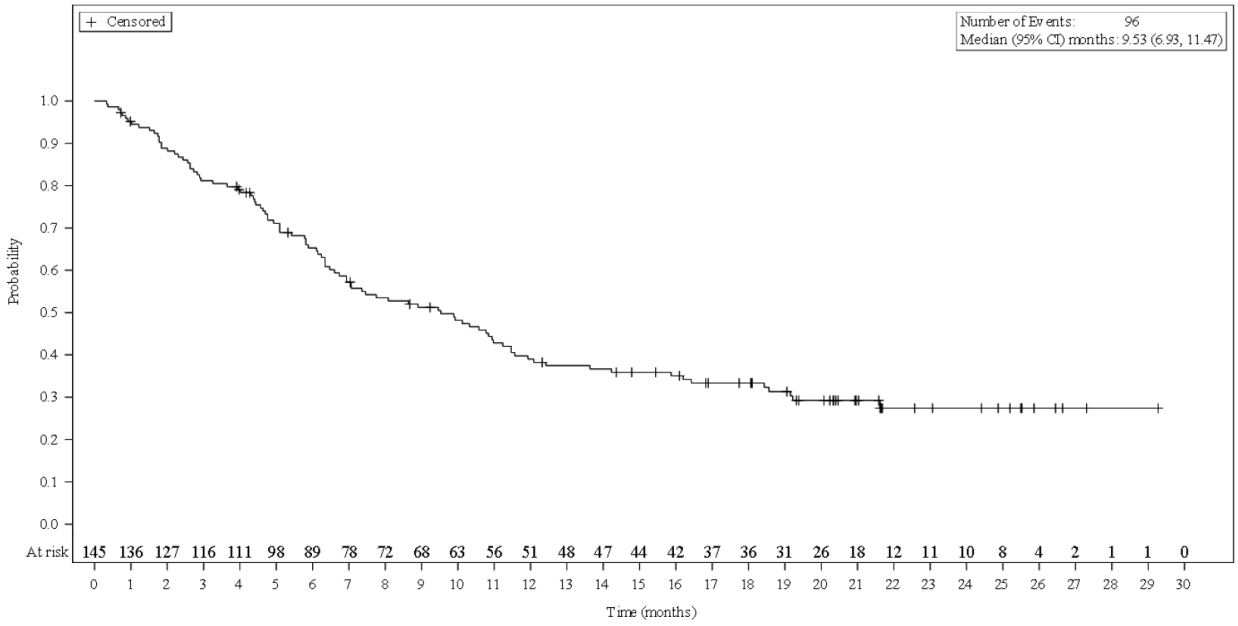
As of final data cut off ([redacted]), median OS was [redacted] months (95% CI: [redacted]) (60).

Figure 11: Kaplan-Meier plot of OS (all-treated population) (6 April 2020 data cut)



Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: CI, confidence interval; OS, overall survival.

Figure 12: Kaplan-Meier plot of OS (all-treated population) (1 March 2021 data cut)



Source: Sobi Clinical overview 2021 (69).

Abbreviations: CI, confidence interval; OS, overall survival.

B.2.6.3. Other secondary endpoints

B.2.6.3.1. Patient-reported Outcomes/Health-Related Quality of Life Assessments

The patient-reported outcomes (PRO)/HRQoL were assessed using the EQ-5D-5L and FACT-Lym questionnaires in the PRO population. There were 130 patients included in the PRO Population (Table 11).

EQ-5D-5L

97.2% of patients in the all-treated population completed the baseline EQ-5D-5L assessment. The completion rate among patients who were treated at each visit was ≥92.0% up to Cycle 9. After Cycle 9, <20 patients were treated (1 March 2021).

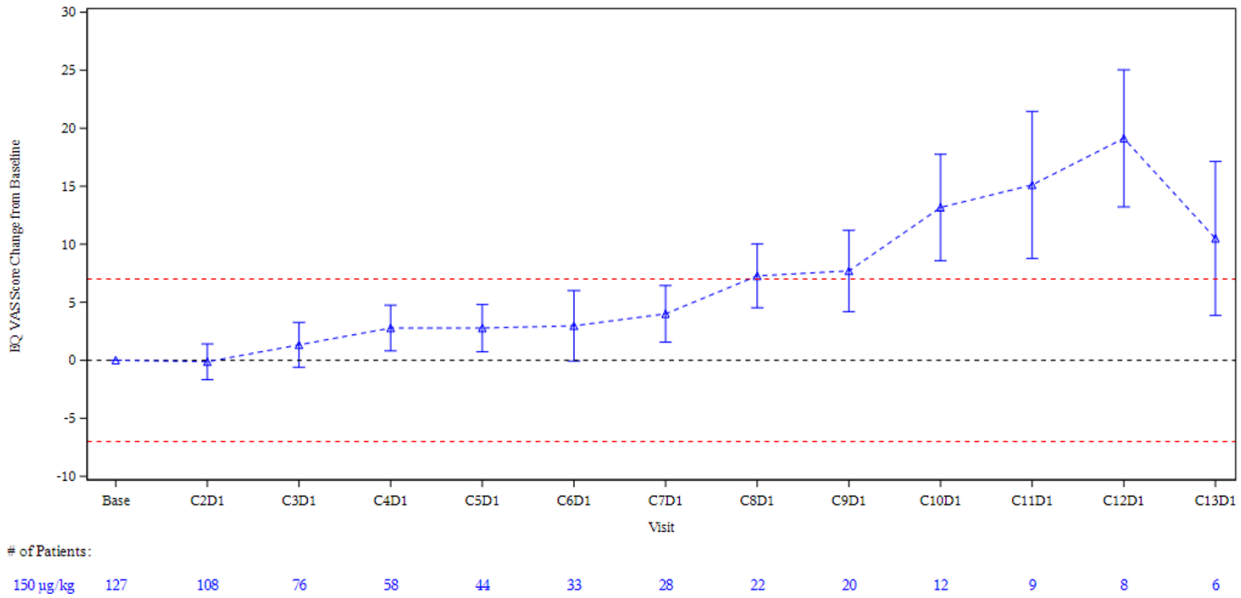
The mean (std) EQ-5D-5L visual analogue scale (VAS) score (on a 1 to 100 scale, with higher scores indicating better health) was 71.4 (19.1) at baseline. A change of 7 points in VAS from the baseline was considered a minimally important difference (MID), defined as the smallest change in a PRO measure that is perceived by patients as beneficial or that would result in a change in treatment (71). During the course of treatment, 41.4% of patients showed

improvement at one or more visits by at least seven points, 39.6% showed deterioration at 1 or more visits by at least seven points and 65.8% remained stable (change <7 points) at one or more visits. When averaging the change from baseline scores for each patient across visits during the course of treatment, more patients showed improvement by at least seven points (27.9%) than deterioration by at least seven points (20.7%) and approximately half of the patients (51.4%) remained stable (1 March 2021).

The mean (standard error [SE]) EQ-5D-5L VAS score change from baseline is presented in Figure 13 (6 April 2020 data cut) and Figure 14 (1 March 2021 data cut).

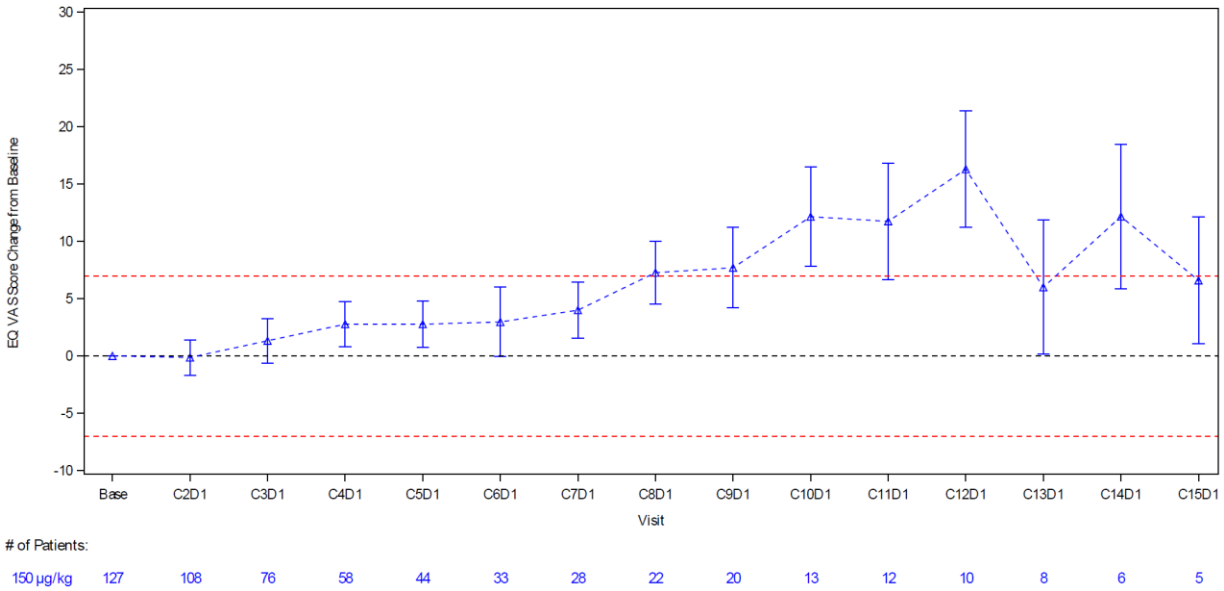
The mean VAS change score showed a trend of improvement on overall health over time. The mean change score reached MID (change of at least seven points) at Cycle 8, Day 1, although the sample size was reduced dramatically compared to baseline. At each visit during treatment, a higher percentage of patients experienced clinically meaningful improvement than experienced deterioration (6 April 2020 and 1 March 2021 data cut).

Figure 13: Mean (SE) plot of EQ-5D-5L VAS score change from baseline (PRO population)† (6 April 2020 data cut)



Source: Sobi 2020 LOTIS-2 CSR (66).
†Baseline is defined as the last nonmissing value before administration of loncastuximab tesirine.
Abbreviations: C, cycle; D, day; EQ-5D-5L, European Quality of Life (EuroQol)-5 Dimensions-5 Levels; PRO, patient-reported outcome; SE, standard error; VAS, visual analog scale.

Figure 14: Mean (SE) plot of EQ-5D-5L VAS score change from baseline (PRO population)† (1 March 2021 data cut)



Source: Sobi Clinical overview 2021 (69).
†Baseline is defined as the last nonmissing value before administration of loncastuximab tesirine. Visits with less than 5 assessments are not displayed.
Abbreviations: C, cycle; D, day; EQ-5D-5L, European Quality of Life (EuroQol)-5 Dimensions-5 Levels; PRO, patient-reported outcome; SE, standard error; VAS, visual analog scale.

No data were available from 1 March 2022 data cut or final data cut ([redacted]) for the EQ-5D-5L outcome.

FACT-Lym

The completion rate for FACT-Lym with scores to calculate at least FACT-Lym Trial Outcome Index (TOI) or Functional Assessment of Cancer Therapy – General (FACT-G) Total or FACT-Lym Total in the All-Treated Population was 93.8% at baseline and ≥88% of patients at each visit completed the FACT-Lym subscale and composite scores up to Cycle 9. After Cycle 9, there were <20 patients in treatment (1 March 2021 data cut).

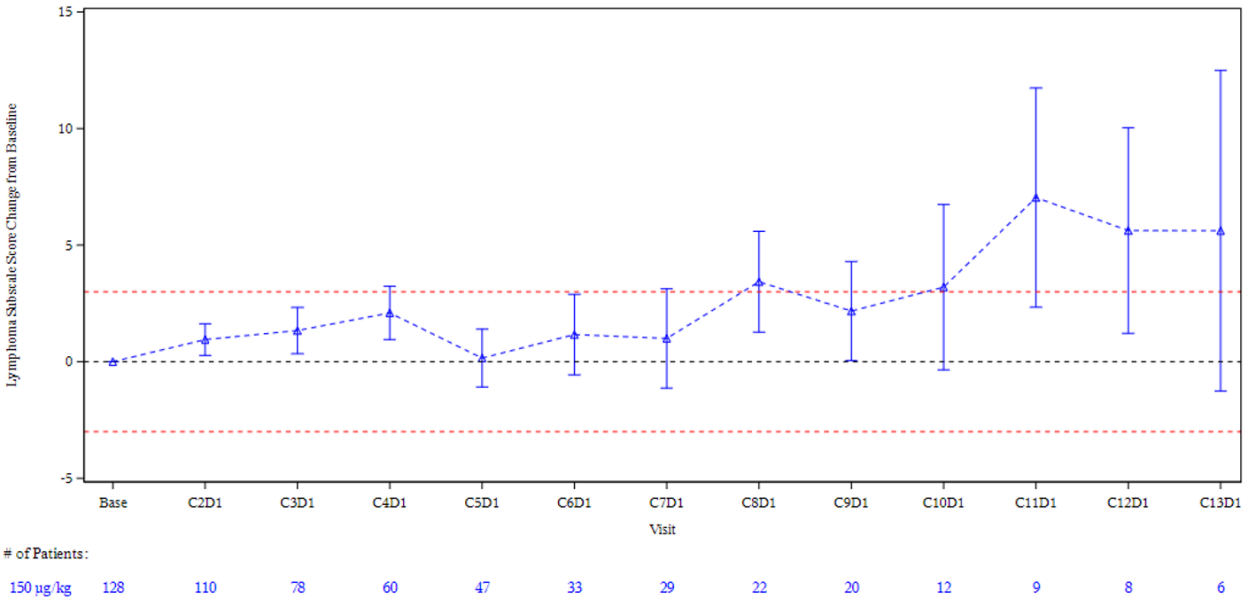
Higher scores indicate higher functioning/QoL (scales range 0 to 28 for PWB, SWB, and FWB, 0 to 24 for EWB, 0 to 60 for lymphoma subscale (LymS), 0 to 116 for TOI, 0 to 108 for FACT-G total, and 0 to168 for FACT-Lym Total) (1 March 2021 data cut).

The mean (SD) baseline FACT-Lym scores were 21.9 (5.23) for PWB; 21.9 (5.70) for SWB, 16.9 (4.62) for EWB, 14.8 (6.32) for FWB, 43.4 (10.34) for LymS, 79.8 (18.39) for TOI, 75.2 (15.65) for FACT-G Total; and 118.4 (23.84) for FACT-Lym Total (1 March 2021 data cut).

Mean changes in all FACT-Lym subscale and composite scores were generally stable over time. FACT-Lym subscales that showed a trend of improvement from baseline over time were emotional well-being (except Cycle 15 Day 1) and LymS (except Cycle 15 Day 1). The subscales of PWB and functional well-being (except Cycle 15 Day 1) were relatively stable from baseline over time and the subscale of social/family well-being showed a trend of deterioration from baseline over time (1 March 2021 data cut).

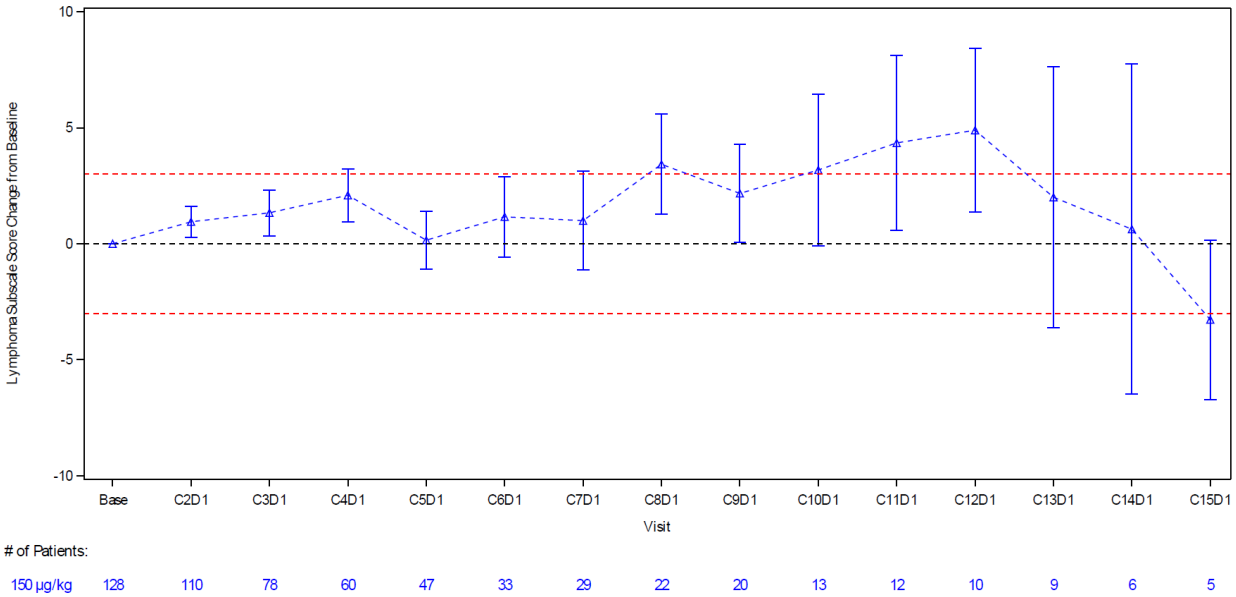
The mean (SE) FACT-Lym Lymphoma Subscale score change from baseline is presented in Figure 15 (6 April 2020 data cut) and Figure 16 (1 March 2021 data cut).

Figure 15: Mean (SE) plot of FACT-Lym lymphoma subscale score change from baseline (PRO population)



Source: Sobi 2020 LOTIS-2 CSR (66).
†Baseline is defined as the last non-missing value before administration of loncastuximab tesirine. Visits with less than 5 assessments were not displayed.
Abbreviations: C, cycle; D, day; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; LymS, lymphoma subscale; PRO, patient-reported outcome; SE, standard error.

Figure 16: Mean (SE) plot of FACT-Lym lymphoma subscale score change from baseline (PRO population) (1 March 2021 data cut)



Source: Sobi Clinical overview 2021 (69).
†Baseline is defined as the last nonmissing value before administration of loncastuximab tesirine. Visits with less than 5 assessments were not displayed.
Abbreviations: C, cycle; D, day; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; LymS, lymphoma subscale; PRO, patient-reported outcome; SE, standard error.

No data were available from 1 March 2022 data cut or final data cut ([redacted]) for the FACT-Lym outcome.

B.2.7. Subgroup analysis

Outcomes on ORR, DOR and survival between the overall cohort and in subgroups with high-risk disease characteristics were consistent (59). In patients who relapsed after CAR T-cell therapy, representing a difficult to treat patient population, subgroup analyses indicated a similar response (ORR of 46.2%) to loncastuximab tesirine compared with the overall cohort (63). Outcomes among patients who received three or >3 prior lines of therapy were also consistent with those from the overall cohort; ORR in these subgroups were 48.6% and 48.9%, respectively (data cut 6 April 2020) (59).

A subgroup analysis was performed on frail patients from LOTIS-2 with age ≥75 years or with ECOG performance status (PS)=2 who did not receive CAR-T prior to nor after treatment with loncastuximab tesirine. The efficacy was [redacted] with a median DOR [redacted] after [redacted]

months. The median PFS was [redacted] months and the median OS was [redacted] months (data cut 6 April 2020) (66).

Data from subgroup analyses of primary and key secondary outcomes (data cuts 6 April 2020 and 1 March 2021) are reported in Appendix E. No subgroup data available for data cuts 1 March 2022 or the final data cut ([redacted]).

B.2.8. Meta-analysis

Pairwise meta-analysis was not conducted.

B.2.9. Indirect and mixed treatment comparisons

The SLR reported in Section B.2.1 and Appendix D identified studies for loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies. However, as LOTIS-2 is a single group study, there was no connected network to enable a network meta-analysis (NMA) or a Bucher indirect comparison to be conducted. To assess the relative effectiveness of loncastuximab tesirine vs comparators and inform the cost-effectiveness model, indirect comparisons for efficacy outcomes (PFS and OS outcomes) were made using an unanchored MAIC approach. Response outcomes were also compared, where data were available.

Of the 45 studies included in the SLR, only two studies (reported in six publications) were relevant for the indirect treatment comparisons (LOTIS-2 (59, 62-65) and GO29365 extension cohort (53)). Due to the sparsity of relevant comparator data, consideration was given to how additional, relevant comparator data could be identified: a full description of the approach taken is provided in Appendix D (Section D2.2). This process led to the inclusion of an additional two studies reported in three publications (4, 5, 72). The studies included in the MAIC are listed in Table 15.

Table 15: List of studies included in MAIC

Study name / author year	Intervention	Included in SLR?	SLR exclusion notes
LOTIS-2, NCT03589469 (59, 62-65)	Loncastuximab tesirine	Yes	NA

Study name / author year	Intervention	Included in SLR?	SLR exclusion notes
GO29365 extension study, NCT02257567 (53)	Polatuzumab vedotin, bendamustine + rituximab	Yes	NA
Hamadani 2022b (72)	Polatuzumab vedotin, bendamustine + rituximab	No	Conference abstract published after SLR search date
CORAL extension studies, NCT00137995 (4, 5)	Mixed chemotherapy	No	Study investigating mixed chemotherapy was excluded as per the PICOS criteria

Abbreviations: MAIC, matching adjusted indirect comparison; NA, not applicable; PICOS, population, intervention, comparator, outcomes, study design; SLR, systematic literature review

The MAIC analyses are described in summary below and further details are provided in Appendix D.

B.2.9.1. Brief description of the approach

As described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, MAIC is a non-parametric likelihood reweighting method that allows a propensity score logistic regression model to be estimated without individual patient data (IPD) in one of the treatment arms (73). For these analyses, individual loncastuximab tesirine-treated patients were assigned statistical weights that adjust for their over- or under-representation relative to that reported for each comparative evidence source (74).

MAIC methodology attempts to adjust for between-trial differences in baseline characteristics. When a common treatment comparator 'connected network' is not available, a MAIC assumes that differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and treatment effect modifiers (73). Therefore, every prognostic variable and treatment effect modifier that is imbalanced between the two studies must be available and included in the adjustment model. The MAIC method utilises patient-level data for the treatment of interest along with published aggregate trial level data for the comparator. For the comparison of loncastuximab tesirine vs relevant comparators a number of MAICs were performed to compare key efficacy outcomes of PFS and OS.

- Two studies were available to conduct MAICs for loncastuximab tesirine vs Pola+BR (53, 72).
- One study was available to conduct a MAIC for loncastuximab tesirine vs chemotherapy (4, 5).

Estimation of the efficacy of loncastuximab tesirine vs comparators was conducted using patient-level clinical trial data for loncastuximab tesirine (from LOTIS-2) re-weighted to match the published, aggregate-level baseline characteristic data for other comparators.

All analyses were run in accordance with the recommendations presented in NICE DSU TSD 18 and Phillippo et al (73, 75).

B.2.9.2. Data sources

The percentage of patients who were progression-free or alive / alive over time were extracted from the published KM curves for PFS and OS, respectively. Digitising software, Engauge Digitizer version 12.1, was used to extract the data, and pseudo individual patient-level data were reconstructed from the extracted survival (supplemented by the number of patients at risk over time, if reported) using the algorithm published by Guyot et al. 2012 (76). Appendix D provides an additional summary of the available median PFS and OS reported for each included study.

Due to the sparsity of relevant data for comparators, where KM curves were not available, the median PFS or OS for the comparator study were used to make a crude estimate of the hazard ratio (HR) for loncastuximab tesirine vs. comparator, using methods described in Tierney et al 2007 (77). This involved estimating the HR from: Median survival time for loncastuximab tesirine/Median survival time for comparator and estimating the corresponding standard error (SE) using the formula:

$$\text{SE log HR} = \sqrt{(1/E1+1/E2)}$$

where E1 and E2 are the number of events in each treatment arm.

Response data (overall response rate [ORR]) were extracted from each of the published studies in the form of number of patients with an event, total number of patients in the relevant treatment arm and the percentage of patients with an event (where reported).

The relative effects of loncastuximab tesirine vs. alternative therapies were quantified as hazard ratios (HR) for overall PFS and OS, with corresponding 95% confidence intervals (CIs) and median survival times. For overall response rate (ORR), odds ratios with corresponding 95% CIs were estimated.

B.2.9.2.1. Loncastuximab tesirine

Patient-level data for loncastuximab tesirine were available from LOTIS-2 to provide evidence for loncastuximab tesirine vs comparators in patients with R/R DLBCL who have received two or more prior multiagent systemic treatment regimens.

Where there were obvious differences in patient recruitment between LOTIS-2 and comparator studies, when possible, the comparator study criteria were applied by excluding patients with a particular characteristic from the LOTIS-2 IPD dataset.

The data cut-off for the LOTIS-2 dataset was 01 March 2022.

B.2.9.2.2. Comparators

A summary of the reasons for exclusion from the MAIC analyses for the studies identified by the SLR is presented in Appendix D. Due to the sparsity and paucity of data identified in the SLR, during interview, clinical experts were asked if they were aware of any relevant comparator data and in addition, recent NICE submissions were hand searched for relevant comparator studies. No additional studies were identified from this research, predominantly due to the lack of data specifically in third- or later-line (the target population for loncastuximab tesirine). It was not considered appropriate to compare third- or later-line with second- or later-line patients as there are a number of sources of evidence suggesting that survival for later-line patients decreases (for example, Radford et al. 2019 (6) [Table 16], Nowakowski 2022 (78)). As no second-line patients were enrolled in LOTIS-2, this difference could not be adjusted for in the analyses.

Table 16: Treatment response for patients with R/R DLBCL by line of therapy (Christie Hospital Trust, Radford 2019)

	Treatment line		
Outcome	**Second-line (n=89)**	**Third-line (n=63)**	**Fourth-line or later (n=41)**
CR, % (95% CI)	27.0 (18.4, 37.6)	17.5 (9.5, 29.5)	2.4 (0.1, 14.4)
PR, % (95% CI)	19.1 (11.8, 29.1)	9.5 (3.9, 20.2)	7.3 (1.9, 21.0)
Median OS, days (95% CI)	320 (276, 490) [n=88]	195 (123, 287)	88 (70, 125)

Source: Radford et al., 2019 (6)
Abbreviations: CI, confidence interval; CR, complete response; OS, overall survival; PR, partial response; R/R DLBCL, relapsed/refractory diffuse large B-cell lymphoma

Table 17 summarises the study characteristics of the four studies included for the MAICs.

Table 17: Summary characteristics of studies included in the MAIC analyses

Comparator	Study name [Author (Year)]	Study design	Aim of study
Loncastuximab tesirine	LOTIS-2 [Caimi 2021 (59)]	Single arm clinical trial	To evaluate the efficacy and safety of loncastuximab tesirine in R/R DLBCL patients
Pola+BR	GO29365 extension study [Sehn 2022 (53)]	Extension to RCT	To further assess safety, efficacy, and pharmacokinetic profile of Pola+BR treatment combination, following initial Pola+BR vs BR randomized arms of GO29365, an additional 106 patients with R/R DLBCL were enrolled into a single-arm extension cohort receiving Pola+BR
Pola+BR	Hamadani 2022b (79)	RWE from US COTA database, representing EMRs from >200 US sites, both academic and community practice	To examine the effectiveness of Pola+BR by line of therapy in patients with R/R DLBCL
Chemotherapy (mixed treatments†)	CORAL extension study [Van den Neste 2016/2017 (4, 5)]	Extension to RCT	To update patient status following participation in the CORAL study, both for those who went on to receive ASCT per-protocol and those who did not proceed to ASCT and who were candidates for a third-line regimen

†Including ICE-like, DHAP-like, gemcitabine-containing regimens
Abbreviations: 1L/2L, first-/second-line; ASCT, autologous stem cell transplant; DHAP, cisplatin, cytarabine and dexamethasone; EMRs, electronic medical records; ICE, ifosfamide, etoposide, and carboplatin; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; RCT, randomised controlled trial; R/R DLBCL, relapsed / refractory diffuse large B-cell lymphoma; RWE, real-world evidence; US, United States.

A summary of the baseline characteristics for the included studies is provided in Appendix D.

B.2.9.3. Identification of prognostic factors and treatment effect modifiers

Identification of all relevant prognostic variables and treatment-effect modifiers was required as part of the matching process.

A preliminary list of matching variables was identified using the clinical opinion of medical experts of the submitting company and compared with published evidence (Zinzani et al. 2021 (80)/NICE review ID3795 [linked publications] (19)):

- Primary Refractory (refractory to first line therapy)
- Prior lines of therapy
- Refractory to last therapy
- IPI
- Disease stage (Ann Arbor)
- Age
- ECOG PS 0-1 vs. >1
- HGBL
- Double / triple Hit LBCL
- De novo vs transformed (transformed indolent non-Hodgkin's lymphoma [TiNHL])
- Cell of origin.

It was noted that if IPI was available for adjustment in a particular treatment comparison, then age, stage and ECOG PS would not be included as additional covariates since they are already included in the calculation of the IPI score (along with extra nodal status). Zinzani et al. 2021 considered all of these variables to be prognostic factors only. The relevance and importance of each of these characteristics were discussed with five UK clinical experts.

The clinical experts confirmed that the current list of matching variables was appropriate (22), whilst highlighting the potential unreliability of results when adjusting for the following variables:

- Double / triple hit LBCL, as not all double hits are high risk patients

- Cell of origin, difficult to include as a predictor since ABCs, generally having worse outcomes than GCB, whereas GCB have double hits
- De novo vs. transformed was considered less important than the other variables listed due to the difficulties of aligning prior therapies if received for follicular lymphoma.

There were also some comments on matching for prior ASCT, however on balance, more clinicians thought it should be excluded (2 vs 1 clinician) due to the fact that this variable does not reflect the characteristics of patients' disease (22). Bulky disease was also proposed as a predictive variable, however none of the comparator studies reported data with a comparable definition for this variable.

It was noted that Zinzani et al. (65) / NICE ID3795 submission (19) considered additional covariates of elevated lactate dehydrogenase (LDH >upper limit of normal [ULN] vs. ≤ULN), neutropenia (absolute neutrophil count [ANC] <1.5x10^9/L vs. ANC ≥1.5x10^9/L), and anaemia (haemoglobin [Hb] <10 g/dL vs. Hb ≥10 g/dL). However, these variables were not identified by the clinicians as key variables for adjustment, nor were they available for any of the comparator studies.

Table 18 summarises the final list of key prognostic factors and treatment effect modifiers that were identified for inclusion in the population-adjustment, and the studies in which these factors were reported. As all included studies were single arm, it was not possible to identify whether some variables were treatment effect modifying.

Table 18: Summary of availability of prognostic factors and treatment effect modifiers for matching

	Loncastuximab tesirine	Pola+BR		Chemotherapy
Factor	**LOTIS-2**	**GO29365 extension**	**COTA US database**	**CORAL extension**
Primary refractory (refractory to first line therapy)	√	√		
Prior lines of therapy	√	√	√	
Refractory to last therapy	√			
IPI	√	√		√
HGBL	√	√	√	
Age†	√	NA	√	NA
Ann Arbor disease stage†	√	NA		NA

	Loncastuximab tesirine	Pola+BR		Chemotherapy
Factor	**LOTIS-2**	**GO29365 extension**	**COTA US database**	**CORAL extension**
ECOG PS†	√	NA		NA
Male‡	√		√	√
Prior ASCT‡	√			√

†Not required if IPI available; ‡Factors not anticipated to have an impact on the indirect comparison, however included where very few available characteristics data reported for comparator study and specifically for CORAL extension study to match previously published Hamadani 2022a (81)
Abbreviations: ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab; NA, not applicable as IPI data available; Pola+BR, polatuzumab plus bendamustine plus rituximab.

B.2.9.4. Data extraction and variable generation

Individual patient-level data were available from LOTIS-2, and relevant characteristics and outcomes were identified for the analysis dataset. This included the baseline characteristics that were also available in the comparator studies of interest and their eligibility criteria.

Table 19 shows the data for the overall LOTIS-2 population (N=145) for each prognostic variable identified for inclusion in the LOTIS-2 vs comparator MAICs.

Table 19: Comparison of baseline characteristics used in MAICs (LOTIS-2 vs Pola+BR comparator)

Characteristic	Description	LOTIS-2 (N=145) Loncastuximab tesirine	GO29365 extension study (N=152)† Pola+BR	COTA US database (N=43) Pola+BR	CORAL extension study (N=278) Chemotherapy
Gender, n (%)	Male	85 (59)	Not matched	NR	175 (63.0)
Histology, n (%)	DLBCL NOS	127 (88)	142 (95)	NR	NR
	HGBL	11 (8)	5 (3)	5 (12)	
	PMBCL	7 (5)	0 (0)	NR	
	Other	0 (0)	3 (2)	NR	
ECOG PS, n (%)	0	58 (40)	44 (29)	NR	NR
	1	78 (54)	87 (57)		
	2	9 (6)	20 (13)		
IPI score, n (%)	≤2	[redacted]	NR	NR	170 (61)
	>2	[redacted]	94 (62)	NR	108 (39)
Disease stage, n (%)	I-II	33 (23)	30 (20)	NR	NR
	III-IV	112 (77)	122 (80)		
Previous systemic therapy	Median (range)	3.0 (2.0, 7.0)	2.0 (1.0, 7.0)	NR	NR
	1 line, n (%)	0 (0)	50 (33)	0 (0)	
	2 lines, n (%)	63 (43)	42 (28)	32 (74)	
	3 lines, n (%)	35 (24)	60 (39) (≥3)	5 (12)	
	3+ lines, n (%)	47 (32)	NR	6 (14)	
Response to 1st line, n (%)	Relapse	99 (68)‡	NR	NR	NR
	Refractory	29 (20)‡	97 (64)¶		
	Other	17 (12)	NR		

Characteristic	Description	LOTIS-2 (N=145) Loncastuximab tesirine	GO29365 extension study (N=152)† Pola+BR	COTA US database (N=43) Pola+BR	CORAL extension study (N=278) Chemotherapy
Response to most recent line of systemic therapy, n (%)	Relapse	43 (30)‡	NR	NR	NR
	Refractory	84 (58)‡	116 (76)§		
	Other	18 (12)	NR		
Previous ASCT, n (%)		21 (14)	NR	NR	75 (27)

†Baseline characteristics only reported for second- or later-line patients (n=152), not the third- or later-line subgroup (n=102)
‡ Relapse defined as CR+PR followed by progression; refractory defined as no response, i.e. stable disease or progressive disease. Note that definitions for LOTIS-2 and GO29365 differ. Refer to discussion in Section B.2.9.6.1
¶ Defined as no response or progression or relapse within 6 months of first antilymphoma therapy end date.
§ Defined as no response or progression or relapse within 6 months of last antilymphoma therapy end date.
Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; MAIC, matching-adjusted indirect comparison; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B-cell lymphoma; Pola+BR, polatuzumab vedotin plus bendamustine plus rituximab; PR, partial response; US, United States.

B.2.9.5. Matching average baseline characteristics between loncastuximab tesirine and comparators

The MAIC approach was applied to make a comparison using IPD for patients receiving loncastuximab tesirine and aggregate level data for each relevant comparator study. Average baseline characteristics were matched between the loncastuximab tesirine patients and trial populations from each comparator study. Individual patients in the LOTIS-2 trial were assigned weights such that their weighted mean baseline characteristics matched those reported for patients in the comparator trial. The analysis followed the approach recommended in NICE DSU TSD 18 (73); weights were obtained from a logistic regression model, with the baseline characteristics used for matching included as predictors in the model. A method of moments was used to ensure the weights exactly balance the mean covariate values between the weighted loncastuximab tesirine IPD and the comparator population. Outcomes were then compared pre- (i.e. naïve comparison) and post-matching between loncastuximab tesirine and the comparator study of interest. The robustness of the analyses was also considered by approximating the effective sample size (ESS). A small ESS is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable.

To account for the fact that weights are estimated rather than fixed and known, standard errors for the MAIC estimates were calculated using a bootstrap estimator (73). The use of a bootstrap estimator can help quantify sampling uncertainty in the estimates. Bootstrapping was performed using the following algorithm:

- Loncastuximab tesirine treated patients were sampled with replacement.
- For each bootstrap dataset, a set of weights was derived using the methodology described above.
- For each bootstrap dataset and corresponding set of weights, the relative treatment effect was estimated using a Cox proportional hazards model to estimate a weighted HR for loncastuximab tesirine relative to comparator treatments.

This procedure was repeated 1,000 times to obtain a distribution of estimates for which the 2.5th and 97.5th percentiles were used to generate the lower and upper confidence interval limits.

B.2.9.6. Results from MAIC analyses

B.2.9.6.1. Efficacy outcome MAIC results: loncastuximab tesirine vs Pola+BR

Two separate comparisons were made to compare loncastuximab tesirine with Pola+BR.

GO29365 extension study

Patients with transformed lymphoma were excluded from the GO29365 extension study and therefore, 29 patients with transformed lymphoma were excluded from the LOTIS-2 dataset when making a comparison with Pola+BR from this dataset. In addition, 14 patients with missing data with respect to relapse / refractory status and no response to first line treatment / time to progressive disease available from LOTIS-2, were also excluded. This yielded a dataset of 102 patients for LOTIS-2, exactly the same number of patients as those in third- or later-line in the GO29365 extension study.

One limitation with the data available from the GO29365 extension study was that the target population of interest for loncastuximab tesirine is third- or later-line, however patient characteristics were only available for the second- or later-line population in the GO29365 extension study. As the majority of patients were third- or later-line (102/152 patients) in the Pola+BR dataset, it was assumed that the characteristics at second- or later-line were representative of the third-line population to allow a population-adjustment to be made.

A further limitation was that only median PFS and median OS with 95% CI and number of events were reported for the third- or later-line subgroup in the GO29365 extension study. This led to a HR (95% CI) estimation for loncastuximab tesirine vs Pola+BR using median survival and number of events, as described previously in Section B.2.9.2.

Table 20 presents the LOTIS-2 (unadjusted and weighted) and the GO29365 extension study baseline characteristics for the five matching variables. Matching was possible based on number of prior lines (2 vs ≥3), refractory to primary treatment (%), IPI score (<3 vs ≥3) and HGBL (%). The definition of refractory to primary treatment and last treatment differed between the studies, with the GO29365 extension study reporting the proportion of refractory patients as a group combined with those who had relapse or progression within six months of completion of therapy. In LOTIS-2, the definition of refractory was stable or progressive disease following treatment. For the primary refractory definition, data were available to enable the criteria from GO29365 extension study to be extended to LOTIS-2 to match the definitions. However,

relevant data were not available for the additional relapse criteria in last refractory and so matching was not possible for this variable. The ESS after matching was n=87.7, which was a reduction of only 14% from the original LOTIS-2 sample size, suggesting good overlap at baseline prior to matching for the selected patient characteristics.

Table 20: Comparison of baseline characteristics loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study)

Treatment (study)	N/ ESS	Prior lines ≥3 (%)	Primary refractory or progression / relapse <6 months (%)	IPI ≥3 (%)	HGBL (%)
Lonca unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	39.0	64.0	62.0	3.0

Abbreviations: ESS, effective sample size; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

The KM plots for OS for patients receiving loncastuximab tesirine for the unadjusted and weighted patient data are shown in Figure 17. Little difference in survival was seen after weighting and the median survival time did not change compared with the unadjusted outcome (Table 21). OS was similar between the two treatments (HR close to 1.0), with no treatment favoured over the other. It was not possible to explore validity of the proportional hazards assumption given the lack of available KM curve for the GO29365 extension study in the third- or later-line subgroup.

Figure 17: Kaplan-Meier plot for OS – loncastuximab tesirine matched to Pola+BR GO29365 extension study characteristics

Abbreviations: Lonca, loncastuximab tesirine; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

Table 21: Summary of OS comparison – loncastuximab tesirine vs Pola+BR (GO29365 extension study)

Treatment (study)	N/ ESS	Events	Median OS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	63	9.5 (7.6, 14.2)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

The KM plots for PFS for patients receiving loncastuximab tesirine for the unadjusted and weighted patient data are shown in Figure 18. PFS for loncastuximab tesirine patients was almost identical pre- and post weighting with only a small change in the 95% CI (Table 22). No treatment was significantly favoured over the other, pre- and post-matching, with the 95% CI crossing 1.0 in both comparisons. It was not possible to explore validity of the proportional hazards assumption given the lack of available KM curve for the GO29365 extension study in the third-or later-line subgroup.

Figure 18: Kaplan-Meier plot for PFS – loncastuximab tesirine matched to Pola+BR GO29365 extension study characteristics

Abbreviations: Lonca, loncastuximab tesirine; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

Table 22: Summary of PFS comparison – loncastuximab tesirine vs Pola+BR (GO29365 extension study)

Treatment (study)	N/ ESS	Events	Median PFS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve comparison (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	79	6.1 (4.5, 8.0)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Response was measured in both studies using the 2014 Lugano classification (32), and the actual number of patients responding in each treatment group was identical for the unadjusted study data. The ESS after weighting was identical to that reported in Table 21 and Table 22. Table 23 presents the unadjusted and weighted odds ratio (OR) results for objective response outcomes. Although the proportion of patients responding after weighting showed a slight decrease vs pre-weighting for loncastuximab tesirine ([redacted], respectively), the OR estimates showed similar odds of response when comparing loncastuximab tesirine with Pola+BR across unweighted and weighted comparisons, with the 95% CI crossing 1.0 for all treatment estimates.

Table 23: Odds ratio for ORR – loncastuximab tesirine vs Pola+BR (GO29365 extension study)

Outcome	Method	Lonca ORR, n/N (%)	Pola+BR ORR, n/N (%)	Lonca vs Pola+BR Odds ratio (95% CI)
ORR	Naïve comparison (unadjusted)	[redacted]	51/102 (50)	[redacted]
	Weighted GLM model	[redacted]		[redacted]
	Weighted sandwich estimator			[redacted]

Abbreviations: CI, confidence interval; GLM, generalised linear model; Lonca, loncastuximab tesirine; ORR, objective response rate; Pola+BR, polatuzumab plus bendamustine plus rituximab.

COTA US real-world evidence study

All patients from LOTIS-2 were included in the IPD dataset for the comparison with Pola+BR from the COTA US electronic medical records database, as there were no apparent exclusions from the COTA database.

The limitation with the data available from the COTA database was the small number of included patients (N=43), however the advantage of this dataset over the GO29365 extension study data was that both PFS and OS data KM curves and numbers at risk were available (from ADC Therapeutics) and could be digitised and compared with data from LOTIS-2.

Table 24 presents the LOTIS-2 (unadjusted and weighted) and the COTA US database patients' baseline characteristics for the four matching variables. Matching was possible based on number of prior lines (2 vs ≥3), HGBL (%), male gender (%) and patients age (<65 vs ≥65, cut-off chosen based on median values reported for the COTA dataset). The ESS after matching was [redacted], which was a [redacted] reduction from the original LOTIS-2 sample size and suggests there was reasonable overlap at baseline prior to matching for the selected patient characteristics.

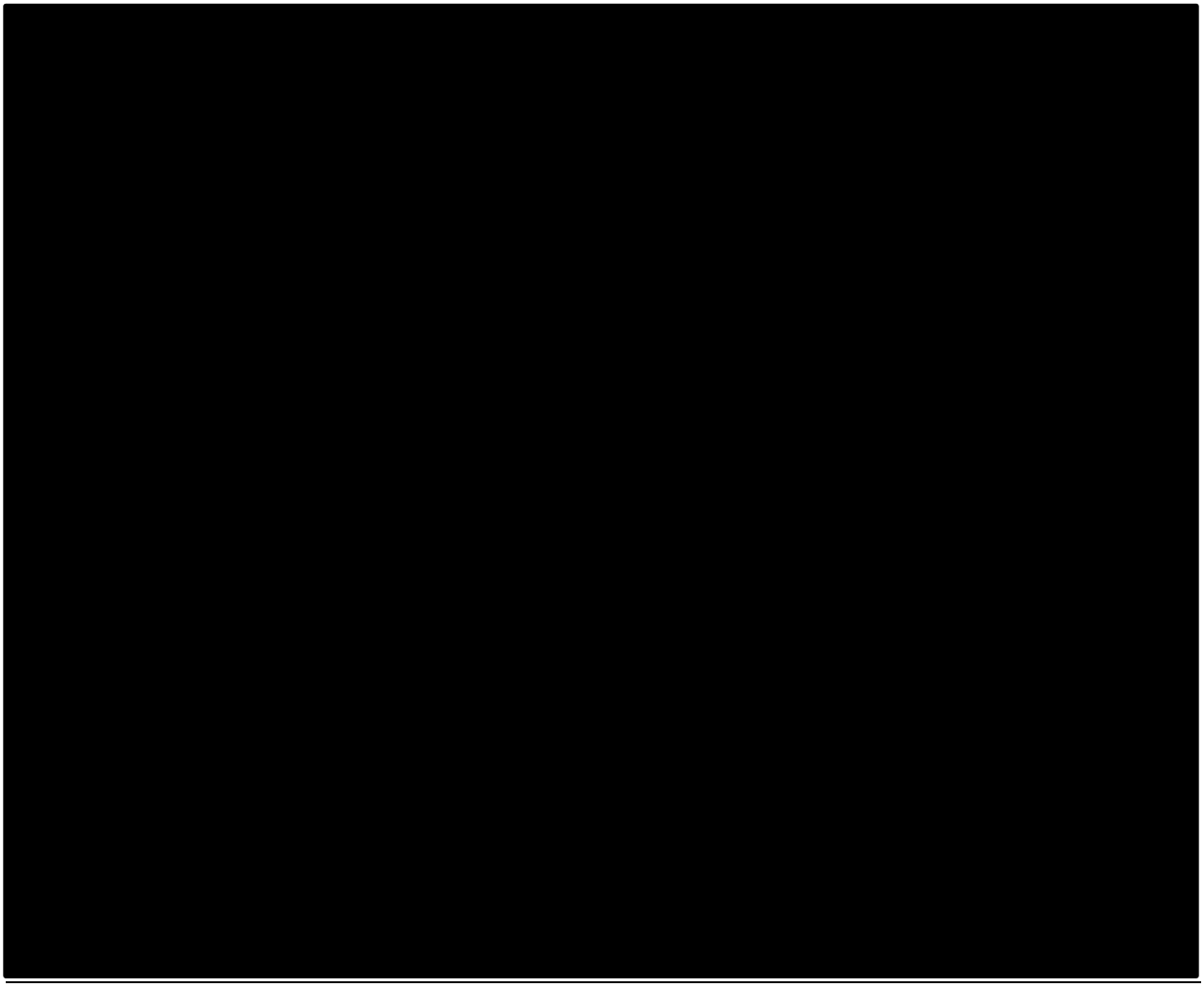
Table 24: Comparison of baseline characteristics loncastuximab tesirine (LOTIS-2) vs Pola+BR (COTA US database)

Treatment (study)	N/ ESS	Age <65 (%)	Male (%)	Prior lines ≥3 (%)	HGBL (%)
Lonca unadjusted (LOTIS-2)	145.0	44.8	58.6	56.6	7.6
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (COTA database)	43.0	50.0	60.0	26.0	12.0

Abbreviations: ESS, effective sample size; HGBL, high grade B-cell lymphoma; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab; US, United States.

The KM plots for OS for patients receiving loncastuximab tesirine for the unadjusted and weighted patient data compared with those receiving Pola+BR are shown in Figure 19. A small improvement in OS was seen after weighting (Table 25). OS was improved for loncastuximab tesirine (HR < 1.0), and in the bootstrap estimate, loncastuximab tesirine offered significantly longer survival than Pola+BR. From a visual inspection of the KM curves, it was noted that the proportional hazards assumption is likely to be violated, due to the cross-over of the curves early on during follow-up.

Figure 19: Kaplan-Meier plot for OS – loncastuximab tesirine matched to Pola+BR patient characteristics (COTA US database)



Abbreviations: Lonca, loncastuximab tesirine; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted; US, United States.

Table 25: Summary of OS comparison – loncastuximab tesirine vs Pola+BR (COTA US database)

Treatment (study)	N/ ESS	Events	Median OS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	145.0	97	9.53 (6.74, 11.47)	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (COTA database)	43.0	32	7.00 (4.95, 10.05)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; US, United States.

The KM plots for PFS for patients receiving loncastuximab tesirine for the unadjusted and weighted patient data compared with those receiving Pola+BR are shown in Figure 20. A small increase in PFS for loncastuximab tesirine patients was seen after weighting (Table 26). Loncastuximab tesirine was significantly favoured over Pola+BR, pre- and post-matching, with the 95% CI remaining <1.0 in both analyses. As with OS, it was noted that the proportional hazards assumption is likely to be violated, due to the cross-over of the curves during follow-up and therefore the HR estimates should be treated with caution.

Figure 20: Kaplan-Meier plot for PFS – loncastuximab tesirine matched to Pola+BR patient characteristics (COTA US database)

Abbreviations: Lonca, loncastuximab tesirine; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted; US, United States.

Table 26: Summary of PFS comparison – loncastuximab tesirine vs Pola+BR (COTA US database)

Treatment (study)	N/ ESS	Events	Median PFS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	145.0	73	4.93 (2.89, 8.31)	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (COTA database)	43.0	37	3.70 (2.59, 4.89)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; US, United States.

It was not clear which classification method was used to record response in the COTA dataset. Table 27 presents the unadjusted and weighted OR results for ORR. The ESS after weighting was identical to that reported in Table 25 and Table 26. Loncastuximab tesirine demonstrated similar odds of overall response when compared with Pola+BR, with the 95% CI for the odds ratio crossing 1.0 in all estimations (unweighted and weighted). There was almost no change in proportion of patients responding when receiving loncastuximab tesirine after weighting.

Table 27: Odds ratio for ORR – Loncastuzimab tesirine vs Pola+BR (COTA US database)

Outcome	Method	Lonca ORR, n/N (%)	Pola+BR ORR, n/N (%)	Lonca vs Pola+BR Odds ratio (95% CI)
ORR	Naïve comparison (unadjusted)	70/145 (48.3)	25/43 (58)	0.67 (0.33, 1.33)
	Weighted GLM model	[redacted]		[redacted]
	Weighted sandwich estimator			[redacted]

Abbreviations: CI, confidence interval; GLM, generalised linear model; Lonca, loncastuximab tesirine; ORR, objective response rate; Pola+BR, polatuzumab plus bendamustine plus rituximab; US, United States.

B.2.9.6.2. Efficacy outcome MAIC results: loncastuximab tesirine vs chemotherapy

One comparison was made to compare loncastuximab tesirine with chemotherapy.

CORAL extension studies

In the mixed chemotherapy population from the CORAL extension study, the oldest patient was 67.7 years old. This was considerably younger than the oldest patient in LOTIS-2, who was 94 years old. Therefore, 65 patients were excluded from the LOTIS-2 dataset as they were aged >67.7 years old, leaving a subgroup of 80 LOTIS-2 patients for inclusion in the comparative analyses.

Table 28 presents the LOTIS-2 (unadjusted and weighted) and the CORAL extension study patients' baseline characteristics for the three matching variables. Very limited characteristic data were available for the CORAL extension study and matching was only possible for male gender (%), patients undergoing previous ASCT (%) and IPI (<3 vs ≥3). The ESS after matching was n=78.1, which was only a 2% reduction from the original LOTIS-2 sample size (n=80)

demonstrating good overlap at baseline for the selected patient characteristics, prior to matching.

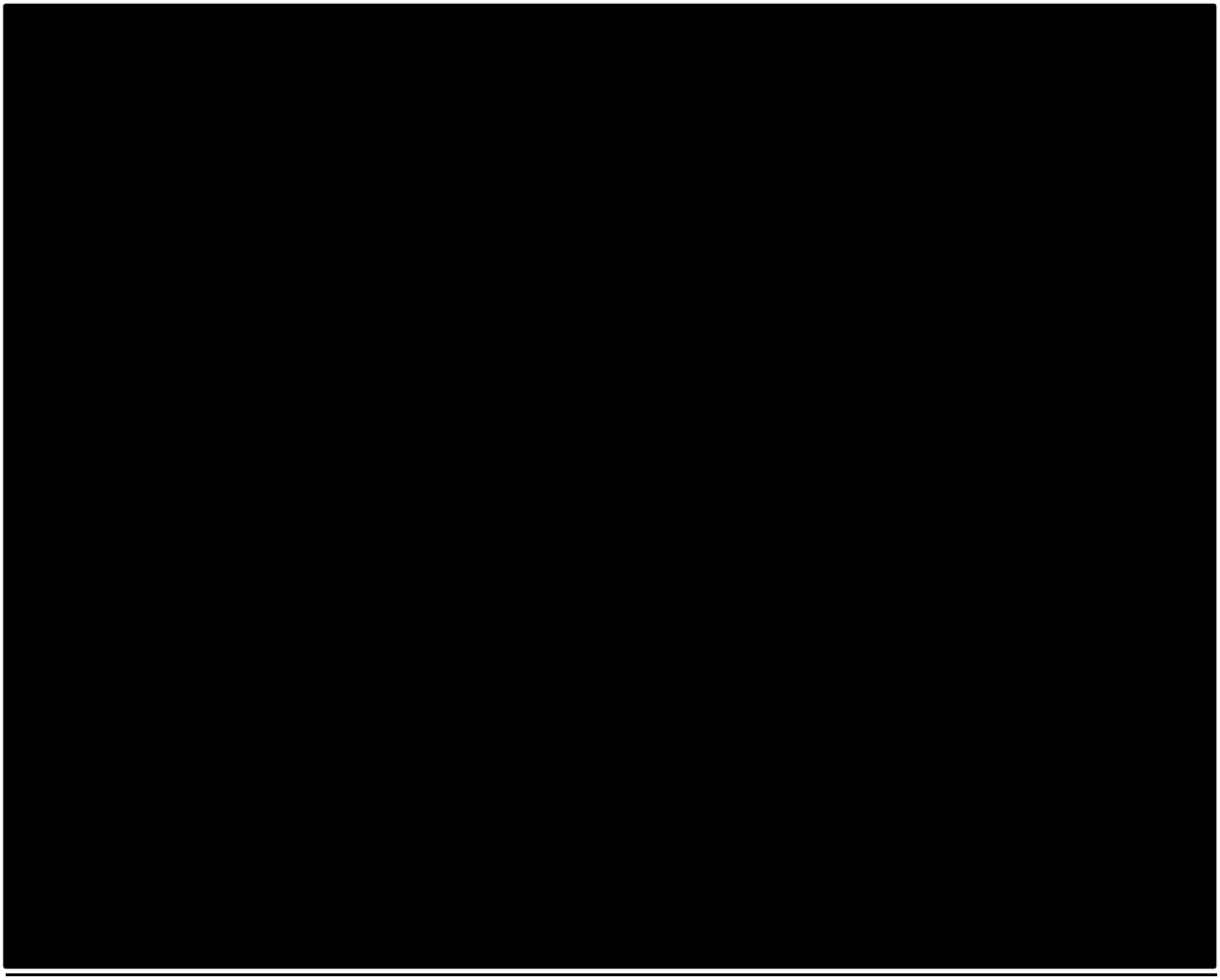
Table 28: Comparison of baseline characteristics loncastuximab tesirine (LOTIS-2) vs mixed chemotherapy (CORAL extension study)

Treatment (study)	N/ ESS	Male (%)	Prior ASCT (%)	IPI ≥3 (%)
Lonca unadjusted (LOTIS-2)	80.0	66.2	21.2	38.8
Lonca weighted (LOTIS-2)	78.1	63.0	27.0	39.0
Chemotherapy (CORAL extension)	266.0	63.0	27.0	39.0

Abbreviations: ASCT, autologous stem cell transplant; ESS, effective sample size; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; N, sample size.

The KM plots for OS for patients receiving loncastuximab tesirine for the unadjusted and weighted patient data are shown in Figure 21. A small improvement in OS for loncastuximab tesirine was seen after weighting (Table 29). OS was significantly improved for patients receiving loncastuximab tesirine compared with those receiving chemotherapy (HR < 1.0), across all comparisons. The results were noted to be very similar to those published in Hamadani 2022a (81), which were based on an older data cut than used for the current comparisons. The validity of the proportional hazards assumption was considered reasonable.

Figure 21: Kaplan-Meier plot for OS – loncastuximab tesirine matched to mixed chemotherapy patient characteristics (CORAL extension study)



Abbreviations: CT, chemotherapy; Lonca, loncastuximab tesirine; OS, overall survival; unadj, unadjusted.

Table 29: Summary of OS comparison – loncastuximab tesirine vs mixed chemotherapy (CORAL extension study)

Treatment (study)	N/ ESS	Events	Median OS, months (95% CI)	Lonca vs chemo HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	80.0	54	10.12 (6.14, 12.09)	0.69 (0.51, 0.94)
Lonca weighted (LOTIS-2)	78.1	52	10.12 (6.34, 13.63)	Standard: 0.67 (0.50, 0.89) Bootstrap: 0.70 (0.51, 0.86)
Chemotherapy (CORAL extension)	266.0	201	5.85 (4.80, 7.14)	Comparator

Abbreviations: chemo, chemotherapy; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival.

No PFS data were available from the CORAL extension study.

Different definitions were used for response in LOTIS-2 (2014 Lugano Classification (32)) compared with CORAL extensions studies (1999 IWG response criteria (82)), however it was assumed these would be comparable for measuring ORR. Table 30 presents the unadjusted and weighted OR results for ORR, the ESS after weighting was identical to that reported in Table 29. Applying a population-adjustment had minimal impact on the relative treatment effect and when considering the point estimate and 95% CI together, loncastuximab tesirine is likely to improve odds of response when compared with chemotherapy.

Table 30: Odds ratio for ORR – Loncastuzimab tesirine vs chemotherapy (CORAL extension study)

Outcome	Method	Lonca ORR, n/N (%)	Chemotherapy ORR, n/N (%)	Lonca vs chemo Odds ratio (95% CI)
ORR	Naïve comparison (unadjusted)	41/80 (51.3)	110/278 (39.6)	1.51 (0.91, 2.50)
	Weighted GLM model	40.7/79.1 (51.5)		1.53 (0.92, 2.53)
	Weighted sandwich estimator			1.53 (0.91, 2.54)

Abbreviations: chemo, chemotherapy; CI, confidence interval; GLM, generalised linear model; Lonca, loncastuximab tesirine; ORR, objective response rate.

B.2.9.6.3. Safety outcome MAIC results: loncastuximab tesirine vs Pola+BR

Only one study reported relevant safety data to inform a comparison between loncastuximab tesirine and Pola+BR.

GO29365 extension study

As with the efficacy outcome comparisons, 102 patients from LOTIS-2 were included in the comparison of safety for the GO29365 extension study.

One limitation with the data available from the GO29365 extension study was that AEs were only available for the second- or later-line population in the GO29365 extension study, compared with third- or later-line in LOTIS-2. It was assumed that the incidence of AEs would be similar enough across treatment lines to allow a comparison of these data.

For safety outcomes, age and ECOG PS were considered the most important variables that influence patient outcome in line with the clinical opinion of medical experts of the submitting company. As these characteristics were incorporated into efficacy comparisons using IPI score, for consistency, IPI score was again used to adjust when comparing safety outcomes. Table 31 presents the LOTIS-2 (unadjusted and weighted) and the GO29365 extension study baseline characteristics for the matching variables, applicable to all safety outcome comparisons. The ESS after matching was n=[redacted], suggesting [redacted] at baseline prior to matching for the IPI score at baseline.

Table 31: Comparison of baseline characteristics loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study) for safety outcomes

Treatment (study)	N/ ESS	IPI ≥3 (%)
Lonca unadjusted (LOTIS-2)	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	62.0

Abbreviations: ESS, effective sample size; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Analyses were conducted for outcomes available from the GO29365 extension study, including treatment discontinuation due to AEs as primary reason for discontinuation; fatal AEs; Grade 3-4: neutropenia, thrombocytopenia, anaemia, infections and infestations and any Grade 3-4 AEs; SAEs: febrile neutropenia, sepsis, pneumonia, pyrexia and any SAE. In the unadjusted comparison, compared with Pola+BR, loncastuximab tesirine was associated with significantly lower odds of Grade 3-4 infections and infestations, and significantly lower odds for SAEs of febrile neutropenia, sepsis, pneumonia, pyrexia and any SAE (Table 32). For all other outcomes, the point estimates for the ORs favoured loncastuximab tesirine (OR < 1.0), however this was not a significant benefit as the 95% CI crossed 1.0.

Table 32: Comparison of safety outcomes in the unadjusted population: loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study)

Outcome	Lonca, n (%) (N=102)	Pola+BR, n (%) (N=151)	Lonca vs Pola+BR Odds ratio (95% CI)
Discontinuations due to AEs (primary reason)	[redacted]	40 (26.5)	[redacted]
AE Grade 3-4			
Neutropenia	[redacted]	49 (32.5)	[redacted]
Thrombocytopenia	[redacted]	31 (20.5)	[redacted]
Anaemia	[redacted]	19 (12.6)	[redacted]
Infections and infestations	[redacted]	33 (21.9)	[redacted]
Any AE, Grade 3-4	[redacted]	122 (80.8)	[redacted]
SAEs, any grade			
Febrile neutropenia	[redacted]	15 (9.9)	[redacted]
Sepsis	[redacted]	15 (9.9)	[redacted]
Pneumonia	[redacted]	14 (9.3)	[redacted]
Pyrexia	[redacted]	13 (8.6)	[redacted]
Any serious AE	[redacted]	86 (57)	[redacted]
Fatal AEs	[redacted]	17 (11.3)	[redacted]

Text in bold and italics indicates significantly lower odds for loncastuximab tesirine
Abbreviations: AE, adverse event; Lonca, loncastuximab tesirine; Pola+BR, polatuzumab plus bendamustine plus rituximab; SAE, serious adverse event.

There was little difference in the numerical values of the odds ratio when the population-adjustment was applied, with all results that were significantly better with loncastuximab tesirine, remaining significantly better in the weighted results (Table 33).

Table 33: Comparison of safety outcomes in the weighted population: loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study)

Outcome	Lonca, n (%) (N=102)	Pola+BR, n (%) (N=151)	Lonca vs Pola+BR Odds ratio (standard 95% CI)	Lonca vs Pola+BR Odds ratio (sandwich estimator 95% CI)
Discontinuations due to AEs (primary reason)	[redacted]	40 (26.5)	[redacted]	[redacted]
AE Grade 3-4				
Neutropenia	[redacted]	49 (32.5)	[redacted]	[redacted]

Outcome	Lonca, n (%) (N=102)	Pola+BR, n (%) (N=151)	Lonca vs Pola+BR Odds ratio (standard 95% CI)	Lonca vs Pola+BR Odds ratio (sandwich estimator 95% CI)
Thrombocytopenia	[redacted]	31 (20.5)	[redacted]	[redacted]
Anaemia	[redacted]	19 (12.6)	[redacted]	[redacted]
Infections and infestations	[redacted]	33 (21.9)	[redacted]	[redacted]
Any AE, Grade 3-4	[redacted]	122 (80.8)	[redacted]	[redacted]
SAEs, any grade				
Febrile neutropenia	[redacted]	15 (9.9)	[redacted]	[redacted]
Sepsis	[redacted]	15 (9.9)	[redacted]	[redacted]
Pneumonia	[redacted]	14 (9.3)	[redacted]	[redacted]
Pyrexia	[redacted]	13 (8.6)	[redacted]	[redacted]
Any serious AE	[redacted]	86 (57)	[redacted]	[redacted]
Fatal AEs	[redacted]	17 (11.3)	[redacted]	[redacted]

Text in bold and italics indicates significantly lower odds for loncastuximab tesirine
Abbreviations: AE, adverse event; Lonca, loncastuximab tesirine; Pola+BR, polatuzumab plus bendamustine plus rituximab; SAE, serious adverse event.

B.2.9.6.4. Safety outcome MAIC results: loncastuximab tesirine vs chemotherapy

No relevant chemotherapy data were available to enable a comparison of safety outcomes between loncastuximab tesirine and chemotherapy.

B.2.9.7. Uncertainties in the indirect and mixed treatment comparisons

The above analyses are associated with uncertainty due to trial heterogeneity and the differences in prognostic factors available from each study, along with small sample sizes for some comparisons.

In addition, an unanchored MAIC assumes that the differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and treatment effect modifiers, which sometimes can be too strong an assumption. Matching adjustments were limited to data reported in the comparator trials and that collected in LOTIS-2. Only the GO29365 extension study reported the proportion of patients who were last line refractory and even then, the definition did not match exactly with LOTIS-2. It was not possible

to adjust for this covariate across any other comparison. In addition, it was noted that for the CORAL extension study, only one key confounding variable was available (IPI), with very limited baseline characteristics reported and consequently, variables that were available were included in the analysis (male gender and prior ASCT), even though these were not identified as key variables of interest.

For the Pola+BR comparisons, in the absence of KM data for OS and PFS in the third- or later-line subgroup from the GO29365 extension study, a crude estimate of the HRs were calculated from the median survival times and number of events.

For the comparison with chemotherapy from the CORAL extensions studies, the relative treatment estimates are considered to be conservative for loncastuximab tesirine. Patients in the CORAL extension were considered to be fitter than those in LOTIS-2 as they were eligible for ASCT and a proportion of those who did not receive ASCT were in response (of 203 patients, 26 were in CR and 30 were in PR) at withdrawal from the initial CORAL study. In addition, worse efficacy is expected in later lines of therapy and therefore, the comparison of OS and ORR between LOTIS-2 and the CORAL extension study may have led to an underestimation of the relative efficacy of loncastuximab tesirine vs chemotherapy. This is as a consequence of the fact that only third-line patients were included in the CORAL extension datasets, while LOTIS-2 also included fourth- and later-line patients (cf Table 16). Despite this potential bias, loncastuximab tesirine demonstrated higher ORR and longer median OS.

In addition, a difference in the definition of OS was noted between the LOTIS-2 and CORAL extension studies. For the CORAL extension studies, OS was defined as the time from relapse post-ASCT (in patients who had ASCT as the most recent therapy) or the time from failure of CORAL induction therapy to death from any cause. In the LOTIS-2 trial, OS was defined as time from loncastuximab tesirine initiation to death from any cause and patients were censored at the earliest of either their last date of assessment or if they received CAR-T therapy, the date they received CAR-T therapy. Therefore, some patients in CORAL will have died or were censored shortly after failure on induction therapy. In contrast, all patients included in LOTIS-2 must have survived between relapse on prior therapy and trial enrolment, and equivalent patients in CORAL surviving to reach third-line treatment will have longer survival time (in months) than had they been enrolled in LOTIS-2.

In the absence of more robust comparative studies, these data provide a directional indication of the relative benefit of loncastuximab tesirine with respect to comparators. The unanchored MAIC approach is helpful given data limitations for the treatments that prevented construction of network meta-analyses for the outcomes of interest.

B.2.10. Adverse reactions

In the all-treated population, the median treatment duration was 45.0 days (range: 1 to 351 days). The median total dose administered was 30,000 µg (range: 7,500 to 112,500 µg), and the median total weight-adjusted dose was 375.68 µg/kg (range: 122.4 to 1264.5 µg/kg). The median average weight-adjusted dose per cycle was 113.50 µg/kg (range: 51.7 to 160.6 µg/kg). The median number of treatment cycles was 3.0 (range: 1 to 15).

B.2.10.1. Summary of treatment-emergent adverse events

An overall summary of TEAEs is presented in Table 34.

Of the 145 patients in the all-treated population, 143 patients (98.6%) had at least one TEAE; 117 patients (80.7%) had at least one TEAE related to loncastuximab tesirine; and 105 patients (72.4%) had at least one TEAE of Grade ≥3. Fifty-seven patients (39.3%) had at least one serious TEAE; eight patients (5.5%) had a TEAE leading to a fatal outcome; and 34 patients (23.4%) had a TEAE leading to withdrawal of treatment. Seven patients (4.8%) had an infusion-related reaction (6 April 2020 data cut).

Data from the 1 March 2021 data cut are reported in Table 34. Data were consistent with those from the 6 April 2020 data cut.

As of final data cut off ([redacted]), all-grade TEAEs [redacted] (60).

Table 34: Overall summary of TEAEs (all-treated population)†

Data cut	6 April 2020	1 March 2021
Population	**All-treated population (N=145)**	**All-treated population (N=145)**
Number of TEAEs	1761	N/A
Patients with any TEAE	143 (98.6)	143 (98.6)
Patients with any Grade 3 or higher TEAE	105 (72.4)	107 (73.8)
Patients with any TEAE related to lonca	117 (80.7)	118 (81.4)
Patients with any TEAE leading to lonca dose delay or reduction	75 (51.7)	75 (51.7)
Patients with any TEAE leading to lonca withdrawal	34 (23.4)	36 (24.8)
Patients with any serious TEAE	57 (39.3)	57 (39.3)
Patients with any TEAE with fatal outcome	8 (5.5)	8 (5.5)
Patients with infusion-related reaction	7 (4.8)	N/A

Source: Sobi 2020 LOTIS-2 CSR (66); Zinzani 2021 LOTIS-2 (1 March 2021) (64).
†"Related" was defined as possibly related, probably related or related including missing relationship. Adverse events were graded using CTCAE version 4.0. Only TEAEs were summarized. For each category (except for number of TEAEs), patients were included only once, even if they experienced multiple events in that category.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; lonca, loncastuximab tesirine; N/A, not available; TEAE, treatment-emergent adverse event.

B.2.10.1.1. Treatment-emergent adverse events by system organ class

Overall, 143 of 145 (98.6%) patients experienced at least one TEAE. The SOCs with the highest incidence (≥10%) of TEAEs are summarised in Table 35. The highest incidence of TEAEs by SOC occurred in General Disorders and Administrative Site Conditions (66.2%), Investigations (56.6%), Blood and Lymphatic Tissue Disorders (56.6%), Metabolism and Nutrition Disorders (53.1%), and Gastrointestinal Disorders (53.1%).

Table 35: Most common (≥10%) TEAEs by System Organ Class (all-treated population)†

System organ class	All-treated population (N=145)
Data cut 6 April 2020	
Patients with any TEAE	143 (98.6)
General disorders and administration site conditions	96 (66.2)
Investigations	82 (56.6)
Blood and lymphatic tissue disorders	82 (56.6)
Metabolism and nutrition disorders	77 (53.1)
Gastrointestinal disorders	77 (53.1)
Skin and subcutaneous tissue disorders	68 (46.9)
Respiratory, thoracic and mediastinal disorders	60 (41.4)
Infections and infestations	48 (33.1)
Musculoskeletal and connective tissue disorders	46 (31.7)
Nervous system disorders	40 (27.6)
Vascular disorders	29 (20.0)
Psychiatric disorders	28 (19.3)
Cardiac disorders	19 (13.1)
Eye disorders	19 (13.1)
Injury, poisoning and procedural complications	16 (11.0)

Source: Sobi 2020 LOTIS-2 CSR (66).
†Adverse events were coded using MedDRA version 22.0. Only TEAEs were summarized. For each System Organ Class, patients were included only once.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

B.2.10.1.2. Treatment-emergent adverse events by preferred term

The most common (≥10%) of TEAEs by preferred term and in decreasing order of incidence are summarised in Table 36.

The most common (≥10% overall) of TEAEs by preferred term were GGT increased (40.7%), neutropenia (39.3%), thrombocytopenia (33.1%), fatigue (27.6%), anaemia (26.2%), nausea (23.4%), cough (22.1%), blood alkaline phosphatase increased (20.0%), oedema peripheral (20.0%), pyrexia (19.3%), diarrhea (17.2%), ALT increased (15.9%), AST increased (15.9%), hypophosphatemia (15.9%), decreased appetite (15.2%), hypokalemia (15.2%), leukopenia (14.5%), hypomagnesemia (13.8%), rash (13.1%), vomiting (13.1%), pruritus (12.4%), constipation (11.7%), dyspnoea (11.7%), abdominal pain (11.0%), insomnia (11.0%), erythema (10.3%), headache (10.3%), photosensitivity reaction (10.3%), and pleural effusion (10.3%).

Table 36: Most common (≥10% Overall) TEAEs by preferred term (all-treated population)[†]

Preferred term	All-treated population (N=145)
Data cut 6 April 2020	
Patients with any TEAE	143 (98.6)
Gamma-glutamyltransferase increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anaemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Blood alkaline phosphatase increased	29 (20.0)
Oedema peripheral	29 (20.0)
Pyrexia	28 (19.3)
Diarrhea	25 (17.2)
Alanine aminotransferase increased	23 (15.9)
Aspartate aminotransferase increased	23 (15.9)
Hypophosphataemia	23 (15.9)
Decreased appetite	22 (15.2)
Hypokalaemia	22 (15.2)
Leukopenia	21 (14.5)
Hypomagnesaemia	20 (13.8)
Rash	19 (13.1)
Vomiting	19 (13.1)
Pruritus	18 (12.4)
Constipation	17 (11.7)
Dyspnoea	17 (11.7)
Abdominal pain	16 (11.0)
Insomnia	16 (11.0)
Erythema	15 (10.3)
Headache	15 (10.3)
Photosensitivity reaction	15 (10.3)
Pleural effusion	15 (10.3)

Source: Sobi 2020 LOTIS-2 CSR (66).
[†]Adverse events were coded using MedDRA version 22.0. Only TEAEs were summarized. For each preferred term, patients were included only once.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

B.2.10.1.3. Treatment-emergent adverse events by severity

Treatment-emergent adverse events by severity experienced by 143 patients (98.6%) are summarised in Table 37.

Table 37: Treatment-emergent adverse events by severity

Treatment-emergent adverse events	Population with TEAEs (N=143)
Data cut 6 April 2020	
Maximum severity Grade 1 TEAEs	7 (4.8%)
Maximum severity Grade 2 TEAEs	31 (21.4%)
Maximum severity Grade 3 TEAEs	61 (42.1%)
Maximum severity Grade 4 TEAEs	36 (24.8%)
Maximum severity Grade 5 TEAEs	8 (5.5%)

Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: TEAE, treatment-emergent adverse event.

Of the 145 patients, there were 105 patients (72.4%) who experienced at least one TEAE of Grade ≥3. The most common (≥5% overall) TEAEs that were Grade ≥3 were; neutropenia (25.5%), thrombocytopenia (17.9%), GGT increased (16.6%), anaemia (10.3%), leukopenia (9.0%), hypophosphatemia (5.5%), and lymphopenia (5.5%) (Table 38).

Table 38: Most common (≥5%) Grade 3 or higher TEAEs by preferred term (all-treated population)†

Preferred term	All-treated population (N=145)
6 April 2020 data cut	
Patients with any TEAE of Grade ≥3	105 (72.4)
Neutropenia	37 (25.5)
Thrombocytopenia	26 (17.9)
Gamma-glutamyltransferase increased	24 (16.6)
Anaemia	15 (10.3)
Leukopenia	13 (9.0)
Hypophosphataemia	8 (5.5)
Lymphopenia	8 (5.5)

Source: Sobi 2020 LOTIS-2 CSR (66).
†Adverse events are coded using MedDRA version 22.0 and graded using CTCAE version 4.0. Only TEAEs are summarised. For each preferred term, patients are included only once.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

B.2.10.1.4. Treatment-emergent adverse events by relationship to study drug

Table 39 presents an overall summary of treatment-related TEAEs.

Of the 145 patients, 117 patients (80.7%) experienced at least one treatment-related TEAE. There were 74 patients (51.0%) who experienced a treatment-related TEAE of Grade ≥3 and 22 patients (15.2%) who experienced a treatment-related SAE. There were 6 patients (4.1%) who experienced a treatment-related TEAE associated with an infusion-related reaction. There were no treatment-related TEAEs that led to a fatal outcome.

Table 39: Overall summary of study drug related TEAEs (all-treated population)[†]

Preferred term	All-treated population (N=145)
Data cut 6 April 2020	
Number of related TEAEs	846
Patients with any related TEAEs	117 (80.7)
Patients with any Grade 3 or higher related TEAEs	74 (51.0)
Patients with any related TEAE leading to ADCT-402 dose delay or reduction	63 (43.4)
Patients with any related TEAE leading to ADCT-402 withdrawal	24 (16.6)
Patients with any serious related TEAE	22 (15.2)
Patients with any related TEAE with fatal outcome	0
Patients with any related TEAE with infusion-related reaction	6 (4.1)

Source: Sobi 2020 LOTIS-2 CSR (66).
[†]"Related" defined as possibly related, probably related or related including missing relationship Adverse events were graded using CTCAE v4.0. Only treatment-emergent adverse events were summarised. For each category (except for number of TEAEs), patients were included only once, even if they experienced multiple events in that category.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

The most common (≥10% overall) treatment-related TEAEs by SOC, preferred term, and maximum CTCAE grade are summarised in Table 40.

The most common (≥10% overall) treatment-related TEAEs by preferred term were GGT increased (34.5%), neutropenia (28.3%), fatigue (19.3%), blood alkaline phosphatase increased (18.6%), thrombocytopenia (17.9%), nausea (16.6%), oedema peripheral (13.8%), anaemia (13.1%), leukopenia (13.1%), AST increased (13.1%), rash (12.4%), ALT increased (11.7%), and photosensitivity reaction (10.3%).

Table 40: Most common (≥10%) study drug related TEAEs by system organ class, preferred term and maximum CTCAE grade (all-treated population)

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Data cut 6 April 2020							
Patients with any study drug related TEAE	16 (11.0)	27 (18.6)	45 (31.0)	29 (20.0)	0	0	117 (80.7)
Blood and lymphatic system disorders	5 (3.4)	9 (6.2)	17 (11.7)	25 (17.2)	0	0	56 (38.6)
Neutropenia	2 (1.4)	10 (6.9)	8 (5.5)	21 (14.5)	0	0	41 (28.3)
Thrombocytopenia	5 (3.4)	5 (3.4)	10 (6.9)	6 (4.1)	0	0	26 (17.9)
Anaemia	2 (1.4)	8 (5.5)	9 (6.2)	0	0	0	19 (13.1)
Leukopenia	3 (2.1)	4 (2.8)	8 (5.5)	4 (2.8)	0	0	19 (13.1)
Gastrointestinal disorders	34 (23.4)	6 (4.1)	3 (2.1)	0	0	0	43 (29.7)
Nausea	19 (13.1)	5 (3.4)	0	0	0	0	24 (16.6)
General disorders and administration site conditions	36 (24.8)	20 (13.8)	5 (3.4)	0	0	0	61 (42.1)
Fatigue	18 (12.4)	10 (6.9)	0	0	0	0	28 (19.3)
Oedema peripheral	14 (9.7)	4 (2.8)	2 (1.4)	0	0	0	20 (13.8)
Investigations	16 (11.0)	21 (14.5)	21 (14.5)	3 (2.1)	0	0	61 (42.1)
Gamma-glutamyltransferase increased	10 (6.9)	20 (13.8)	18 (12.4)	2 (1.4)	0	0	50 (34.5)
Blood alkaline phosphatase increased	20 (13.8)	7 (4.8)	0	0	0	0	27 (18.6)
Aspartate aminotransferase increased	13 (9.0)	5 (3.4)	1 (0.7)	0	0	0	19 (13.1)
Alanine aminotransferase increased	9 (6.2)	4 (2.8)	4 (2.8)	0	0	0	17 (11.7)
Skin and subcutaneous tissue disorders	35 (24.1)	20 (13.8)	6 (4.1)	0	0	0	61 (42.1)
Rash	12 (8.3)	5 (3.4)	1 (0.7)	0	0	0	18 (12.4)
Photosensitivity reaction	7 (4.8)	5 (3.4)	3 (2.1)	0	0	0	15 (10.3)

Source: Sobi 2020 LOTIS-2 CSR (66).
[†]Related is defined as possibly related, probably related, or related including missing relationship. Adverse events are coded using MedDRA version 22.0. Only TEAEs are summarised. For each preferred term, patients are included only once.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

B.2.10.2. Death and other serious adverse events

B.2.10.2.1. Deaths

Table 41 summarises all deaths during the study and within 30 days of the last dose of study drug without taking new anticancer therapy. A total of 77 patients (53.1%) died during the study. Of these, 60 patients (41.4%) died due to progression of the underlying DLBCL (disease progression), and 17 patients (11.7%) died due to other reasons. There were 10 deaths within 30 days of last dose (five deaths due to disease progression and five deaths due to other reasons).

Table 41: Summary of deaths (all-treated population)

	All-treated population (N=145)
Death during study	77 (53.1)
Disease progression	60 (41.4)
Other	17 (11.7)
Death within 30 days of last dose without taking new anticancer therapy	10 (6.9)
Disease progression	5 (3.4)
Other	5 (3.4)

Source: Sobi 2020 LOTIS-2 CSR (66).

Treatment-emergent adverse events with a fatal outcome

Table 42 summarises TEAEs with a fatal outcome by SOC, preferred term and maximum CTCAE grade. There were eight patients (5.5%) with TEAEs leading to a fatal outcome, none of which was considered related to loncastuximab tesirine. TEAEs leading to a fatal outcome in one patient each were DLBCL, sepsis, small intestinal perforation, haemoptysis, septic shock, pneumonia, disease progression, and acute kidney injury (Table 42). In addition, there were two patients with a nontreatment-emergent AE leading to death that was considered by the investigator to be possibly related to loncastuximab tesirine; one patient with acute respiratory distress syndrome and one patient with interstitial lung disease.

Table 42: TEAEs with fatal outcome by system organ class, preferred term, and maximum CTCAE grade (all-treated population)[†]

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Patients with any fatal TEAE	0	0	0	0	8 (5.5)	0	8 (5.5)
Gastrointestinal disorders	0	0	0	0	1 (0.7)	0	1 (0.7)
Small intestinal perforation	0	0	0	0	1 (0.7)	0	1 (0.7)
General disorders and administration site conditions	0	0	0	0	1 (0.7)	0	1 (0.7)
Disease progression	0	0	0	0	1 (0.7)	0	1 (0.7)
Infections and infestations	0	0	0	0	3 (2.1)	0	3 (2.1)
Pneumonia	0	0	0	0	1 (0.7)	0	1 (0.7)
Sepsis	0	0	0	0	1 (0.7)	0	1 (0.7)
Septic shock	0	0	0	0	1 (0.7)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (0.7)	0	1 (0.7)
Diffuse large B-cell lymphoma	0	0	0	0	1 (0.7)	0	1 (0.7)
Renal and urinary disorders	0	0	0	0	1 (0.7)	0	1 (0.7)
Acute kidney injury	0	0	0	0	1 (0.7)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.7)	0	1 (0.7)
Haemoptysis	0	0	0	0	1 (0.7)	0	1 (0.7)

Source: Sobi 2020 LOTIS-2 CSR (66).

[†]Adverse events are coded using MedDRA version 22.0 and graded using CTCAE v4.0. Only treatment-emergent adverse events are summarised. For each system organ class and preferred term, patients are included only once at the maximum severity. AE sorting is done by SOC, use alphabetical order, within a SOC, sort PTs by decreasing frequency order.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

B.2.10.2.2. Other serious adverse events

Treatment-emergent serious adverse events

Table 43 summarises serious TEAEs by SOC, preferred term and maximum CTCAE Grade. Of the 145 participants, 57 (39.3%) experienced at least one treatment-emergent SAE. There were eight participants with treatment-emergent SAEs leading to a fatal outcome.

The most common (>5% overall) SOCs with treatment-emergent SAEs were infection and infestation (12 patients; 8.3%), general disorders and administrative site conditions (11 participants; 7.6%), gastrointestinal disorders (nine participants; 6.2%), metabolism and nutrition disorders (eight participants; 5.5%), and respiratory, thoracic and mediastinal disorders (eight participants; 5.5%) (Table 43).

There were no treatment-emergent SAEs by preferred term that occurred in ≥5% of patients. Serious TEAEs that were experienced by ≥2% of patients were hypercalcemia (4.1%), febrile neutropenia (3.4%), pyrexia (2.8%), abdominal pain (2.1%), and pleural effusion (2.1%).

Table 43: Serious TEAEs by system organ class, preferred term and maximum CTCAE grade (all-treated population)†

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Patients with any serious TEAE	2 (1.4)	6 (4.1)	34 (23.4)	7 (4.8)	8 (5.5)	0	57 (39.3)
Blood and lymphatic system disorders	0	0	6 (4.1)	1 (0.7)	0	0	7 (4.8)
Febrile neutropenia	0	0	5 (3.4)	0	0	0	5 (3.4)
Anaemia	0	0	2 (1.4)	0	0	0	2 (1.4)
Neutropenia	0	0	0	1 (0.7)	0	0	1 (0.7)
Cardiac disorders	0	0	2 (1.4)	1 (0.7)	0	0	3 (2.1)
Pericardial effusion	0	0	1 (0.7)	1 (0.7)	0	0	2 (1.4)
Pericarditis	0	0	1 (0.7)	0	0	0	1 (0.7)
Gastrointestinal disorders	0	0	6 (4.1)	2 (1.4)	1 (0.7)	0	9 (6.2)
Abdominal pain	0	0	2 (1.4)	1 (0.7)	0	0	3 (2.1)
Ascites	0	0	1 (0.7)	0	0	0	1 (0.7)
Diarrhoea	0	0	1 (0.7)	0	0	0	1 (0.7)
Dysphagia	0	0	1 (0.7)	0	0	0	1 (0.7)
Intestinal obstruction	0	0	0	1 (0.7)	0	0	1 (0.7)
Small intestinal obstruction	0	0	1 (0.7)	0	0	0	1 (0.7)
Small intestinal perforation	0	0	0	0	1 (0.7)	0	1 (0.7)
General disorders and administration site conditions	2 (1.4)	3 (2.1)	5 (3.4)	0	1 (0.7)	0	11 (7.6)
Pyrexia	2 (1.4)	1 (0.7)	1 (0.7)	0	0	0	4 (2.8)
Non-cardiac chest pain	0	1 (0.7)	1 (0.7)	0	0	0	2 (1.4)
Disease progression	0	0	0	0	1 (0.7)	0	1 (0.7)
Face oedema	0	0	1 (0.7)	0	0	0	1 (0.7)
Fatigue	0	1 (0.7)	0	0	0	0	1 (0.7)
Oedema peripheral	0	0	1 (0.7)	0	0	0	1 (0.7)
Pain	0	0	1 (0.7)	0	0	0	1 (0.7)
Infections and infestations	0	2 (1.4)	7 (4.8)	0	3 (2.1)	0	12 (8.3)

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Pneumonia	0	0	1 (0.7)	0	1 (0.7)	0	2 (1.4)
Escherichia sepsis	0	0	1 (0.7)	0	0	0	1 (0.7)
Influenza	0	1 (0.7)	0	0	0	0	1 (0.7)
Klebsiella infection	0	0	1 (0.7)	0	0	0	1 (0.7)
Lung infection	0	0	1 (0.7)	0	0	0	1 (0.7)
Metapneumovirus infection	0	0	1 (0.7)	0	0	0	1 (0.7)
Pneumonia fungal	0	1 (0.7)	0	0	0	0	1 (0.7)
Rhinovirus infection	0	0	1 (0.7)	0	0	0	1 (0.7)
Sepsis	0	0	0	0	1 (0.7)	0	1 (0.7)
Septic shock	0	0	0	0	1 (0.7)	0	1 (0.7)
Soft tissue infection	0	0	1 (0.7)	0	0	0	1 (0.7)
Urinary tract infection bacterial	0	0	1 (0.7)	0	0	0	1 (0.7)
Injury, poisoning and procedural complications	0	0	1 (0.7)	0	0	0	1 (0.7)
Fall	0	0	1 (0.7)	0	0	0	1 (0.7)
Metabolism and nutrition disorders	0	0	6 (4.1)	2 (1.4)	0	0	8 (5.5)
Hypercalcaemia	0	0	4 (2.8)	2 (1.4)	0	0	6 (4.1)
Dehydration	0	0	1 (0.7)	0	0	0	1 (0.7)
Hyponatraemia	0	0	1 (0.7)	0	0	0	1 (0.7)
Musculoskeletal and connective tissue disorders	0	0	1 (0.7)	0	0	0	1 (0.7)
Neck pain	0	0	1 (0.7)	0	0	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (0.7)	0	1 (0.7)
Diffuse large B-cell lymphoma	0	0	0	0	1 (0.7)	0	1 (0.7)
Nervous system disorders	0	2 (1.4)	2 (1.4)	1 (0.7)	0	0	5 (3.4)
Headache	0	2 (1.4)	0	0	0	0	2 (1.4)
Facial nerve disorder	0	0	1 (0.7)	0	0	0	1 (0.7)
Psychomotor skills impaired	0	0	0	1 (0.7)	0	0	1 (0.7)

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Syncope	0	0	1 (0.7)	0	0	0	1 (0.7)
Psychiatric disorders	0	2 (1.4)	2 (1.4)	0	0	0	4 (2.8)
Mental status changes	0	2 (1.4)	0	0	0	0	2 (1.4)
Confusional state	0	0	1 (0.7)	0	0	0	1 (0.7)
Intentional self-injury	0	0	1 (0.7)	0	0	0	1 (0.7)
Renal and urinary disorders	0	0	3 (2.1)	0	1 (0.7)	0	4 (2.8)
Acute kidney injury	0	0	1 (0.7)	0	1 (0.7)	0	2 (1.4)
Hydronephrosis	0	0	1 (0.7)	0	0	0	1 (0.7)
Ureterolithiasis	0	0	1 (0.7)	0	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	2 (1.4)	5 (3.4)	0	1 (0.7)	0	8 (5.5)
Pleural effusion	0	1 (0.7)	2 (1.4)	0	0	0	3 (2.1)
Cough	0	0	1 (0.7)	0	0	0	1 (0.7)
Dyspnoea	0	0	1 (0.7)	0	0	0	1 (0.7)
Haemoptysis	0	0	0	0	1 (0.7)	0	1 (0.7)
Pleuritic pain	0	1 (0.7)	0	0	0	0	1 (0.7)
Pneumonitis	0	0	1 (0.7)	0	0	0	1 (0.7)
Vascular disorders	0	1 (0.7)	2 (1.4)	1 (0.7)	0	0	4 (2.8)
Deep vein thrombosis	0	1 (0.7)	0	0	0	0	1 (0.7)
Embolism	0	1 (0.7)	0	0	0	0	1 (0.7)
Haematoma	0	0	0	1 (0.7)	0	0	1 (0.7)
Hypotension	0	0	1 (0.7)	0	0	0	1 (0.7)
Thrombosis	0	0	1 (0.7)	0	0	0	1 (0.7)

Source: Sobi 2020 LOTIS-2 CSR (66).

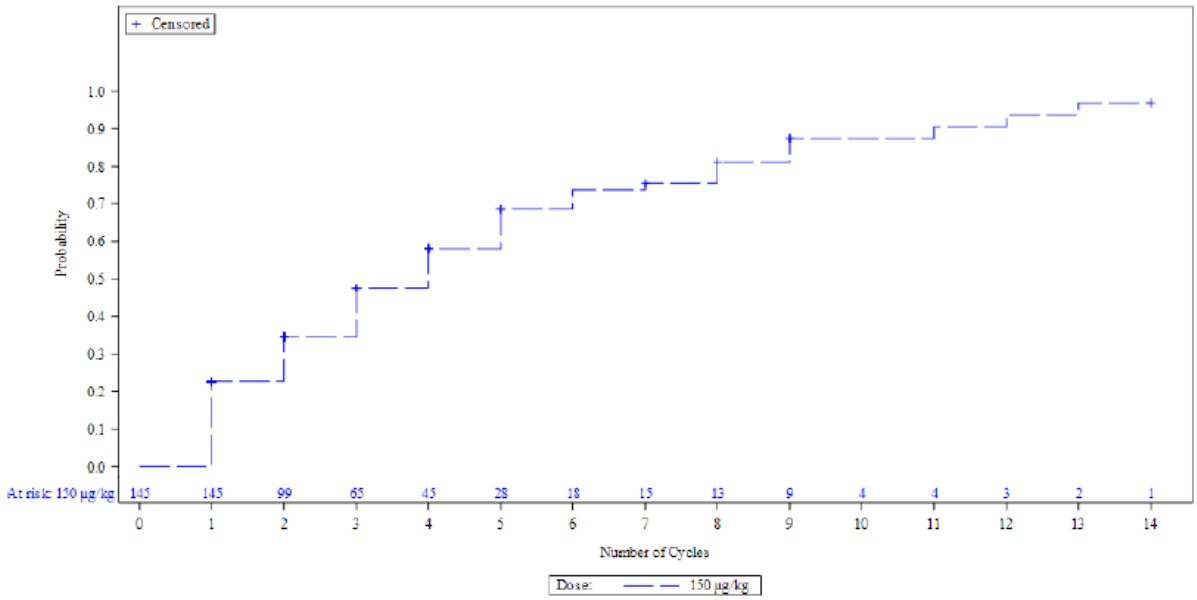
[†]Adverse events were coded using MedDRA version 22.0 and graded using CTCAE v4.0. Only treatment-emergent adverse events were summarised. For each system organ class and preferred term, patients were included only once at the maximum severity. AE sorting was done by SOC, use alphabetical order, within a SOC, sort PTs by decreasing frequency order.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

B.2.10.2.3. Other significant adverse events leading to dose modifications

Dose modifications due to TEAEs included TEAEs leading to loncastuximab tesirine withdrawal, dose delay, dose reduction, or infusion interruption. Figure 22 presents a Kaplan-Meier plot of time to first AE leading to dose modification.

Figure 22: Kaplan-Meier plot of time to first AE leading to dose modification analysis (all-treated population) (6 April 2020 data cut)



Source: Sobi 2020 LOTIS-2 CSR (66).
Abbreviations: AE, adverse event.

Treatment-emergent adverse events leading to drug withdrawal

Table 44 summarises TEAEs leading to loncastuximab tesirine withdrawal by SOC, preferred term and maximum CTCAE grade.

Of 145 patients, 34 participants (23.4%) experienced at least one TEAE leading to loncastuximab tesirine withdrawal. The most common (≥2% overall) TEAEs leading to loncastuximab tesirine withdrawal were GGT increased (15 patients; 10.3%), oedema peripheral (four participants; 2.8%), localised oedema (three participants; 2.1%), and pleural effusion (three participants; 2.1%).

Table 44: TEAEs leading to drug withdrawal by SOC, PT, and maximum CTCAE grade (all-treated population)[†]

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Data cut 6 April 2020							
Patients with any treatment withdrawal TEAE	2 (1.4)	13 (9.0)	13 (9.0)	2 (1.4)	4 (2.8)	0	34 (23.4)
Blood and lymphatic system disorders	0	0	2 (1.4)	1 (0.7)	0	0	3 (2.1)
Thrombocytopenia	0	0	1 (0.7)	1 (0.7)	0	0	2 (1.4)
Neutropenia	0	0	1 (0.7)	0	0	0	1 (0.7)
Cardiac disorders	0	0	1 (0.7)	1 (0.7)	0	0	2 (1.4)
Pericardial effusion	0	0	1 (0.7)	1 (0.7)	0	0	2 (1.4)
Gastrointestinal disorders	0	0	1 (0.7)	0	1 (0.7)	0	2 (1.4)
Small intestinal obstruction	0	0	1 (0.7)	0	0	0	1 (0.7)
Small intestinal perforation	0	0	0	0	1 (0.7)	0	1 (0.7)
General disorders and administration site conditions	2 (1.4)	3 (2.1)	0	0	1 (0.7)	0	6 (4.1)
Oedema peripheral	1 (0.7)	3 (2.1)	0	0	0	0	4 (2.8)
Localised oedema	2 (1.4)	1 (0.7)	0	0	0	0	3 (2.1)
Face oedema	1 (0.7)	1 (0.7)	0	0	0	0	2 (1.4)
Disease progression	0	0	0	0	1 (0.7)	0	1 (0.7)
Infections and infestations	0	1 (0.7)	0	0	1 (0.7)	0	2 (1.4)
Influenza	0	1 (0.7)	0	0	0	0	1 (0.7)
Pneumonia	0	0	0	0	1 (0.7)	0	1 (0.7)
Investigations	0	9 (6.2)	6 (4.1)	0	0	0	15 (10.3)
Gamma-glutamyltransferase increased	0	9 (6.2)	6 (4.1)	0	0	0	15 (10.3)
Blood alkaline phosphatase increased	1 (0.7)	0	0	0	0	0	1 (0.7)
Metabolism and nutrition disorders	0	0	1 (0.7)	0	0	0	1 (0.7)
Hyponatraemia	0	0	1 (0.7)	0	0	0	1 (0.7)
Psychiatric disorders	0	0	1 (0.7)	0	0	0	1 (0.7)
Confusional state	0	0	1 (0.7)	0	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	2 (1.4)	2 (1.4)	0	1 (0.7)	0	5 (3.4)

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Pleural effusion	0	1 (0.7)	2 (1.4)	0	0	0	3 (2.1)
Haemoptysis	0	0	0	0	1 (0.7)	0	1 (0.7)
Nasal oedema	0	1 (0.7)	0	0	0	0	1 (0.7)
Pharyngeal oedema	0	1 (0.7)	0	0	0	0	1 (0.7)
Skin and subcutaneous tissue disorders	1 (0.7)	1 (0.7)	0	0	0	0	2 (1.4)
Photosensitivity reaction	0	1 (0.7)	0	0	0	0	1 (0.7)
Pruritus	1 (0.7)	0	0	0	0	0	1 (0.7)

Source: Sobi 2020 LOTIS-2 CSR (66).

[†]Adverse events are coded using MedDRA version 22.0 and graded using CTCAE v4.0. Only TEAEs are summarised. For each SOC and PT, patients are included only once at the maximum severity. AE sorting is done by SOC, use alphabetical order, within a SOC, sort PTs by decreasing frequency order.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Treatment-emergent adverse events leading to dose delay

Overall, 74 participants (51.0%) experienced at least one TEAE leading to dose delay. TEAEs leading to dose delay for ≥5% of participants are summarised by PT and maximum CTCAE grade in Table 45.

The most common (>5% overall) TEAEs leading to dose delay were GGT increased (30 patients; 20.7%), neutropenia (18 participants; 12.4%), and thrombocytopenia (13 participants; 9.0%).

Treatment-emergent adverse events leading to dose reduction

Table 46 summarises TEAEs leading to dose reduction by SOC, preferred term, and maximum CTCAE grade. Of the 145 patients in this study, 11 participants (7.6%) experienced at least one TEAE leading to dose reduction. The most common TEAE that led to dose reduction was GGT increased in six participants (4.1%). Other TEAEs leading to dose reduction occurred in one participant (0.7%) each: thrombocytopenia, fatigue, oedema peripheral, Klebsiella infection, urinary tract infection bacterial, dyspnoea, and skin exfoliation.

B.2.10.2.4. Subgroup analysis

Of the 145 participants in this study, 128 participants (88.3%) experienced at least one of the selected TEAEs. There were three patients (2.1%) who experienced a selected TEAE of Grade 4 (one participant with pericardial effusion and two participants with GGT increased) (Table 47).

Table 45: TEAEs leading to loncastuximab tesirine dose delay for ≥5% of patients by PT and maximum CTCAE grade (all-treated population)†

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
6 April 2020 data cut							
Patient with any TEAE leading to dose delay	4 (2.8)	19 (13.1)	35 (24.1)	16 (11.0)	0	0	74 (51.0)
Gamma-glutamyltransferase increased	0	15 (10.3)	14 (9.7)	1 (0.7)	0	0	30 (20.7)
Neutropenia	0	1 (0.7)	5 (3.4)	12 (8.3)	0	0	18 (12.4)
Thrombocytopenia	0	0	11 (7.6)	2 (1.4)	0	0	13 (9.0)

Source: Sobi 2020 LOTIS-2 CSR (66).
†Adverse events were coded using MedDRA version 22.0 and graded using CTCAE v4.0. Only TEAEs were summarised. For each PT, patients were included only once at the maximum severity.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TEAE, treatment-emergent adverse event

Table 46: TEAEs leading to dose reduction by SOC, PT, and maximum CTCAE grade (all-treated population)†

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
6 April 2020 data cut							
Patients with any dose reduction TEAE	0	9 (6.2)	2 (1.4)	0	0	0	11 (7.6)
Blood and lymphatic system disorders	0	0	1 (0.7)	0	0	0	1 (0.7)
Thrombocytopenia	0	0	1 (0.7)	0	0	0	1 (0.7)
General disorders and administration site conditions	0	2 (1.4)	0	0	0	0	2 (1.4)
Fatigue	0	1 (0.7)	0	0	0	0	1 (0.7)
Oedema peripheral	0	1 (0.7)	0	0	0	0	1 (0.7)
Infections and infestations	0	0	1 (0.7)	0	0	0	1 (0.7)
Klebsiella infection	0	0	1 (0.7)	0	0	0	1 (0.7)
Urinary tract infection bacterial	0	0	1 (0.7)	0	0	0	1 (0.7)

System organ class preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	All grades n (%)
Investigations	0	6 (4.1)	0	0	0	0	6 (4.1)
Gamma-glutamyltransferase increased	0	6 (4.1)	0	0	0	0	6 (4.1)
Respiratory, thoracic and mediastinal disorders	1 (0.7)	0	0	0	0	0	1 (0.7)
Dyspnoea	1 (0.7)	0	0	0	0	0	1 (0.7)
Skin and subcutaneous tissue disorders	0	1 (0.7)	0	0	0	0	1 (0.7)
Skin exfoliation	0	1 (0.7)	0	0	0	0	1 (0.7)

Source: Sobi 2020 LOTIS-2 CSR (66).
[†]Adverse events were coded using MedDRA version 22.0 and graded using CTCAE v4.0. Only TEAEs were summarised. For each SOC and PT, patients were included only once at the maximum severity. AE sorting is done by SOC, use alphabetical order, within a SOC, sort PTs by decreasing frequency order.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Table 47: Selected TEAEs by grouped AE and PT (all-treated population)[†]

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)
6 April 2020 data cut						
Patient with any selected TEAE	37 (25.5)	47 (32.4)	41 (28.3)	3 (2.1)	0	128 (88.3)
Oedema or effusion	21 (14.5)	17 (11.7)	6 (4.1)	1 (0.7)	0	45 (31.0)
Oedema peripheral	21 (14.5)	6 (4.1)	2 (1.4)	0	0	29 (20.0)
Pleural effusion	4 (2.8)	8 (5.5)	3 (2.1)	0	0	15 (10.3)
Localized oedema	4 (2.8)	2 (1.4)	0	0	0	6 (4.1)
Ascites	2 (1.4)	0	3 (2.1)	0	0	5 (3.4)
Pericardial effusion	1 (0.7)	0	2 (1.4)	1 (0.7)	0	4 (2.8)
Swelling	1 (0.7)	3 (2.1)	0	0	0	4 (2.8)
Peripheral swelling	1 (0.7)	2 (1.4)	0	0	0	3 (2.1)
Fluid overload	0	1 (0.7)	0	0	0	1 (0.7)
Generalised oedema	1 (0.7)	0	0	0	0	1 (0.7)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)
Infusion site swelling	1 (0.7)	0	0	0	0	1 (0.7)
Testicular swelling	1 (0.7)	0	0	0	0	1 (0.7)
Liver function test	21 (14.5)	24 (16.6)	27 (18.6)	2 (1.4)	0	74 (51.0)
Gamma-glutamyltransferase increased	12 (8.3)	23 (15.9)	22 (15.2)	2 (1.4)	0	59 (40.7)
Blood alkaline phosphatase increased	20 (13.8)	8 (5.5)	1 (0.7)	0	0	29 (20.0)
Alanine aminotransferase increased	14 (9.7)	5 (3.4)	4 (2.8)	0	0	23 (15.9)
Aspartate aminotransferase increased	16 (11.0)	6 (4.1)	1 (0.7)	0	0	23 (15.9)
Hypoalbuminaemia	5 (3.4)	2 (1.4)	0	0	0	7 (4.8)
Ascites	2 (1.4)	0	3 (2.1)	0	0	5 (3.4)
Blood bilirubin increased	0	2 (1.4)	2 (1.4)	0	0	4 (2.8)
Hepatic enzyme increased	0	1 (0.7)	0	0	0	1 (0.7)
Skin reactions and nail disorders	38 (26.2)	19 (13.1)	6 (4.1)	0	0	63 (43.4)
Rash	13 (9.0)	5 (3.4)	1 (0.7)	0	0	19 (13.1)
Pruritis	14 (9.7)	4 (2.8)	0	0	0	18 (12.4)
Erythema	11 (7.6)	3 (2.1)	1 (0.7)	0	0	15 (10.3)
Photosensitivity reaction	7 (4.8)	5 (3.4)	3 (2.1)	0	0	15 (10.3)
Rash maculo-papular	1 (0.7)	6 (4.1)	1 (0.7)	0	0	8 (5.5)
Dry skin	2 (1.4)	2 (1.4)	0	0	0	4 (2.8)
Blister	2 (1.4)	1 (0.7)	0	0	0	3 (2.1)
Skin exfoliation	2 (1.4)	1 (0.7)	0	0	0	3 (2.1)
Skin hyperpigmentation	3 (2.1)	0	0	0	0	3 (2.1)
Rash erythematous	1 (0.7)	1 (0.7)	0	0	0	2 (1.4)
Rash pruritic	1 (0.7)	1 (0.7)	0	0	0	2 (1.4)
Rash pustular	1 (0.7)	0	1 (0.7)	0	0	2 (1.4)
Skin discoloration	2 (1.4)	0	0	0	0	2 (1.4)
Blood blister	1 (0.7)	0	0	0	0	1 (0.7)
Dermatitis	1 (0.7)	0	0	0	0	1 (0.7)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)
Dermatitis bullous	0	1 (0.7)	0	0	0	1 (0.7)
Dermatitis exfoliative generalised	1 (0.7)	0	0	0	0	1 (0.7)
Drug hypersensitivity	0	1 (0.7)	0	0	0	1 (0.7)
Generalised erythema	1 (0.7)	0	0	0	0	1 (0.7)
Generalised oedema	1 (0.7)	0	0	0	0	1 (0.7)
Pruritus allergic	1 (0.7)	0	0	0	0	1 (0.7)
Skin irritation	1 (0.7)	0	0	0	0	1 (0.7)
Skin ulcer	1 (0.7)	0	0	0	0	1 (0.7)

Source: Sobi 2020 LOTIS-2 CSR (66).
[†]Adverse events were coded using MedDRA version 22.0 and graded using CTCAE v4.0. Only TEAEs were summarised. For each AE group and PT, patients were included only once.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TEAE, treatment-emergent adverse event.

B.2.11. Ongoing studies

Loncastuximab tesirine is currently being evaluated in the following studies (Table 48).

Table 48. Ongoing trials with loncastuximab tesirine

Study	Population	Description
ADCT-402-311 (LOTIS-5) (NCT04384484)	R/R DLBCL	Phase 3 randomised study of lonca combined with rituximab vs immunochemotherapy rituximab/gemcitabine/oxaliplatin) in patients with R/R DLBCL who are not candidates for ASCT due to ECOG PS and/or comorbidities
ADCT-402-105 (LOTIS-7) (NCT04970901)	R/R B-NHL	Phase 1, multicentre, open-label, multi-arm study to evaluate the safety and anti-cancer activity of lonca in combination with other anticancer agents in patients with R/R B-NHL
ADCT-402-203 (LOTIS-9) (NCT05144009)	R/R DLBCL, HGBL, or Grade 3b FL	Phase 2 Open-label Study of Loncastuximab Tesirine in Combination With Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients With Diffuse Large B-cell Lymphoma (DLBCL)

Key: ASCT, autologous stem cell transplant; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; lonca, loncastuximab tesirine; MCL, mantle cell lymphoma; PS, performance status; R/R, relapsed/refractory.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the available clinical evidence

The Phase 2 trial LOTIS-2 evaluated the efficacy and safety of loncastuximab tesirine in adults with R/R DLBCL and HGBL after two or more lines of systemic therapy.

- Loncastuximab tesirine was effective, producing durable responses in heavily pre-treated patients with DLBCL:
  - In the all-treated population, the ORR was 48.3% (70/145 patients; 95% CI: 39.9% to 56.7%). BORs included 35 patients (24.1%) with CR and 35 patients (24.1%) with PR (data cut 6 April 2020). Responses were also achieved in patients who failed third-line treatment, including those who received CAR T-cell therapy at third-line.
  - As of the final data cut ([redacted]), ORR was [redacted], with [redacted] of patients achieving complete response (60); [redacted] and [redacted] of the patients who achieved CR [redacted].

[redacted] (60). Clinical opinion received by the Company suggests that it is reasonable to assume that patients who are progression free at two years following treatment can be discharged and regarded as 'cured' (22).

- Clinical experts in the UK indicated the major advantage of loncastuximab tesirine being a fast-acting treatment. The median time to first response (CR or PR) was 41.0 days (range: 35 to 247 days) and the mean time was 51.5 days (6 April 2020 and 1 March 2021 data cuts) (83).

- The median DOR was 10.25 months (95% CI: 6.87 to not estimable); the probability of maintaining response was 68.1% at six months, 63.8% at nine months, and 38.3% at 12 months (data cut 6 April 2020). As of the final data cut ([redacted]), the median duration of response (DOR) was [redacted]

- The median PFS was 4.93 months (95% CI: 2.89, 8.31) and the median OS was 9.92 months (95% CI: 6.74, 11.47) (6 April 2020 data cut). As of the final data cut ([redacted]), the median PFS was [redacted] months (95% CI: [redacted]) and the median OS was [redacted] months (95% CI: [redacted]) (60).

- Loncastuximab tesirine produced durable responses in patients with double hit/triple hit genetics, advanced stage disease (Stage III/IV), transformed disease, primary refractory disease, and disease which was refractory to all prior therapies; and was also effective in elderly patients and in patients who had previous CD19-directed CAR-T therapy.

- EQ-5D-5L and FACT-Lym questionnaires demonstrated improvement in QoL for patients who responded to treatment.

- Loncastuximab tesirine demonstrated a strong safety profile compared with other similar therapies. Most TEAEs were Grade ≤3, with minimal number of Grade 4 or 5 TEAEs. No new safety concerns were identified and no increase in toxicity was observed in patients aged ≥65 years.

The sparsity of available comparator data in the target population to inform the MAIC comparisons confirmed the findings from the clinician interviews, which suggested lack of a consistent treatment approach at third- or later-line for these patients, particularly with respect to the choice of chemotherapy regimen. However, the data that were available for the treatment

most commonly considered SoC in this line of treatment, Pola+BR, suggest that loncastuximab tesirine is at least as effective as Pola+BR, with the HR for OS and PFS likely to be closest to the estimates obtained from the comparison with the real-world COTA database study, where loncastuximab tesirine offered significantly longer survival outcomes (robust SE based on bootstrap estimates). For the comparison with chemotherapy, loncastuximab tesirine also showed a significant OS advantage.

B.2.12.2. Strengths and limitations of the data package

LOTIS-2 was a single-arm study with a trial population of 145 and no randomisation to a control arm. Due to the nature of single-arm design, there is a lack of direct evidence identified for loncastuximab tesirine versus relevant comparators to inform relative efficacy. Inferences of the relative effect of loncastuximab tesirine can only rely on indirect comparisons with efficacy outcomes from other comparator trials with different patient populations and trial parameters. Although an open-label design can be associated with limitations such as possible higher patient dropout, or concerns regarding patients' reporting of adverse events, these concerns have been mitigated by setting objective endpoints such as OS, PFS which are less prone to biases resulting from patient or investigator expectations. Independent reviewers were also used to ensure objective evaluation of assessments. Moreover, all patients were followed every 12 weeks for up to 3 years after treatment discontinuation (59). The duration of follow-up of the pivotal trial is longer than most cancer treatments and other approved therapies (30-month follow-up in Pola+BR study (11). This further provides assurances of its efficacy and tolerability. Loncastuximab tesirine has shown antitumor activity with an acceptable toxicity profile in a difficult to treat group of patients with R/R DLBCL, who are at high risk of a poor prognosis. The overall health state and health-related quality of life were stable or improved in high-risk patients during the course of treatment. From Cycle 3 of treatment, 40% of patients consistently reported improved EQ-VAS scores by at least the minimally important difference (MID), suggesting that loncastuximab tesirine was associated with QoL benefits as early as after 2 cycles of treatment (6 weeks) (84).

Heterogeneity in prior treatments and baseline imbalance may arise with the trial design of different drugs. It is notable that the studies of other drugs approved for patients with R/R DLBCL did not consistently include patients who had at least two prior lines of treatment, who have poor prognosis and more challenging to manage. For example, the study of Pola+BR included a significant proportion of second-line patients (27%) and no patients with HGBL-

DH/TH (52). It therefore remains unknown if these recently approved drugs are effective in these heavily pre-treated patients.

LOTIS-2 included patients with high-risk disease characteristics, such as age >65 years (representing 55% of patients enrolled), ≥3 prior lines of therapy (56%), DH/TH lymphoma (10%), double- or triple-expressor DLBCL (14%) and advanced disease (Stage III–IV; 77%) (59). The patient population enrolled represents a difficult to treat population, based on treatment refractoriness and treatment history, where all patients in LOTIS-2 received ≥2 prior lines of systemic therapy (59). By contrast, studies of targeted therapies included patients from earlier treatment lines; during GO29365 (pivotal study evaluating Pola+BR) 27.5% of patients received only one prior systemic therapy, respectively (52).

In the inclusion criteria, the definition of 'refractory' was more stringent in LOTIS-2 compared to other trials as patients with a response who relapsed within six months were not excluded. The durable clinical antitumour activity of loncastuximab tesirine compared with recently approved drugs, including activity in difficult-to-treat subgroups, suggest it could change practice as a potential treatment option for patients with R/R DLBCL who have received two or more previous systemic therapies, delivering to the unmet need in this large group of patients with poor prognosis and a lack of an established SoC. Safety data from the trial further demonstrated a clinically meaningful reduction in neutropenia, thrombocytopenia, anaemia, infections and any serious AE. No new safety concerns were identified and there was no increase in toxicity in patients ≥65 years vs younger patients.

Outcomes on tumour response, DOR and survival between the overall cohort and in subgroups with high-risk disease characteristics were consistent; subgroups included age ≥75 years, HGBL, DH/TH lymphoma, double/triple expressor DLBCL, >3 lines of prior therapy and cell-of-origin (COO) subtype (59). However, while these results are encouraging, it should be noted that results for some subgroup analyses were informed by small patient numbers, and any conclusions should be considered in this context.

No head-to-head data are available for loncastuximab tesirine versus the comparators listed in the scope. Inferences of the effect of loncastuximab tesirine can only rely on indirect comparisons with efficacy outcomes from other comparator trials with different patient populations and trial parameters. In addition, the available data to inform the MAIC is taken from published evidence in which limited baseline characteristics for the 3L subgroup are reported

hindering the comparison of data. It is known that prognosis is particularly poor for patients with R/R DLBCL after ≥2 or more lines of systemic therapy due to the progressive nature of the disease and the cumulative adverse effects of prior treatments (4-6). Therefore, if patients are not compared with treatment received within the same line of therapy, there may be more patients with further advanced disease in one comparator versus another, resulting in bias in the survival outcomes. Given the impact of the number of prior lines of treatment, this should be taken into consideration when interpreting the results.

B.3. Cost effectiveness

- A cost-utility analysis with a lifetime time horizon was conducted to evaluate the cost-effectiveness of loncastuximab tesirine compared with Pola+BR and chemotherapy.
- The population included in the cost-effectiveness analysis consists of adults with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy.
- Pola+BR has been shown to be more effective than chemotherapy, with experts indicating they would use Pola+BR in all patients, provided they were willing to accept the additional toxicity. A UK RWE study suggests that the majority of use is in third-line-plus patients (21). As such, the primary comparison in this analysis is with Pola+BR. A proportion of patients are still treated with chemotherapy and so a comparison with chemotherapy has also been included.
- The model was structured as a partitioned survival model (PSM), comprised of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. Patients can be either on or off initial treatment in the PF and PD states based on time-to-treatment discontinuation (TTD).
- To inform the clinical inputs for loncastuximab tesirine, IPD from the LOTIS-2 study were used for PFS, OS and TTD.
- Outcomes for pola+BR were extrapolated from GO29365 and outcomes for LOTIS-2 were weighted to match this population. Outcomes for chemotherapy were informed by the MAIC.
- EQ-5D-5L scores from LOTIS-2 were mapped to the EQ-5D-3L.
- Grade ≥3 TEAEs occurring in ≥5% of patients were obtained from LOTIS-2 for loncastuximab tesirine and from TA649 for Pola+BR (11). The CORAL extension studies do not report safety data. AE rates for chemotherapy were taken from TA567 (18) and TA649 (11).
- Patients treated with Pola+BR would expect to receive 1.82 QALYs, an absolute shortfall of 9.84 QALYs and a proportional shortfall of 0.84. Patients treated with chemotherapy would expect to receive 0.92 QALYs, an absolute shortfall of 10.74 QALYs and a proportional shortfall of 0.92, meeting the criteria for a multiplier of 1.2 for QALY gains.
- In the base case (with PAS price) analysis, loncastuximab tesirine dominates Pola+BR (loncastuximab tesirine was associated with a cost saving of [redacted] and an incremental QALY gain of [redacted]).
- Scenario analyses using RWE for Pola+BR suggest that these results may be conservative, as the data sources used to inform the comparators arms in the model may provide an optimistic assessment of survival.
- Probabilistic analysis indicated that loncastuximab tesirine was dominant in [redacted]% of simulations, more effective in [redacted]% of simulations and cost saving in [redacted]% of simulations.
- Compared with chemotherapy, in the base case analysis (with PAS price), loncastuximab tesirine has an incremental cost-effectiveness ratio (ICER) of £48,986 per QALY gained (loncastuximab tesirine was associated with incremental costs [redacted] and incremental QALYs [redacted])

B.3.1. Published cost-effectiveness studies

A broad systematic literature review (SLR) was conducted in October 2022 to identify cost-effectiveness studies from the published literature. A summary of published cost-effectiveness studies is provided in Table 49. A complete description of the search strategies is presented in Appendix G.

A total of 461 papers were identified through the electronic searches. Upon the removal of duplicate papers, 394 titles and abstracts were reviewed. A total of 69 papers were potentially relevant and were ordered for full paper review. At this stage, a further 28 papers were excluded. Hand-searching yielded 19 additional relevant publications, resulting in a total of 60 publications for final inclusion in the review.

Seven included studies (one conference abstract, three public summary documents, and three HTA submissions) reported UK data and were deemed relevant for the NICE decision problem. Of these, one reported a budget impact analysis and six reported cost-effectiveness or cost-utility analyses (11, 15, 18, 85-87). The six HTAs including cost-utility analyses are summarised in Table 49.

Table 49. Summary list of published cost-effectiveness studies

Study	Year published	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA559 Axicabtagene ciloleucel (15)	2018	Partitioned survival model with 3 health states (progression-free, progressed disease, death). Time horizon of 44 years. UK NHS perspective.One month cycle length with half cycle correction.	Adult patients with R/R DLBCL, PMBCL and tFL who were ineligible for auto-SCT	Incremental QALYs: 4.30 (vs BSC)	Incremental costs: £289,571 (vs BSC)	£67,323 (vs BSC)
NICE TA567 Tisagenlecleucel (18)	2019	Partitioned survival model with 3 health states (progression-free, progressed disease, death). Time horizon of 46 years. UK NHS perspective. One week cycle length with half cycle correction.	Adult patients with R/R DLBCL	–	–	Deterministic Company base-case (tisa-cel PAS): £47,684 (vs R-GEMOx); £47,526 (vs R-GDP) Probablistic Company base-case with R-GemOx as salvage chemotherapy (with PAS): £50,963 (vs R-GEMOx) Probablistic Company base-case with R-GDP as salvage chemotherapy (with PAS): £50,963 (vs R-GEMOx)
NICE TA649 Polatuzumab vedotin (11)	2020	Partitioned survival model with 3 health states (progression-free, progressed disease, death). Time horizon of 45 years. UK NHS perspective. One month cycle	Patients with R/R DLBCL ineligible for SCT	Incremental; QALYs: 0.68 (vs BR; Company base-case); 0.67 (vs BR; Company updated base-case)	Incremental costs vs BR: £18,019 (Company base-case); £17,440 (Company updated base-case); £19,904 (ERG preferred);	Company base-case: £26,877 (vs BR) Company updated base-case: £25,307 (vs BR)

Study	Year published	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		length with half cycle correction. One week cycle length.			£21,061 (revised base-case)	
SMC Axicabtagene ciloleucel (85)	2019	Partitioned survival model with 3 health states (progression-free, progressed disease, death). Time horizon of 44 years. UK NHS perspective.	Adult patients with R/R DLBCL and PMBCL, after two or more lines of systemic therapy	–	Cost per course: axi-cel, £280,451; tisa-cel, £282,000	£49,136 (vs BSC)
SMC Tisagenlecleucel (86)	2019	Partitioned survival model with 3 health states (progression-free, progressed disease, death). Time horizon of 46 years. UK NHS perspective.	Adult patients with R/R DLBCL after two or more lines of systemic therapy	–	Cost per course: axi-cel, £280,451; tisa-cel, £282,000	Company base-case: £44,330 (vs R-GemOx); £44,151 (vs R-GDP) Alternative base-case using CORAL as source for comparator arm modelling: £48,116 (vs R-GemOx); £47,903 (vs R-GDP)
SMC: Polatuzumab vedotin (87)	2020	Partitioned survival model with 3 health states (progression-free, progressed disease, death). Time horizon of 45 years. UK NHS perspective.	Adult patients with R/R DLBCL ineligible for HSCT receiving Pola+BR	–	Cost per cycle: polatuzumab £11,060	£27,396 (vs BR; with PAS)

Source: (11, 15, 18) (85-87)

Abbreviations: BR, bendamustine + rituximab; BSC, best supportive care; DLBCL, diffuse large-B-cell lymphoma; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PMBCL, primary mediastinal large B cell lymphoma; NHS, National Health Service; PAS, Patient Access Scheme; PMBCL, primary mediastinal large B-cell lymphoma; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years; R-GDP, rituximab + cisplatin, gemcitabine, dexamethasone; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R, relapsed or refractory; SCT, stem cell transplant; SMC, Scottish Medicines Consortium; TA, technology appraisal; tLF, transformed follicular lymphoma; UK, United Kingdom.

B.3.2. Economic analysis

No existing economic evaluations of loncastuximab were identified in the cost-effectiveness SLR (Section B.3.1). It was therefore necessary to develop a *de novo* cost-effectiveness model (CEM) for the purpose of this submission.

B.3.2.1. Patient population

The population included in the cost-effectiveness analysis consists of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy. This is in line with the marketing authorisation for loncastuximab and the final scope issued by NICE.

B.3.2.2. Model structure

The cost-effectiveness analysis uses a partitioned survival analysis (PartSA) model, with the following mutually exclusive health states:

- Progression-free disease
- Progressed disease
- Death.

A PartSA was implemented in line with NICE DSU guidance presented in TSD 19 (88) and is in line with the approach taken in previous NICE technology appraisals in R/R DLBCL, including:

- TA559 – Axi-cel (15)
- TA567 – Tisa-cel (18)
- TA649 – Pola+BR (11)
- ID3795 – Taf + len (19)

Using a PartSA approach, health state membership is determined using extrapolated survival outcomes. PFS and OS curves are estimated for each comparator and at each time point the proportion of patients that are progression-free at each time point is determined by the PFS curve. The proportion that are alive with progressed disease is given by the difference between the OS and PFS curves and the proportion that are dead is given by 1 minus the OS curve. This provides a direct link between the trial outcomes and health state membership in the economic

model. The time-to-discontinuation (TTD) curve informs the number of individuals remaining on treatment with their initial treatment. A cycle length of one week has been applied, and half-cycle correction implemented using the life table method (89). A discount rate of 3.5% per annum was applied to cost and health outcomes in line with current NICE guidelines (90)

The model schematic Is presented in Figure 23.

Figure 23: Model schematic

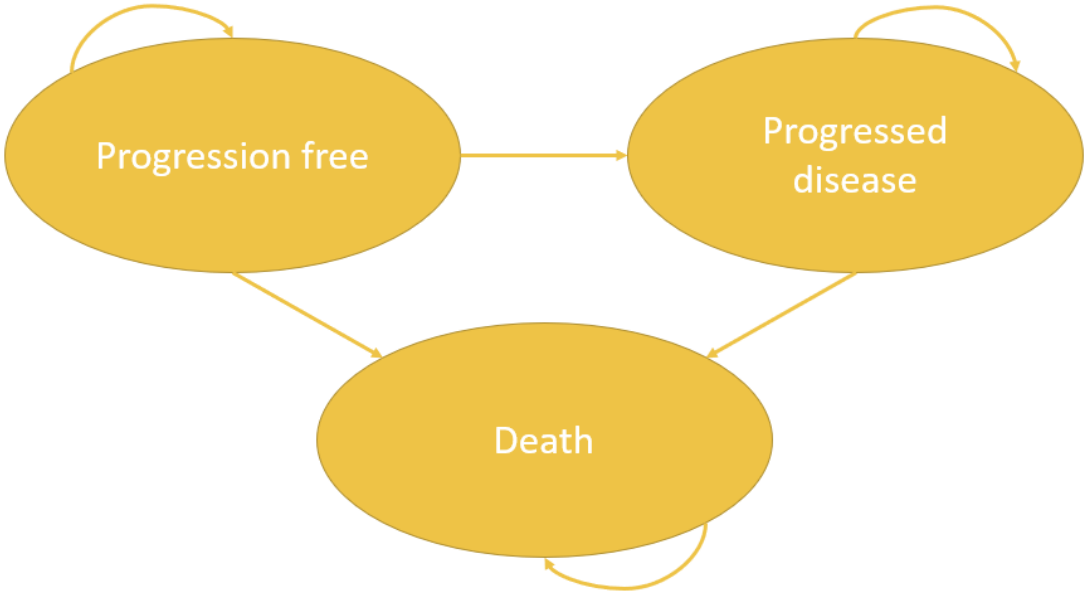


Table 50 summarises the features of the economic analysis.

Table 50. Features of the economic analysis

	Previous evaluations					Current evaluation	
Factor	**TA306 (17)**	**TA559 (15)**	**TA567 (18)**	**TA649 (11)**	**ID3795 (19)**	**Chosen values**	**Justification**
Time horizon	Lifetime (23 years)	Lifetime (44 years)	Lifetime (46 years)	Lifetime (45 years)	Lifetime (45 years)	Lifetime (40 years)	A lifetime time horizon has been adopted to capture costs and benefits over a patient's lifetime, in line with the NICE reference case
Treatment waning effect?	No	No	No	No	No	No	KM curves for loncastuximab are mature and there is no evidence of a waning effect in the clinical data
Source of utilities	Literature values (PFS: 0.76; PD: 0.68)	EQ-5D data collected in ZUMA-1 (PFS: 0.72; PD: 0.65)	EQ-5D data collected in JULIET (PFS: 0.83; PD: 0.71)	Values from TA559	Values from TA559	EQ-5D data from LOTIS-2, with scenarios using data from previous appraisals	HRQoL data from LOTIS-2 best matches the NICE reference case
Source of costs	Clinician survey on type and frequency of resource use in DLBCL. Unit costs from BNF, NHS reference costs and PSSRU.	Resource use based on TA306 for SOC, with additional resource use for CAR-T therapy. Unit costs From eMIT BNF, NHS reference costs and PSSRU.	Resource use based on NG52 for SOC, with additional resource use for CAR-T therapy. Unit costs From eMIT BNF, NHS reference costs and PSSRU.	Resource use from TA306. Unit costs From eMIT BNF, NHS reference costs and PSSRU.	Resource use from previous Tas and L-MIND clinical trial. Unit costs From eMIT BNF, NHS reference costs and PSSRU.	Resource use from TA306. Unit costs From eMIT BNF, NHS reference costs and PSSRU.	Resource use is based on values that have been accepted in previous evaluations. Cost sources of standard UK sources aligned with the reference case.

Abbreviations: BNF, British National Formulary; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; eMIT, electronic market information tool; HRQoL, health-related quality of life; KM, Kaplan-Meier; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PFS, progression-free survival; PSSRU, personal social services research unit; TA, technology appraisal; SOC, standard of care.

B.3.2.3. Intervention technology and comparators

The intervention is loncastuximab tesirine, administered intravenously on Day 1 of each 21-day cycle, at 150 µg/kg for two cycles, then 75 µg/kg thereafter, for up to one year or until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision.

Comparators included in the model are:

- Pola+BR
  - Polatuzumab vedotin 1.8mg/kg via IV infusion on Day 1 of each three-week cycle, for up to six cycles
  - Bendamustine 90 mg/m2/day on Day 1 and Day 2 of each cycle, for up to six cycles
  - Rituximab 375 mg/m2 on Day 1 of each cycle, for up to six cycles
- Chemotherapy, including:
  - DHAP (cisplatin, cytarabine, dexamethasone)
  - GDP (cisplatin, gemcitabine, dexamethasone)
  - ICE (ifosfamide, carboplatin, etoposide)
  - IVE (ifosfamide, epirubicin and etoposide)
  - R-GemOx (rituximab + gemcitabine + oxaliplatin)
  - BR (bendamustine and rituximab)

Clinical experts stated that Pola+BR was more effective than chemotherapy, with one of the clinical experts saying they would use Pola+BR in all patients, provided they were willing to accept the additional toxicity. A second clinician said that the driver behind this decision was whether they had previously received treatment and that they would look for a trial or compassionate access to bispecifics rather than use chemotherapy (22). While Pola+BR can be used at second-line as well as third-line-plus, data from a UK RWE study suggests that the

majority of use is in third-line-plus patients (21). As such, the primary comparison in this analysis is with Pola+BR.

A proportion of patients are still treated with chemotherapy and so a comparison with chemotherapy has also been included. The company sought clinical opinion on which chemotherapy regimens were most widely used at third line in R/R DLBCL. The clinicians stated that DHAP, ICE and IVE would not be used at this line as they are considered too toxic (22). The most commonly mentioned regimen was RGemOX, however (R)GDP, DECC, PEPC, gemcitabine monotherapy and R+lenalidomide were also considered as options and third-line-plus. It was highlighted that the wide range of treatments used was due to a lack of differentiation between options, with the key driver behind treatment choice being toxicity rather than efficacy. For the base-case analysis RGemOx has been selected as a representative chemotherapy regimen, as it was the most widely cited by clinicians.

As outlined in Section B1.1, clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients that are not eligible for HSCT or CAR-T therapy. As such, CAR-T therapies such as axicabtagene ciloleucel have not been included as comparators in the model (22).

Additionally, pixantrone has not been included as a comparator. Previously appraisals of intervention for R/R DLBCL including TA559, TA567, TA649 and GID-TA10645 removed pixantrone as a comparator either at the scoping stage or through the committee process. The respective committees were informed by clinical experts that pixantrone is rarely used in the UK; therefore, they concluded in each case that it was not a relevant comparator. This was confirmed by clinical experts consulted by the company, who unanimously stated that pixantrone does not from part of the treatment pathway (22).

B.3.3. Clinical parameters and variables

B.3.3.1. Survival outcomes

B.3.3.1.1. Data sources

To inform outcomes for loncastuximab tesirine, including TTD, PFS and OS, IPD from LOTIS-2 were used. As LOTIS-2 is a single-arm study, outcomes for Pola+BR and chemotherapy were informed by the MAIC analyses (Section B.2.9).

Outcomes from the GO29365 study were used to inform the model base-case for the comparison with Pola+BR, with scenario analyses presented using the COTA electronic medical record (EMR) data. While the MAIC analyses comparing to the GO29365 study were limited by the lack of baseline characteristics or KM data for the third-line-plus population, there were also limitations in the comparison to the COTA EMR as there were limited characteristics available for matching. RWE from the UK has suggested outcomes for patients treated with Pola+BR are worse than observed in the clinical trial (21, 53). Thus, though both data sources are subject to uncertainty, a comparison using the GO29365 data is expected to be conservative for loncastuximab tesirine and this has been used to inform the base-case analysis. However, both sources are relevant and a comparison with the COTA data has been provided in scenario analysis.

The MAIC indicated that the proportional hazards assumption does not hold between loncastuximab tesirine and Pola+BR for either OS or PFS (Section B.2.9). As such, the comparison uses directly extrapolated outcomes for Pola+BR and loncastuximab tesirine, with the MAIC weights applied to the loncastuximab tesirine arm. As no KM data are available for the third-line-plus population in GO29365, extrapolations were based on the full population and hazard ratios were applied for being in third-line-plus.

Outcomes for the chemotherapy arm are informed by the CORAL extension studies (4, 5). These do not provide data specifically on RGemOx; across the two studies, 44 patients (16%) were treated with gemcitabine containing regimens. However, given the paucity of data on specific chemotherapy regimens, this was deemed to be the most appropriate evidence to inform outcomes at third-line-plus. As outlined in Section B.3.2.3, clinical opinion provided to the company was that there is little differentiation on efficacy between treatment options at third line and beyond, with the choice of therapy being driven by toxicity. Additionally, the CORAL extension studies were judged to be the most appropriate source for third-line-plus chemotherapy outcomes by the committee in TA567.

The proportional hazards assumption for the comparison with chemotherapy does hold, the Schoenfeld test was borderline significant (p=0.09) but log-cumulative hazard plots support the PH assumptions. The base-case analysis for the comparison with chemotherapy uses directly extrapolated outcomes from LOTIS-2, as this was confirmed by clinicians to be generalisable to UK clinical practice, with hazard ratios applied for chemotherapy (22). As such, the base case

analysis for each comparison considers different populations and a fully incremental analysis was not possible. Appendix N presents additional analyses with fully incremental ICERs.

B.3.3.1.2. Methods

Standard parametric survival analysis consisted of fitting six parametric distributions to the observed data: exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma distributions. The process of selecting the most appropriate parametric model was assessed using goodness-of-fit statistics, visual comparison with KM curves and clinical expert validation of long-term extrapolations and the underlying hazard functions. The standard parametric survival analyses followed the approach outlined in the NICE DSU technical support document 14 (91). Where the standard methods for extrapolation did not provide a good fit, consideration was also given to more flexible methods. Spline models with up to five degrees of freedom were also considered, using the hazards, odds and normal scales.

No assumptions around cure have been included in the model base-case, as the proportion of patients that might achieve a long-term remission was deemed to be uncertain. However, clinical experts did highlight that patients that are progression-free after 2 years are often discharged from care and there is evidence of a plateau in survival for patients treated with loncastuximab, without the need for further therapies (60). Scenarios including assumptions about cure have been included in the scenario analyses, assuming patients that remain progression-free at 2, 5 and 10 years can be considered cured. These patients would return to general population utility values but would be expected to have slightly elevated mortality. In line with the committee preference in TA649, an SMR of 1.41 has been applied to general population mortality for cured patients (11).

The CORAL extension trials took place before the advent of CAR-T therapies and no patients in either cohort were reported to go on to receive a CAR-T. Clinical experts consulted by the company largely felt that CAR-T would not be used as a subsequent therapy for patients treated with loncastuximab tesirine (Section B.3.5.1.3). In the extrapolations of loncastuximab tesirine, the impact of subsequent CAR-T therapy has been removed from the OS curves using a two-stage method (91), similar to those used in treatment switching analyses. Further details are provided in Section B.3.3.1.3.1. This was not done for comparisons to Pola+BR, as CAR-T therapies were used as subsequent treatments, and it was not possible to adjust both arms.

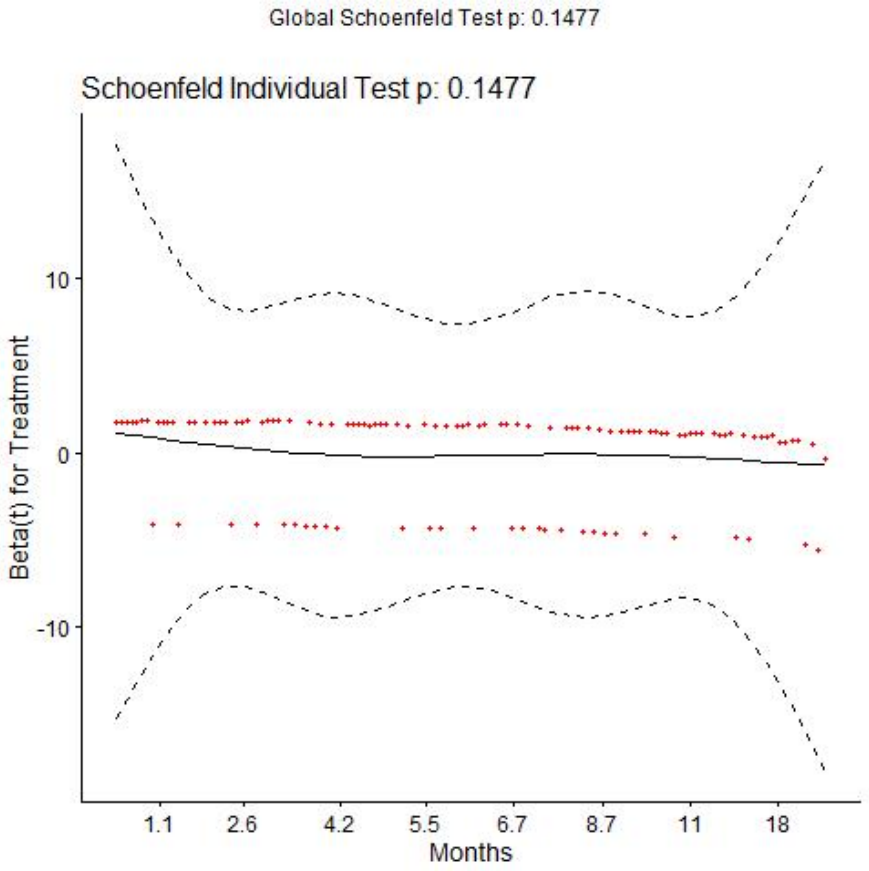
Additional survival analyses to inform scenario analyses are presented in Appendix O, including comparisons to the COTA EMR data and analyses of LOTIS-2 data weighted to match the CORAL extension studies.

B.3.3.1.3. Loncastuximab vs Pola+BR

B.3.3.1.3.1. OS

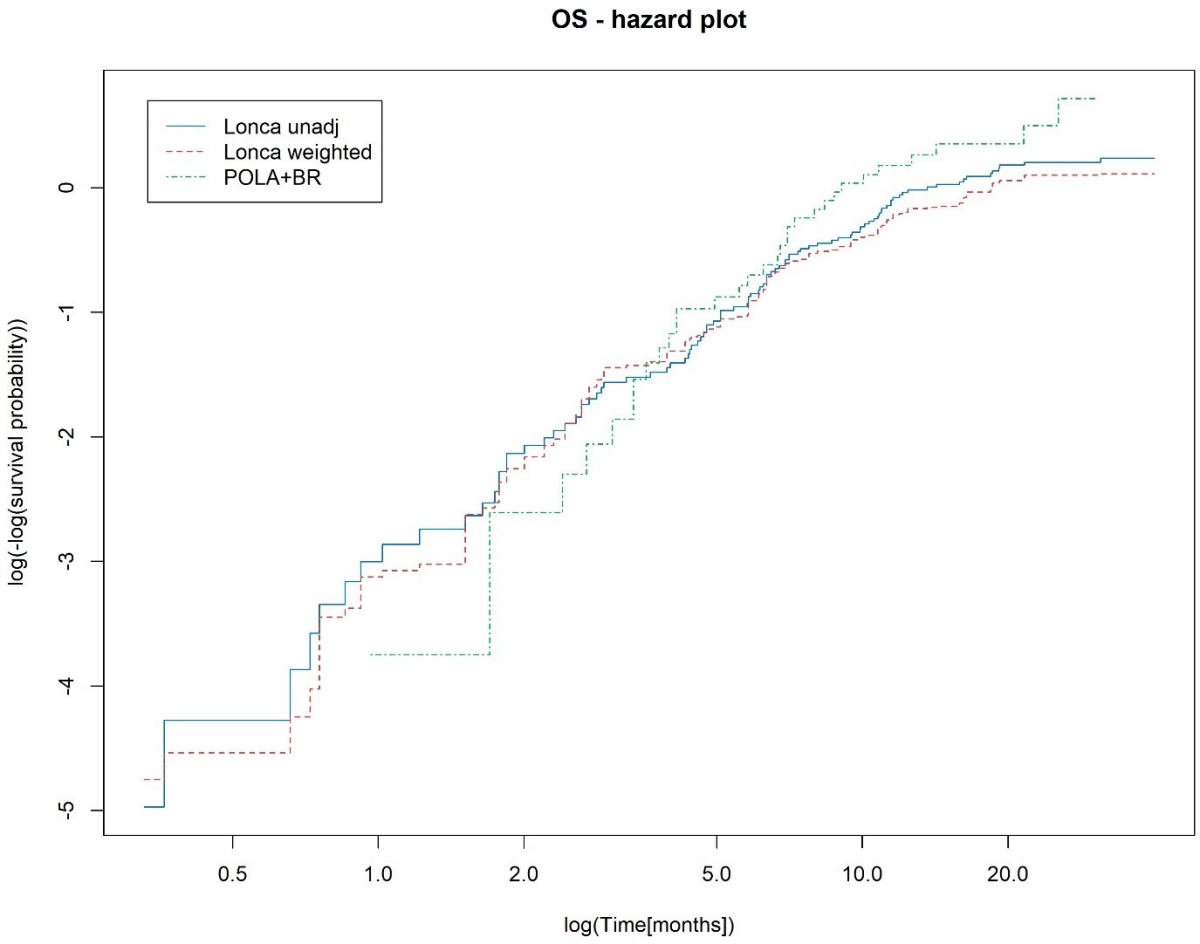
Outputs of the MAIC indicated that the proportional hazards assumption does not hold between loncastuximab tesirine and Pola+BR for OS. While the Schoenfeld residuals test (Figure 24) does not reject the assumption of proportion hazards, the log-cumulative hazard plots cross (Figure 25). As such, outcomes for Pola+BR and loncastuximab tesirine were extrapolated separately. This comparison has been made using the COTA EMR data as the proportional hazards (PH) tests cannot be applied to summary data.

Figure 24: OS Schoenfeld test, loncastuximab tesirine and Pola+BR (COTA database)



Abbreviations: OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure 25: OS log-cumulative hazard plot, loncastuximab tesirine and Pola+BR (COTA database)



Abbreviations: Lonca, loncastuximab tesirine; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

Table 51 presents the parameters for each parametric survival distribution for loncastuximab tesirine, where weights from the MAIC have been applied to compare against GO29365.

Table 51: Parameters and goodness-of-fit statistics for loncastuximab tesirine weighted vs GO29365, OS

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	313.4	321.3
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	328.8	334.1

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	312.2	317.5
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	334.1	336.7
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	314.9	320.2
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	316.7	321.9
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Directly extrapolated outcomes for Pola+BR from GO29365 are presented in Table 52. These outcomes are based on KM data for the entire population, including patients treated at second-line. To generate outcomes for the third-line-plus populations, a hazard ratio was applied. A hazard ratio for second-line vs third-line-plus can be generated from the median survival times. Assuming that the hazard for the overall population is the weighted average of the hazard for the second-line and third-line-plus populations, the hazard ratio for the third-line-plus population can be calculated as shown below.

$$H_{Overall} = \%_{2L} * H_{2L} + \%_{3L+} * H_{3L+} = (\%_{2L} * HR_{2L\,vs\,3L+} + \%_{3L+}) * H_{3L+}$$

$$H_{3L+} = \frac{H_{Overall}}{(\%_{2L} * HR_{2L\,vs\,3L+} + \%_{3L+})}$$

Table 53 presents the hazard ratio for the third-line-plus population.

Table 52: Parameters and goodness-of-fit statistics for GO29365, OS

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	383.7	392.7
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	404.5	410.4
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	392.3	398.2

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	405.0	407.0
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	387.8	393.8
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	391.8	397.8
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Table 53: Hazard ratio for the 3L+ population

Population	N	Median survival (months)	HR, 2L vs 3L+ (95% CI)	HR, 3L+ vs overall (95% CI)
2L	50	18.4	-	-
3L+	102	9.5	0.52 (0.37 to 0.72)	1.19 (1.10 to 1.26)

Abbreviations: 2L, second-line; 3L+, third-line plus; CI, confidence interval; HR, hazard ratio.

Figure 26 and Figure 27 present a comparison of extrapolations with the OS KM curve, and the long-term extrapolations for loncastuximab tesirine respectively. Table 54 presents a summary of the long-term extrapolations.

Figure 26: Parametric fits for OS compared with KM data – loncastuximab tesirine

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 27: Long-term OS extrapolations – loncastuximab tesirine

Abbreviations: OS, overall survival

Table 54: Summary of long-term extrapolations for OS – loncastuximab tesirine

	Exponential	Gamma	Gompertz	Loglogistic	Lognormal	Weibull
Median survival (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival

Figure 28 presents the long-term extrapolations for Pola+BR. Table 55 presents a summary of the long-term extrapolations.

Figure 28: Long-term OS extrapolations - Pola+BR

Abbreviations: OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table 55: Summary of long-term extrapolations for OS – Pola+BR

	Exponential	Gamma	Gompertz	Loglogistic	Lognormal	Weibull
Median survival (months)						
2-year survival						
5-year survival						
10-year survival						

Abbreviations: OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

The Gompertz model exhibits the best fit to the loncastuximab tesirine data, followed by the generalised gamma model. The Gompertz model shows a plateau in survival after the trial

period, with hazards approaching 0 and approximately [redacted] of patients essentially returning to general population mortality risk. Clinical experts considered that it was possible that plateau in survival would be observed, as the risk of death decrease over time. One explained that patients that remain progression-free after two years are often discharged from care. These patients would have mortality above the general population, but not substantially higher. However, the plateau seen in the Gompertz curve was considered overly optimistic, as it shows very little mortality after the trial period and a long-term survival between [redacted] and [redacted] was considered more appropriate. The generalised gamma curve shows a reduction in mortality over time that was better aligned with clinicians expectations.

For Pola+BR, the generalised gamma curve shows the best fit to the data, followed by the lognormal and log-logistic models. As with loncastuximab tesirine, clinicians stated that mortality would reduce over time. The generalised gamma curve shows the best fit to the observed data and exhibits the expected pattern of survival for Pola+BR.

As such, the generalised gamma curve was selected to extrapolate OS for loncastuximab tesirine and Pola+BR, with alternative distributions tested in scenario analysis. Figure 29 and Figure 30 present predicted vs observed hazards for loncastuximab tesirine and Pola+BR extrapolations respectively. In both cases, the hazard functions show a peak in the hazard in the initial period, followed by a decline.

Figure 29: Observed vs predicted hazards - loncastuximab tesirine OS

Abbreviations: OS, overall survival.

Figure 30: Observed vs predicted hazards - Pola+BR OS

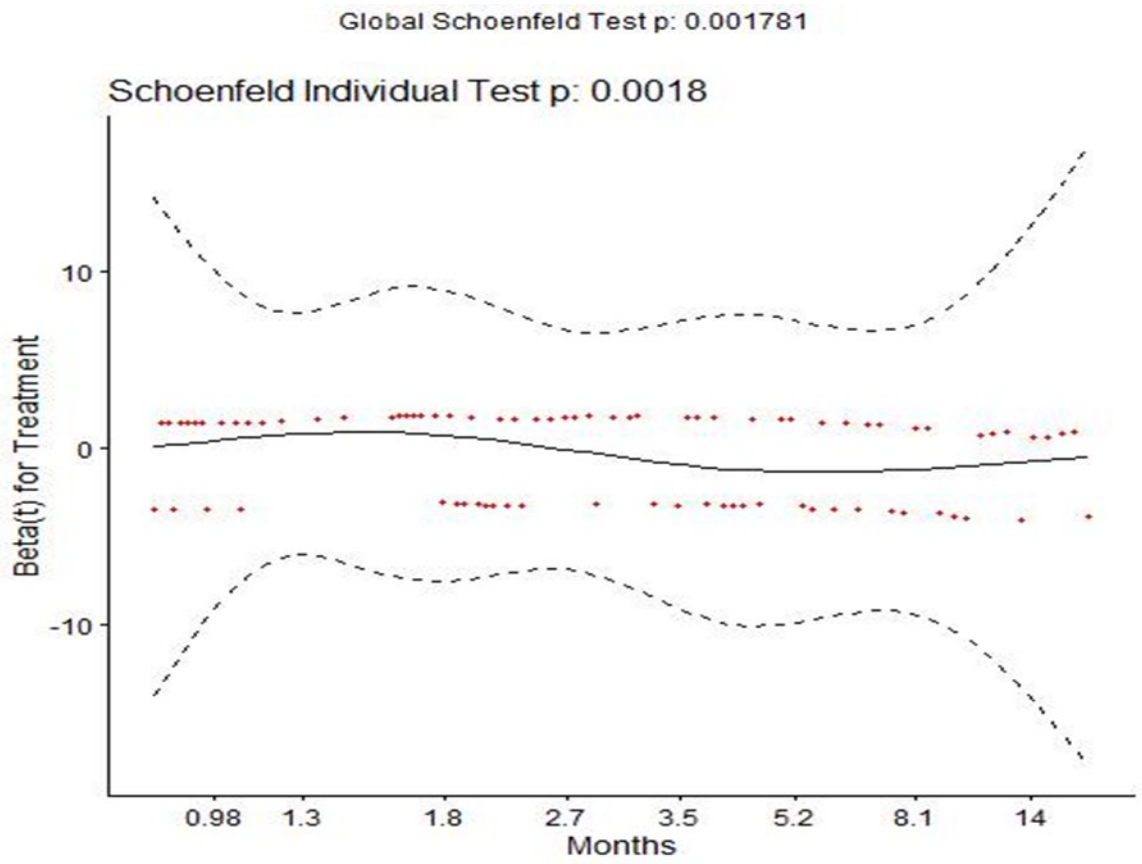
Note: These are predicted and observed hazards for the overall population.

Abbreviations: OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

B.3.3.1.3.2.PFS

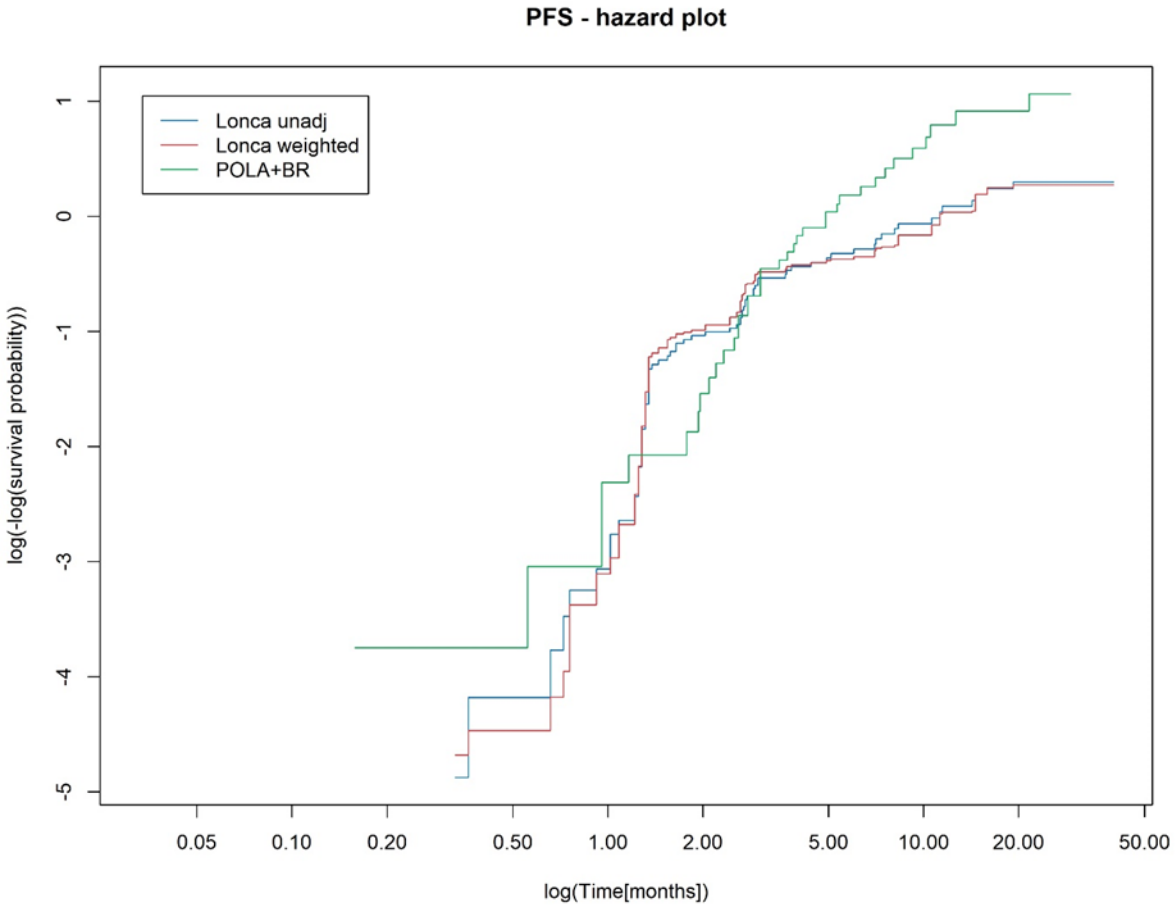
As with OS, the outputs of the MAIC indicated that the proportional hazards assumptions does not hold between loncastuximab tesirine and Pola+BR for PFS. The Schoenfeld residuals test (Figure 31) rejects the assumption of proportion hazards and the log-cumulative hazard plots cross (Figure 32). As such, outcomes for Pola+BR and loncastuximab tesirine were extrapolated separately. This comparison has been made using the COTA EMR data as the PH tests cannot be applied to summary data.

Figure 31: PFS Schoenfeld test, loncastuximab tesirine and Pola+BR



Abbreviations: PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Figure 32: PFS log-cumulative hazard plot, loncastuximab tesirine and Pola+BR



Abbreviations: Lonca, loncastuximab tesirine; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; unadj, unadjusted.

The fit statistics and parameters for each parametric survival distribution for progression-free survival with loncastuximab tesirine are presented in Table 56 and for Pola+BR in Table 57. Table 58 presents the hazard ratios for third-line-plus vs the overall population in GO29365.

Table 56: Parameters and goodness-of-fit statistics for loncastuximab tesirine weighted vs GO29365, PFS

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	326.0	334.9
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	371.9	377.9

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	344.3	350.3
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	383.0	386.0
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	345.9	351.9
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	350.6	356.6
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Table 57: Parameters and goodness-of-fit statistics for GO29365, PFS

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	404.4	413.4
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	426.4	432.4
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	418.0	423.9
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	425.1	428.1
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	406.3	412.3
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	410.0	416.0
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Table 58: Hazard ratio for the third-line-plus population

Population	N	Median survival (months)	HR, 2L vs 3L+ (95% CI)	HR, 3L+ vs overall (95% CI)
2L	50	11.5	-	-
3L+	102	6.1	0.53 (0.38 to 0.74)	1.18 (1.09 to 1.26)

Abbreviations: 2L, second-line; 3L+, third-line plus; CI, confidence interval; HR, hazard ratio.

Figure 33 and Figure 34 present a comparison of extrapolations with the PFS KM curve, and the long-term extrapolations for loncastuximab tesirine respectively. Table 59 presents a summary of the long-term extrapolations.

Figure 33: Parametric fits for PFS compared with KM data – loncastuximab tesirine

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 34: Long-term PFS extrapolations – loncastuximab tesirine

Abbreviations: PFS, progression-free survival.

Table 59: Summary of long-term extrapolations for PFS – loncastuximab tesirine

	Exponential	Gamma	Gompertz	Loglogistic	Lognormal	Weibull
Median survival (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1- year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival.

Figure 35 presents the long-term extrapolations for Pola+BR and Table 60 summarises the long-term outcomes.

Figure 35: Long-term extrapolations for PFS - Pola+BR

Abbreviations: PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table 60: Summary of long-term extrapolations for PFS – Pola+BR

	Exponential	Gamma	Gompertz	Loglogistic	Lognormal	Weibull
Median survival (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1- year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

The generalised gamma model shows the best statistical fit for loncastuximab tesirine and Pola+BR, and clinical experts explained that the pattern of survival for PFS was likely to be similar to OS, with a reduction in events after two years. As such the generalised gamma curve was selected to extrapolate PFS for loncastuximab tesirine and Pola+BR in the base-case.

Figure 36 and Figure 37 present predicted vs observed hazards for PFS for loncastuximab tesirine and Pola+BR respectively.

Figure 36: Predicted vs observed PFS hazards – loncastuximab tesirine

Abbreviations: PFS, progression-free survival.

Figure 37: Predicted vs observed PFS hazards - Pola+BR

Abbreviations: PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

B.3.3.1.3.3. TTD

Table 61 presents the parameters and goodness-of-fit statistics for extrapolations of TTD for loncastuximab tesirine and Figure 38 presents a comparison of extrapolations with KM data. The generalised gamma model shows a good fit to the data and was selected for the base-case analysis. Time on treatment was capped at one year, per the trial protocol.

Table 61: Parameters and goodness-of-fit statistics for loncastuximab tesirine weighted vs COTA, TTD

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	544.7	553.6
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	547.	553.0

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	560.6	566.5
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	562.2	565.1
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	584.2	590.2
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	581.0	586.9
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence intervals; SE, standard error; TTD, time to discontinuation; UCI, upper confidence interval.

Figure 38: Parametric fits for TTD compared with KM data – loncastuximab tesirine

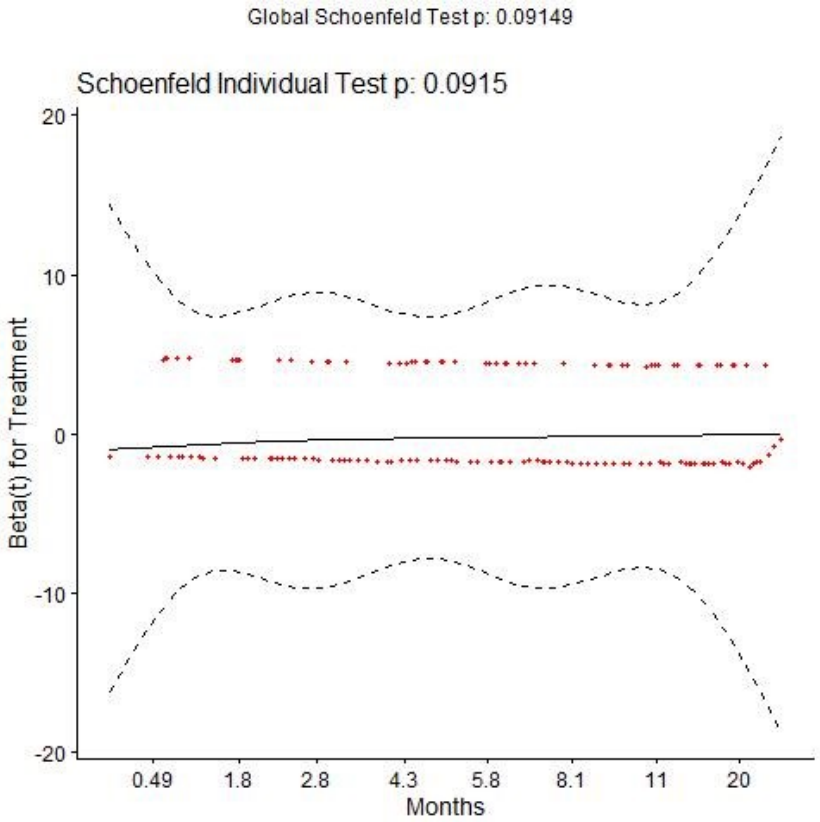
Abbreviations: KM, Kaplan-Meier; TTD, time to discontinuation.

For Pola+BR, patients were assumed to receive 6 cycles of treatment, unless they progressed prior to completion.

B.3.3.1.4. Loncastuximab tesirine vs chemotherapy

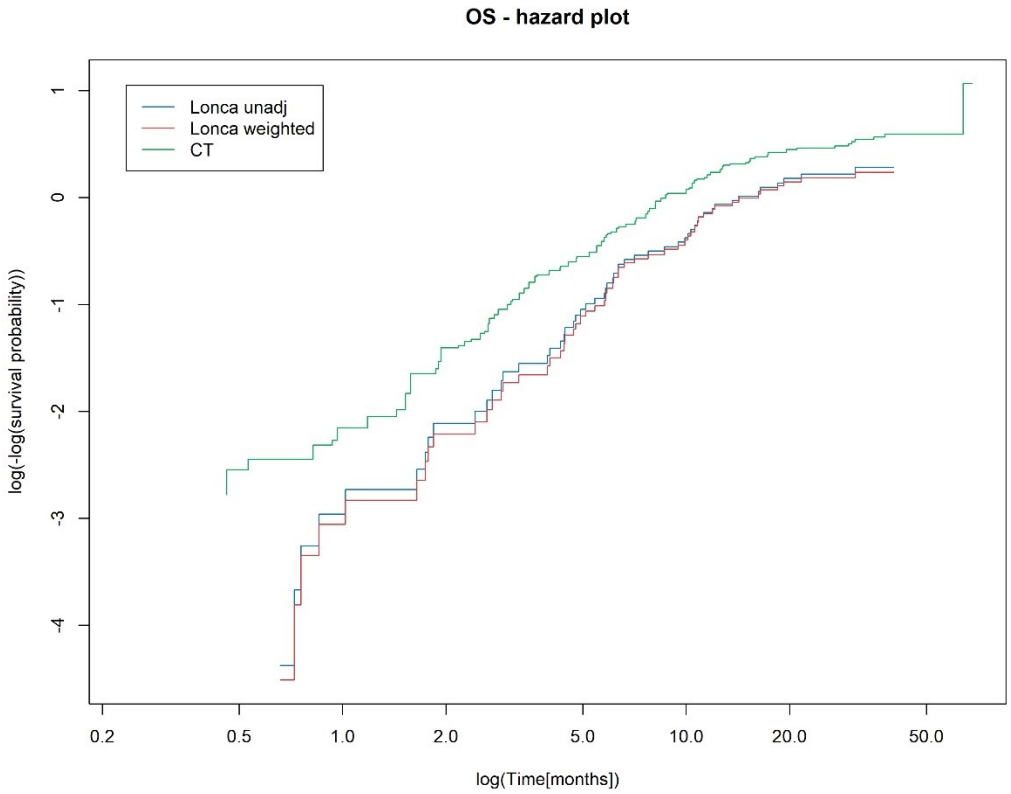
Outputs of the MAIC demonstrate that the proportion hazards assumption holds between loncastuximab tesirine and chemotherapy for OS. The Schoenfeld residuals test does not reject the assumption of proportion hazards, and the log-cumulative hazard plots appear to show proportionality. As such, OS outcomes for chemotherapy were estimated by applying the HR from the MAIC to curves for loncastuximab tesirine.

Figure 39: OS Schoenfeld test, loncastuximab tesirine and chemotherapy



Abbreviations: OS, overall survival.

Figure 40: OS log-cumulative hazard plot, loncastuximab tesirine and chemotherapy



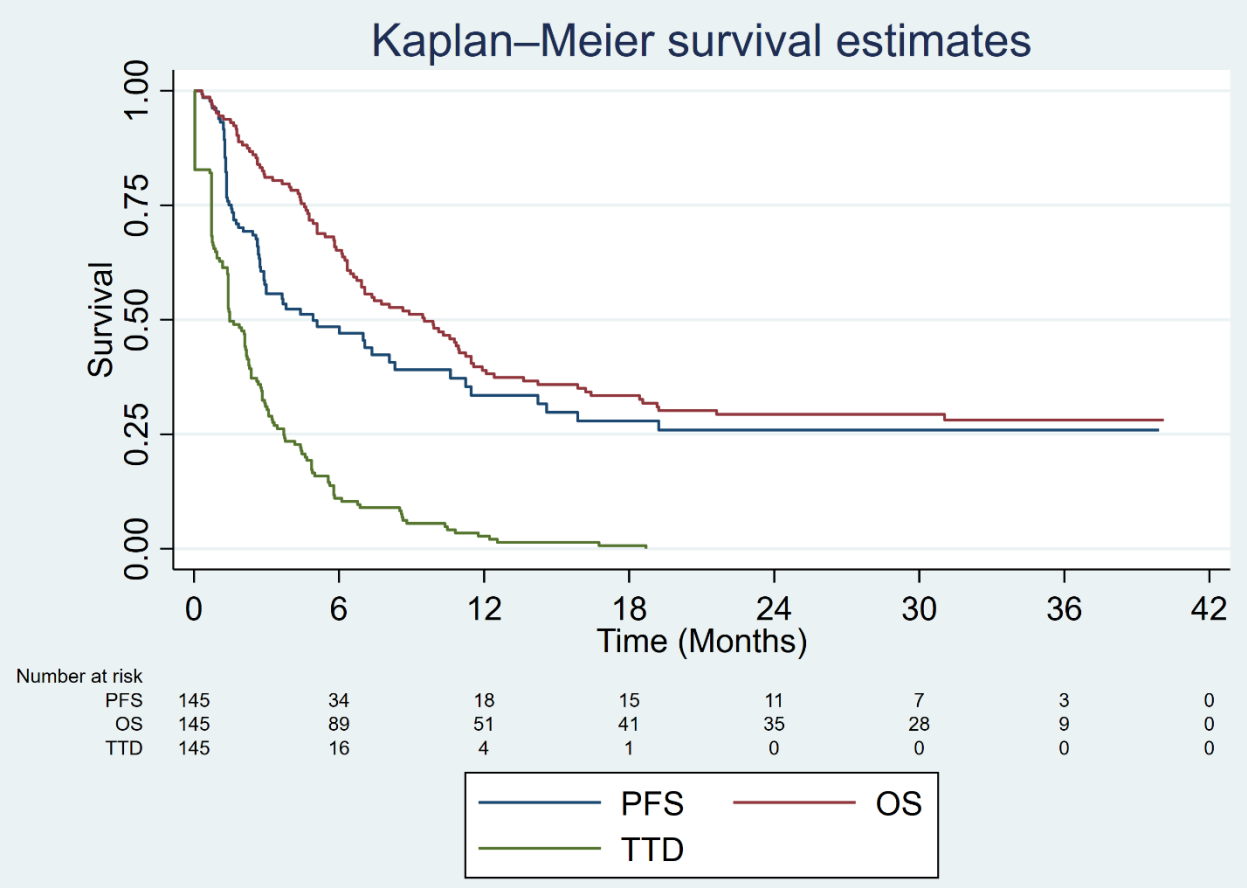
Abbreviations: CT, chemotherapy; Lonca, loncastuximab tesirine; OS, overall survival; unadj, unadjusted.

B.3.3.1.4.1. Survival extrapolations for loncastuximab tesirine

Survival extrapolation was conducted for loncastuximab tesirine and comparator arms of the model. Standard parametric survival analysis consisted of fitting six parametric distributions to the observed data: exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma distributions. The process of selecting the most appropriate parametric model was assessed using goodness-of-fit statistics, visual comparison with KM curves and clinical expert validation of long-term extrapolations and the underlying hazard functions. The standard parametric survival analyses followed the approach outlined in the NICE DSU technical support document 14 (91). Where the standard methods for extrapolation did not provide a good fit, consideration was also given to more flexible methods. Spline models with up to 5 degrees of freedom were also considered, using the hazards, odds and normal scales.

Figure 41 presents the PFS, OS and TTD curves for loncastuximab tesirine.

Figure 41: PFS, OS and TTD curves for loncastuximab tesirine



Abbreviations: OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

B.3.3.1.4.2. Overall survival

For the analysis of OS, a two-stage estimation method was applied to remove the impact of CAR-T. A secondary baseline was defined using the time of discontinuation from loncastuximab tesirine, and survival post-discontinuation was estimated. Accelerated failure time (AFT) models were then estimated, including a covariate for subsequent use of CAR-T, as well as age, number of prior therapies, response to first-line and previous line of treatment, ECOG score at baseline and disease stage at diagnosis. Log-logistic, log-normal, Weibull and generalised gamma models were tested and the log-logistic model was used in the base-case as it shows the best statistical fit. Counterfactual survival times were then generated for each patient and analysed using standard methods. Figure 42 presents the observed and adjusted KM curves.

Figure 42: Observed and counterfactual survival times

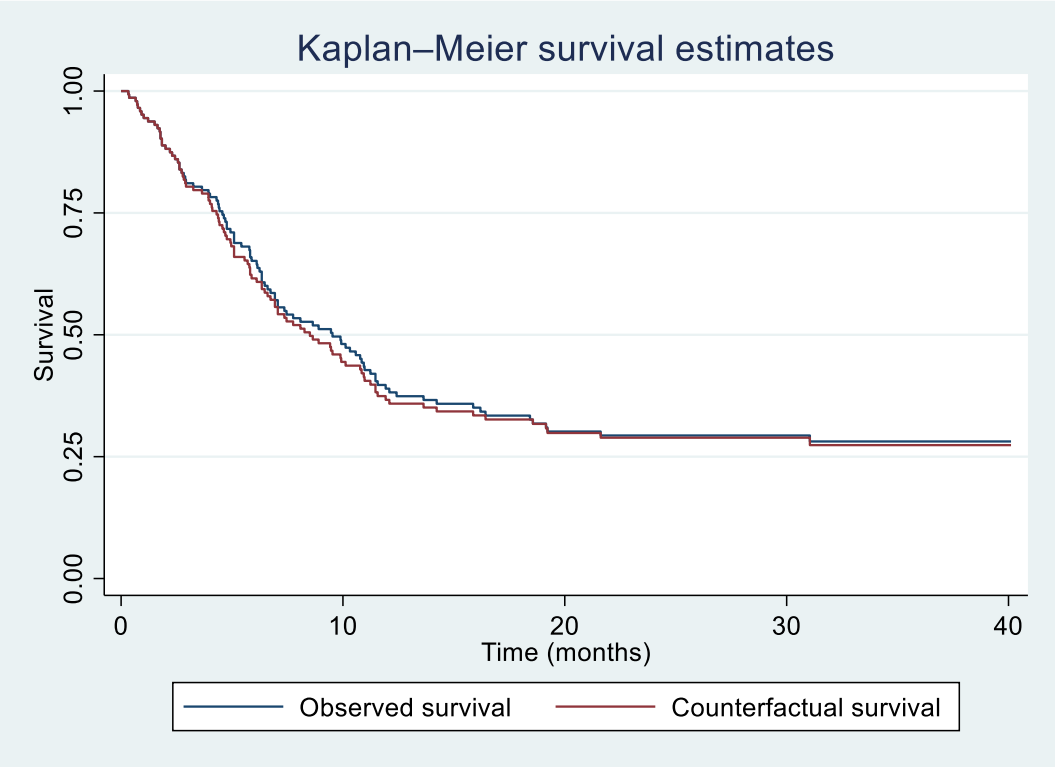


Table 62 presents the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for each parametric survival distribution for loncastuximab tesirine, while Figure 43 shows the parametric fits compared with the KM data. The Gompertz and generalised gamma distributions were associated with the lowest AIC/BIC statistics. As with the comparison to Pola+BR, the generalised gamma curve has been selected as the base-case model for OS using the LOTIS-2 population, as it aligns with clinical input that mortality will slow over time but is unlikely to exhibit the plateau seen in the Gompertz curve.

Table 62: Goodness-of-fit statistics and parameters for OS

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	428.7	437.6
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	452.6	458.6
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	429.6	435.5
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	457.2	460.1
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	431.9	437.8
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	433.8	439.7
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; LCI, lower confidence interval; OS, overall survival; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Figure 43: Parametric fits for OS compared with KM data – loncastuximab tesirine

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 44: Long-term OS extrapolations, loncastuximab tesirine

Abbreviations: OS, overall survival.

Table 63: Summary of long-term extrapolations for OS – loncastuximab tesirine

	Exponential	Gamma	Gompertz	Loglogistic	Lognormal	Weibull
Median survival (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2- year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival.

Figure 45: Smoothed OS hazard and predicted hazard for the generalised gamma curve

Abbreviations: OS, overall survival.

B.3.3.1.4.3. Progression-free survival

Table 64 presents the AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) values for each parametric survival distribution for loncastuximab tesirine, while Figure 46 show the parametric fits compared with the KM data. The generalised gamma distributions provided a good visual fit to the observed data and was associated with the lowest AIC/BIC statistics. Figure 47 compares the smoothed hazard function for PFS to the predicted hazard from the generalised gamma model. The model shows a good fit to the hazard function, and it was not considered necessary to fit more flexible models. As in the comparison to Pola+BR, the generalised gamma function was applied in the model base case.

Table 64: Goodness-of-fit statistics and parameters for PFS

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	326.0	334.9
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	371.9	377.9
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	344.3	350.3
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	383.0	386.0
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	345.9	351.9
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	350.6	356.6
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Figure 46: Parametric fits for PFS compared with KM data - loncastuximab tesirine

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 65: Summary of long-term extrapolations for PFS – loncastuximab tesirine

	Exponential	Gamma	Gompertz	Loglogistic	Lognormal	Weibull
Median survival (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1- year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival.

Figure 47: Smoothed PFS hazard and predicted hazard for the generalised gamma curve

Abbreviations: PFS, progression-free survival.

B.3.3.1.4.4. Time-to-discontinuation

Table 66 presents the AIC and BIC values for each parametric survival distribution for loncastuximab tesirine, while Figure 48 show the parametric fits compared with the KM data.

The generalised gamma distributions provided a good visual fit to the observed data and was associated with the lowest AIC/BIC statistics. Figure 49 compares the smoothed hazard function for TTD to the predicted hazard from the generalised gamma model. The maximum treatment duration is one year and time on treatment was capped in the CEM. The generalised gamma function was applied in the model base case.

Table 66: Goodness-of-fit statistics and parameters for TTD

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	544.7	553.6
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	547.0	553.0
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	560.6	566.5
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	562.2	565.1
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	584.2	590.2
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	581.0	586.9
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; LCI, lower confidence interval; SE, standard error; TTD, time to discontinuation; UCI, upper confidence interval.

Figure 48: Parametric fits for TTD compared with KM data – loncastuximab tesirine

Abbreviations: KM, Kaplan-Meier; TTD, time to discontinuation.

Figure 49: Smoothed TTD hazard and predicted hazard for the generalised gamma curve

Abbreviations: TTD, time to discontinuation.

B.3.3.1.4.5. Chemotherapy outcomes

The OS hazard ratio for chemotherapy is taken from the MAIC described in Section B.2.9. This analysis used IPD from the March 2022 data-cut of LOTIS-2 and aggregate data from two extension studies of the CORAL trial. Patients in the LOTIS-2 trial were selected based on the eligibility criteria and population characteristics of the CORAL extension studies. Patients in the LOTIS-2 trial were excluded if they were older than 67 years (the maximum age in the CORAL extension studies) or if they had with missing values in the baseline characteristics to be matched. Patients were matched on sex, prior ASCT and baseline IPI score. Table 28 compares the baseline characteristics of the studies before and after matching. Table 29 presents a comparison of the OS outcomes. After matching, the hazard ratio for loncastuximab tesirine compared to chemotherapy was 0.67 (0.50 to 0.89), implying a hazard ratio for chemotherapy compared to loncastuximab tesirine of 1.49 (1.12 to 2.08).

The CORAL extension studies did not report PFS outcomes for chemotherapy and there are no MAIC analyses comparing PFS for chemotherapy and loncastuximab tesirine. Therefore, it was assumed that the HR for PFS was equal to the OS HR.

The modelled chemotherapy regimens have a fixed treatment duration (Section B.3.5.1), thus TTD is not applicable to chemotherapy. Patients are assumed to receive all cycles of treatment unless they progress prior to completion of treatment.

B.3.3.2. Patient characteristics

Age, sex, body weight and body surface area (BSA) characteristics were used to inform inputs such as drug costs throughout the analysis. Table 67 presents the baseline patient characteristics of the target population, obtained from LOTIS-2 (59).

Table 67: Baseline characteristics used in model

Baseline characteristic	Mean (SD)
Baseline age, years	62.72
Male, %	41%
Body weight, kg	77.1 (18.7)
BSA, m^2	1.86 (0.2)

Abbreviations: BSA, body surface area; SD, standard deviation.

B.3.3.3. General population mortality

The probability of death in each cycle was capped by general population mortality. Age- and gender-specific probabilities of death were taken from published national life tables for England and Wales, using data for 2020 (92).

B.3.3.4. Adverse events

Grade ≥3 TEAEs occurring in ≥5% of patients were obtained from LOTIS-2 for loncastuximab tesirine and from TA649 for Pola+BR (11). The CORAL extension studies do not report safety data. AE rates for chemotherapy were taken from TA567 and TA649 (11, 18). Any Grade ≥3 AE occurring in at least 5% of patients in the salvage chemotherapy arm in TA567 and in the BR arm of GO29365 was included, with the rates pooled across both studies. Adverse events were assumed to incur a one-off cost and QALY loss in the first cycle of the model. The incidence of adverse events by model arm is presented in Table 68.

Table 68: Incidence of adverse events

	Incidence – loncastuximab tesirine	Incidence - chemotherapy	Incidence - Pola+BR
Neutropenia	25.5%	60.4%	40.0%
Thrombocytopenia	17.9%	63.5%	40.0%
Gamma-glutamyltransferase increase	16.6%	0.0%	0%
Anaemia	10.3%	20.8%	24.2%
Leukopenia	9.0%	3.1%	11.1%
Hypophosphatemia	5.5%	1.1%	2.2%
Lymphopenia	5.5%	0.0%	11.1%
Hypokalaemia	0%	14.6%	6.7%
Febrile neutropenia	0%	18.7%	11.1%
Lower respiratory tract infection	0%	4.2%	8.9%
Diarrhoea	0%	5.2%	4.4%
Fatigue	0%	8.4%	4.4%
Nausea	0%	10.4%	0%
Vomiting	0%	7.3%	0%

Abbreviations: Pola+BR, polatuzumab plus bendamustine plus rituximab.

B.3.4. Measurement and valuation of health effects

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

The EQ-5D-5L was collected on Day 1 of each 21-day treatment cycle and at the end of treatment (EOT) visit in LOTIS-2. 138 patients had a valid measurement of baseline utility.

B.3.4.2. Mapping

The EQ-5D-5L data collected were mapped to EQ-5D-3L utility index scores using the mapping function developed by the DSU (93), as per NICE guidelines. There was a total of 788 observations of utility scores across the trial period.

Table 69: Summary of UK EQ-5D-3L utility scores by visit

Visit	N	Mean	SD	Mean CFB	SD
Baseline (Cycle 1, Day 1)	138	0.707	0.254	0.000	0.000
Cycle 2, Day 1	113	0.724	0.230	-0.003	0.162
Cycle 3, Day 1	81	0.745	0.245	0.001	0.187
Cycle 4, Day 1	63	0.724	0.265	-0.022	0.224
Cycle 5, Day 1	46	0.705	0.232	-0.034	0.204
Cycle 6, Day 1	33	0.700	0.282	0.005	0.195
Cycle 7, Day 1	28	0.730	0.182	0.004	0.183
Cycle 8, Day 1	23	0.696	0.248	-0.026	0.191
Cycle 9, Day 1	20	0.694	0.242	0.003	0.149
Cycle 10, Day 1	13	0.711	0.190	0.009	0.160
Cycle 11, Day 1	12	0.646	0.294	-0.029	0.155
Cycle 12, Day 1	10	0.623	0.259	-0.021	0.115
Cycle 13, Day 1	8	0.762	0.155	0.014	0.177
Cycle 14, Day 1	5	0.754	0.150	0.017	0.174
Cycle 15, Day 1	5	0.774	0.149	-0.015	0.125
Cycle 16, Day 1	4	0.733	0.183	-0.080	0.110
Cycle 17, Day 1	4	0.707	0.192	-0.106	0.097
Cycle 18, Day 1	3	0.751	0.206	-0.070	0.062
Cycle 19, Day 1	2	0.853	0.190	-0.002	0.003
Cycle 20, Day 1	2	0.890	0.139	0.034	0.049
Cycle 21, Day 1	2	0.831	0.222	-0.025	0.035
Cycle 22, Day 1	2	0.846	0.201	-0.009	0.013
Cycle 23, Day 1	1	0.988	0.000	0.000	0.000
Cycle 24, Day 1	1	0.988	0.000	0.000	0.000
Cycle 25, Day 1	1	0.988	0.000	0.000	0.000
Cycle 26, Day 1	1	0.988	0.000	0.000	0.000
EOT	101	0.626	0.288	-0.124	0.245
Unscheduled visit	66	0.704	0.164	-0.019	0.221
Total	**788**	**0.706**	**0.243**	**-0.023**	**0.180**

Abbreviations: CFB, change from baseline; EOT, end of treatment; SD, standard deviation

The mean EQ-5D-3L utility score at baseline was 0.707 (SD 0.254). Mean utility scores were consistent over cycles 1 to 9, where more than 10% of patients remain on treatment, and the

mean CFB remains small at all time points, with the exception of the EOT visit, where the mean CFB was -0.124.

B.3.4.3. Health-related quality of life studies

The SLR identified 13 studies that met the pre-defined inclusion criteria (11, 15, 18, 94-103).

Of the 13 included studies, four met the NICE reference case requirements for Health state utility value (HSUV) evidence, in that they reported utility values derived from a representative UK population or using UK tariffs, and were elicited using a preference based measure, such as time trade-off (TTO) or standard gamble, and an appropriate method for valuing health states (11, 15, 18, 103).

One UK-based retrospective cohort study was included in the analysis which was relevant to the NICE reference case (103). The patient population comprised of DLBCL patients from the UK's population-based Haematological Malignancy Research Network. Using the EQ-5D-5L instrument, the study reported utility values for health states defined by progressed disease at different stages of treatment.

Three NICE HTA evaluations for pharmaceutical interventions used to treat R/R DLBCL were also included (11, 15, 18). All three submissions reported disutility decrements, with two specifically focusing on adverse events related to treatment (11, 15). The NICE TA559 (15) and NICE TA649 (11) appraisals for axicabtagene ciloleucel and polatuzumab vedotin, respectively, used the ZUMA-1 trial to derive most of their utility values. The health states reported in these two submissions were defined by response criteria and progression of disease. The NICE TA567 (18) appraisal for tisagenlecleucel used the JULIET trial to derive utility and disutility values. There were three utility values reported in the TA567 submission for progression free, progressed disease, and death health states. The EQ-5D-5L and EQ-5D-3L instruments were used to derive utilities in the NICE TA649 (11) and NICE TA559 (15) appraisals, respectively, whilst the SF-36 instrument was used in the NICE TA567 evaluation (18).

A summary of the methods of the systematic literature review to identify health-related quality of life data is provided in Appendix H.

B.3.4.4. Adverse reactions

The impact of AEs on HRQoL is captured as a one-off QALY loss applied in the first cycle of the model. The AE rates for each comparator (Section B.3.3.4), the mean durations of each AE and the AE disutility associated with any Grade ≥3 AE from LOTIS-2 were used to calculate a QALY loss for each treatment. The mean AE disutility of 0.045 calculated from the mixed effects regression model (Section B.3.4.5) was assumed to apply to all AEs in the model. A scenario is presented that uses AE disutilities from previous appraisals (11, 18). AE disutilities for each treatment are presented in Table 70. The average duration of each event was calculated from LOTIS-2 data.

Table 70: AE disutilities and durations

	Disutility (LOTIS-2)	Duration (days)	Disutility (scenario)
Neutropenia	0.045	8.95	0.090
Thrombocytopenia		13.45	0.110
Gamma-glutamyltransferase increase		0†	0.000
Anaemia		5.67	0.250
Leukopenia		9.05	0.090
Hypophosphatemia		6.08	0.250
Lymphopenia		16.64	0.090
Hypokalaemia		7.14	0.090
Febrile neutropenia		5.5	0.150
Lower respiratory tract infection		6.75	0.200
Diarrhoea		6.75	0.100
Fatigue		2	0.012
Nausea		6.75‡	0.050
Vomiting		6.75‡	0.050

†Assumed to have no impact of quality of life
‡Assumed equal to diarrhoea
Abbreviations: AE, adverse event.

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

EQ-5D-5L scores from LOTIS-2 were mapped to the EQ-5D-3L (Section B.3.4.2) and analysed using mixed-effects repeated-measures linear regression models with a random intercept for each patient to account for multiple observations. All models adjusted for baseline utility centred

on the mean. This excluded 16 observations in patients without a baseline measurement. Two models have been estimated, the first adjusts for progression status and ongoing Grade ≥3 AEs (Table 71), and the second adjusts for progression status only (Table 72). The model incorporating ongoing AEs was used for the base case analysis. In line with the NICE Process and methods guide, utility values applied in the model have been adjusted for age, using general population utility values for the UK taken from Hernandez-Alava et al, 2022 (104). A multiplicative method was used to adjust utility values in each cycle.

Table 71: Utility analysis adjusting for progression status and ongoing AEs

	Coefficient	SE	LCI	UCI
Baseline utility	0.739	0.039	0.662	0.817
Progressed disease	-0.056	0.021	-0.098	-0.015
Ongoing AE	-0.045	0.016	-0.076	-0.014
Constant	0.693	0.011	0.673	0.714

Abbreviations: AE, adverse vent; LCI, lower confidence interval; SE, standard error; UCI, upper confidence interval.

Table 72: Utility analysis adjusting for progression status

	Coefficient	SE	LCI	UCI
Baseline utility	0.749	0.040	0.672	0.827
Progressed disease	-0.058	0.021	-0.100	-0.016
Constant	0.685	0.010	0.665	0.706

Abbreviations: AE, adverse vent; LCI, lower confidence interval; SE, standard error; UCI, upper confidence interval.

Scenarios using HSUVs applied in previous economic analyses have also been included in the model. Utility values from the ZUMA-1 (axi-cel) clinical trial, or the JULIET (tisa-cel) trial have been included. Use of ZUMA-1 data in TA649 (Pola+BR) was criticised by the committee, however no preferable values were identified. Scenarios using the absolute values have been included, alongside scenarios applying the progression decrement from each trial to the baseline value from LOTIS-2. Modelled health state utility values from previous appraisals are presented in Table 73.

Table 73: Health state utility values

Health state	Utility value (disutility associated with progression)	Source
Progression-free	0.72	ZUMA-1 (54)
	0.83	JULIET (55)

Health state	Utility value (disutility associated with progression)	Source
Progressed disease	0.65 (0.07)	ZUMA-1 (54)
	0.71 (0.12)	JULIET (55)

Utility values used in the analysis are provided in Table 74.

Table 74: Summary of utility values for the cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI	Reference in submission	Justification
Progression-free	0.685 (0.011)	0.673 to 0.714	Section B.3.4.5, Page 168	These are utility values collected in the pivotal clinical trial for lonca which best match the reference case.
Disutility for PD	-0.056 (0.021)	-0.098 to -0.015		
AE disutility	-0.045 (0.16)	-0.076 to -0.014		

Abbreviations: AE, adverse event; CI, confidence interval; lonca, loncastuximab tesirine; PD, progressed disease

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

An SLR was conducted to identify cost and resource use data relevant to the decision problem from the published literature as summarised in Appendix I.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Acquisition costs

The acquisition costs for loncastuximab tesirine, Pola+BR and RGemOx are presented in Table 75. All costs were sourced from the electronic marketing information tool (eMIT) where available or the British National Formulary (BNF) (105). Relative dose intensity (RDI) data have been taken from LOTIS-2 for loncastuximab tesirine, and from TA649 for Pola+BR. Costs for drugs dosed by weight or BSA are calculated including vial wastage using the method of moments, assuming a normal distribution around the mean weight or BSA (106). Where multiple vial sizes are available costs are calculated using the smallest possible vial wastage.

Table 75: Drug acquisition costs

Regimen	Drug	Strength	Units/pack	Cost/pack	Target dose	RDI	Cost/cycle
Loncastuximab	Loncastuximab tesirine	10 mg	1	List price: £15,200.00 PAS price: [redacted]	150 µg/kg for 2 cycles, 75 µg/kg thereafter	98.09%	Cycles 1 & 2: [redacted] Cycle 3+: [redacted]
	Dexamethasone	4 mg	50	£19.62	4 mg orally, twice daily for 3 days	98.09%	£2.35
Pola+BR	Polatuzumab vedotin	30 mg	1	£2,370.00	1.8 mg/kg	99.5%	£11,687.32
		140 mg	1	£11,060.00			
	Bendamustine	25 mg	5	£34.08	90 mg/m^2	95.4%	£65.91
		100 mg	5	£82.89			
	Rituximab	100 mg	1	£157.17	375 mg/m^2	99.4%	£1,169.94
		500 mg	1	£785.84			
RGemOx	Rituximab	100 mg	1	£157.17	375 mg/m^2	100%	£1,177.00
		500 mg	1	£785.84			
	Gemcitabine	200 mg	1	£8.59	1000 mg/m^2	100%	£39.40
		1000 mg	1	£3.30			
	Oxaliplatin	50 mg	1	£46.78	100 mg/m^2	100%	£66.61
		100 mg	1	£60.29			
		200 mg	1	£20.45			

Abbreviations: Pola+BR, polatuzumab plus bendamustine rituximab; RDI, relative dose intensity; R-GemOx, rituximab, gemcitabine and oxaliplatin; TBC, to be confirmed.

B.3.5.1.2. Administration costs

Drug administration costs were taken from the National schedule of NHS costs (107). All regimens were assumed to be delivered in an outpatient setting and loncastuximab tesirine and Pola+BR were assumed to incur the cost of delivering more complex parenteral chemotherapy on Day 1 of each treatment cycle. Pola+BR also incurs the cost of delivering subsequent elements on Day 2 of each treatment cycle. Chemotherapy was assumed to incur the cost an extended infusion, to allow for the infusion of premedication.

Table 76: Drug administration costs by currency code

Currency code	Description	Setting	Cost
SB13Z	Deliver more Complex Parenteral Chemotherapy at First Attendance	Outpatient	£258.56
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	Outpatient	£342.66
SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle	Outpatient	£438.38

Table 77: Drug administration costs by regimen

Regimen	Per cycle administration cost
Loncastuximab tesirine	£258.56
Pola+BR	£696.94
RGemOx	£342.66

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

B.3.5.1.3. Subsequent therapies

The cost of subsequent therapies is applied as a one-off cost at the time of a PFS event. The rates of subsequent therapy use are informed by data from LOTIS-2, clinical opinion, and published data. Clinical input provided to the company varied on the number of patients expected to receive further treatment after loncastuximab tesirine, and on the type of therapy received. Estimates of the proportion of patients who would receive further treatment varied between 25% and 60%. Clinicians did not think that pattern of subsequent treatments would differ between loncastuximab tesirine, Pola+BR and chemotherapy when used at the same point in the treatment pathway.

When asked which treatments patients might receive after loncastuximab tesirine, clinicians stated that chemotherapy may still be used, but that this will largely be palliative. Two clinicians said they would consider using tafasitimab with lenalidomide, however this is not currently recommended by NICE. The other common treatment option would be to enter patients into trials of bispecifics. It was agreed that ASCT would not be used after loncastuximab tesirine, and that use of AlloSCT would be rare.

12 of the 145 patients in LOTIS-2 (8%) went on to receive an SCT, with 7 of these being AlloSCT, three ASCT and two unknowns. While UK clinicians did not think that ASCT would be used after loncastuximab tesirine, the rate in the trial was low and the costs of ASCT have been included. The COTA data does not report how many patients went on to SCT and based on clinical input it was assumed that the rate of SCT use in the Pola+BR arm was equal to the loncastuximab tesirine arm. A scenario using data from the GO29365 extension was considered, in which 4 patients (3%) went on to SCT, 1 ASCT and 3 AlloSCT. 80 of 266 patients (30%) of patients in the CORAL extension study went on the receive an SCT. 59 patients (22%) had an ASCT and 21 patients (8%) had an AlloSCT. While this rate is higher than would be expected in clinical practice, it reflects the population of the CORAL studies, which clinicians stated was likely to be fitter than expected in clinical practice due to the design of the CORAL study. The costs of ASCT and AlloSCT is based inflated costs from TA576 using the NHS Cost Inflation Index, giving a cost of £30,965.89 for ASCT and £89,107.60 for AlloSCT.

Three of the five clinicians stated CAR-T would not be used after loncastuximab tesirine. They highlighted that patients are unlikely to become eligible at 4th line or beyond if they were ineligible when receiving loncastuximab tesirine and the lack of data on repeatedly targeting CD19. One of the clinicians said they were unlikely to use CAR-T after loncastuximab tesirine currently, though it is possible that they would consider loncastuximab tesirine to bridge to CAR-T in the future, if available. The final clinician also felt that loncastuximab tesirine could be used to bridge to CAR-T if patients have a good response to treatment, but also highlighted that these patients may have a long remission without further treatment. 16 patients (11%) in LOTIS-2 went on to have to receive CAR-T. In the comparison to Pola+BR, the cost and effects of CAR-T are included, and it is assumed that the rate of CAR-T therapy would be the same between arms. In the comparison to chemotherapy, it is assumed that no one would go on to receive CAR-T and the impact of CAR-T on the loncastuximab tesirine OS curve is removed.

Excluding CAR-T and SCT, 54% of patients in LOTIS-2 went on to receive subsequent treatment. This is assumed to be chemotherapy, and has been costed as RGemOx, giving a total cost of £7,327 per course and an average cost of £3,957 per progression.

Table 78: Cost of subsequent treatment, loncastuximab tesirine vs Pola+BR

Regimen	Chemotherapy	ASCT	AlloSCT	CAR-T	Average cost
Loncastuximab tesirine	54%	3%	8%	11%	£48,004.37
Pola+BR	54%	3%	8%	11%	£48,004.37

Abbreviations: AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor; Pola+BR, polatuzumab plus bendamustine and rituximab.

Table 79: Cost of subsequent treatment, loncastuximab tesirine vs chemotherapy

Regimen	Chemotherapy	ASCT	AlloSCT	CAR-T	Average cost
Loncastuximab tesirine	54%	3%	8%	0%	£12,180.53
Chemotherapy	54%	22%	8%	0%	£18,175.84

Abbreviations: AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor; RGemOx; rituximab, gemcitabine and oxaliplatin.

B.3.5.2. Health state unit cost and resource use

Table 80 presents the cost per unit for each type of resource included in the model, whilst Table 81 presents the annual frequency of resource use in each health state.

Table 80: Supportive care resource use unit costs included in the model

Procedure	Cost per unit	Source
Professional and social services		
Residential care (day)	£148.00	Jones and Burns 2021; crude average of local authority & private residential care per permanent resident day
Day care (day)	£66.00	Jones and Burns 2021; local authority own-provision day care
Home care (day)	£35.91	National Audit Office: End of life care; per diem cost of community care = £28 (assumed by the National Audit Office to be the same as the cost of home care); inflated from 2007/08 to 2020/21 using the Hospital & Community Health Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021
Hospice (day)	£169.31	National Audit Office: End of life care; per diem cost of hospice care = £132; inflated from 2007/08 to 2020/21 using the Hospital & Community Health Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021

Procedure	Cost per unit	Source
Health care professionals and hospital resource use		
Oncologist (visit)	£224.55	NHS Reference Costs 2020/21; WF01A, service code 370, Medical Oncology
Haematologist (visit)	£214.56	NHS Reference Costs 2020/21; WF01A, service code 303, Clinical Haematology
Radiologist (visit)	£185.20	NHS Reference Costs 2020/21; WF01A, service code 800, Clinical Oncology (Previously Radiotherapy)
Nurse (visit)	£51.84	NHS Reference Costs 2020/21; N02AF; District nurse, adult, face to face
Specialist nurse (visit)	£51.84	NHS Reference Costs 2020/21; N02AF; District nurse, adult, face to face
GP (visit)	£39.23	Jones and Burns 2021; section 10.3b, General practitioner, unit costs
District nurse (visit)	£51.84	NHS Reference Costs 2020/21; N02AF; District nurse, adult, face to face
CT scan	£167.31	NHS Reference Costs 2020/21; RD27Z, Computerised Tomography Scan of more than Three Areas
Inpatient day	£413.35	NHS Ref Costs 2017/18; SA17G, Excess Bed Days; inflated from 2017/18 to 2020/21 using the Hospital & Community Health Services (HCHS) inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021 as excess bed days are no longer reported
Palliative care team	£231.88	NHS Reference Costs 2020/21; SD03A, Hospital Specialist Palliative Care Support, 19 years and over
Treatment follow-up		
Full blood counts	£3.63	NHS Reference Costs 2020/21; DAPS05, Directly Accessed Pathology Services: Haematology
LDH	£3.63	NHS Reference Costs 2020/21; DAPS05, Directly Accessed Pathology Services: Haematology
Liver function	£3.63	NHS Reference Costs 2020/21; DAPS05, Directly Accessed Pathology Services: Haematology
Renal function	£3.63	NHS Reference Costs 2020/21; DAPS05, Directly Accessed Pathology Services: Haematology
Immunoglobulin	£3.63	NHS Reference Costs 2020/21; DAPS05, Directly Accessed Pathology Services: Haematology
Calcium phosphate	£3.63	NHS Reference Costs 2020/21; DAPS05, Directly Accessed Pathology Services: Haematology

Abbreviations: CT, Computerised Tomography; GP, General Practitioner; LDH, lactate dehydrogenase test; NHS, National Health Service.

Table 81: Annual frequency of resource use in PFS and PD

Procedure	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
Professional and social services				

Procedure	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
Residential care (day)	39.00	9.80	0.00	TA306, ERG Report, Table 37. Annual frequency calculated from 28-day resource use
Day care (day)	14.60	3.70	24.40	TA306, ERG Report, Table 37. Annual frequency calculated from 28-day resource use
Home care (day)	60.90	22.20	121.70	TA306, ERG Report, Table 37
Hospice (day)	0.70	0.20	12.10	TA306, ERG Report, Table 38
Health care professionals and hospital resource use				
Oncologist (visit)	21.80	5.50	4.30	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
Haematologist (visit)	10.20	2.50	13.00	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
Radiologist (visit)	21.80	4.30	0.00	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
Nurse (visit)	52.20	13.00	0.00	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
Specialist nurse (visit)	8.70	2.20	32.60	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
GP (visit)	26.10	6.50	43.00	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
District nurse (visit)	19.60	5.00	52.20	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
CT scan	4.00	4.00	0.00	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use
Inpatient day	3.20	3.20	2.70	TA306, ERG Report, Table 40
Palliative care team	0.00	0.00	17.30	TA306, ERG Report, Table 40
Treatment follow-up				
Full blood counts	43.40	43.40	13.00	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use
LDH	26.10	26.10	4.30	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use

Procedure	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
Liver function	43.40	43.40	13.00	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use
Renal function	43.40	43.40	4.30	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use
Immunoglobulin	8.70	8.70	4.30	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use
Calcium phosphate	8.70	8.70	13.00	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use
Haematologist (visit)	3.10	3.10	2.70	TA306, ERG Report, Table 40
Oncologist (visit)	0.60	0.60	0.30	TA306, ERG Report, Table 40
Nurse (visit)	4.90	4.90	2.10	TA306, ERG Report, Table 40
Radiologist (visit)	0.03	0.03	0.03	TA306, ERG Report, Table 40
GP (visit)	0.13	0.13	0.07	TA306, ERG Report, Table 40

Abbreviations: CT, Computerised Tomography; ERG, Evidence Review Group; GP, General Practitioner; LDH, lactate dehydrogenase test; PD, progressed disease; PFS, progression-free survival.

B.3.5.3. Adverse reaction unit costs and resource use

The unit costs associated with the management of the identified AEs are presented in Table 82, whilst the incidence of each identified AE is presented in Section B.3.3.4.

Table 82: Unit costs of treatment-related AEs included in the economic model

Procedure	Cost per unit	Source
Neutropenia	£366.66	NICE TA567
Thrombocytopenia	£414.46	NICE TA567
Gamma-glutamyltransferase increase	£0	No additional costs are associated with gamma-glutamyltransferase increase
Anaemia	£409.10	NICE TA567
Leukopenia	£313.67	NICE TA649; inflated from 2017/18 to 2020/21 using the Hospital & Community Health Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021
Hypophosphatemia	£543.69	Assumed equal to hypokalaemia, as per NICE TA567
Lymphopenia	£1,580.60	NICE GID-TA10645; inflated from 2019/20 to 2020/21 using the Hospital & Community Health

		Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021
Hypokalaemia	£543.69	NICE GID-TA10645; inflated from 2019/20 to 2020/21 using the Hospital & Community Health Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021
Febrile neutropenia	£1,991.45	NICE TA649; inflated from 2017/18 to 2020/21 using the Hospital & Community Health Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021
Lower respiratory tract infection	£407.35	NICE TA649; inflated from 2017/18 to 2020/21 using the Hospital & Community Health Services inflation index and the NHS Cost Inflation Index reported in Jones and Burns 2021

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

B.3.5.4. Miscellaneous unit costs and resource use

No additional costs have been included in the model.

B.3.6. Severity

When compared to chemotherapy, loncastuximab tesirine meets the criteria to apply a severity weight of 1.2 to QALYs. Based on a mean age at baseline of 62.75 and a population of 41% women, the expected general population QALYs would be 11.66, calculated using lifetables from England and Wales and general population utility values from the DSU.

Comparatively, patients treated with chemotherapy would expect to receive 0.92 QALYs, an absolute shortfall of 10.74 QALYs and a proportional shortfall of 0.92, meeting the criteria for a multiplier of 1.2 for QALY gains. Patients treated with Pola+BR would expect to receive 1.82 QALYs, an absolute shortfall of 9.84 QALYs and a proportional shortfall of 0.84.

Table 83. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	41% female	Section B.3.3.1
Starting age	62.75	Section B.3.3.1

Abbreviations: QALY, quality adjusted life year

Table 84. Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years - Chemotherapy	Undiscounted life years – Pola+BR
Progression-free	0.685	1.15	1.37
Progressed disease	0.629	0.59	2.30

Abbreviations: Pola+BR, polatuzumab plus bendamustine rituximab; QALY, quality adjusted life year

Table 85. Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
11.66	Chemotherapy: 0.92	10.74	0.92
	Pola+BR: 1.82	9.84	0.84

Abbreviations: Pola+BR, polatuzumab plus bendamustine rituximab; QALY, quality adjusted life year

In both cases, the modelled outcomes are expected to be optimistic estimates, and in scenario analyses the total QALYs falls. In previous submissions, the committee has considered R/R DLBCL to be a serious, highly life-limiting condition, with Pola+BR, axicantagene ciloleucel and tisgenlecleucel all meeting the requirements to be considered a life-extending end-of-life treatment when compared to chemotherapy.

Despite these advancements in treatment, R/R DLBCL remains a highly severe and aggressive condition. This analysis shows that patients treated with chemotherapy have an average life-expectancy of 19 months, with a median life-expectancy of six months. The total QALY gain in the model is driven a small number of patients that achieve long-term remission, however the majority of patients (70%) have a life-expectancy below one year. 65% of patients of would be expected to survive less than 10 months and would receive less than 0.58 QALYs, a proportional shortfall of 0.95.

B.3.7. Uncertainty

R/R DLBCL is a relatively rare condition and, like all treatments for small patient populations, formal evidence generation is particularly difficult. Therefore, RWE should be readily considered alongside trial data to aid committee decision-making.

B.3.8. Managed access proposal

Not applicable.

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

B.3.9.1. Summary of base case analysis inputs

A summary of the base case analysis inputs and variables of the base-case analysis inputs are provided in Table 86.

Table 86. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	Section B.3.2.2
Discount rate, outcomes	3.5%	Fixed	
Time horizon	40 years	Fixed	
Baseline age, years	62.72	Normal	Section B.3.3.2
Female, %	0.41	Fixed	
Body weight, kg	77.10	Normal	
BSA, m^2	1.86	Normal	
Survival outcomes, loncastuximab vs Pola+BR			
OS, loncastuximab	Generalised gamma	Multivariate normal	Section B.3.3.1.3
PFS, loncastuximab	Generalised gamma	Multivariate normal	
TTD, loncastuximab	Generalised gamma	Multivariate normal	
OS, Pola+BR	Generalised gamma	Multivariate normal	
PFS, Pola+BR	Generalised gamma	Multivariate normal	
Survival outcomes, loncastuximab vs chemotherapy			
OS, loncastuximab	Generalised gamma	Multivariate normal	Section B.3.3.1.4
PFS, loncastuximab	Generalised gamma	Multivariate normal	
TTD, loncastuximab	Generalised gamma	Multivariate normal	
OS HR, chemotherapy	1.49	Log-normal	
PFS HR, chemotherapy	1.49	Log-normal	
Utilities			
PFS utility	0.69	Multivariate normal	Section B.3.4.5
PD disutility	-0.06	Multivariate normal	
AE disutility	-0.05	Multivariate normal	
Drug costs			
Loncastuximab 10mg Cost/pack	[redacted]	Fixed	Section B.3.5.1
Dexamethasone 4mg Cost/pack	£19.62	Fixed	
Polatuzumab vedotin 30mg Cost/pack	£2,370.00	Fixed	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Polatuzumab vedotin 100mg Cost/pack	£11,060.00	Fixed	
Bendamustine 25mg Cost/pack	£34.08	Fixed	
Bendamustine 100mg Cost/pack	£82.89	Fixed	
Rituximab 100mg Cost/pack	£157.17	Fixed	
Rituximab 500mg Cost/pack	£785.84	Fixed	
Gemcitabine 1g powder for solution for infusion vials	£8.59	Fixed	
Gemcitabine 200mg powder for solution for infusion vials	£3.30	Fixed	
Oxaliplatin 100mg/20ml solution for infusion vials / Packsize 1	£46.78	Fixed	
Oxaliplatin 200mg/40ml solution for infusion vials / Packsize 1	£60.29	Fixed	
Oxaliplatin 50mg/10ml solution for infusion vials / Packsize 1	£20.45	Fixed	
Other costs			
Subsequent treatment	Table 78; Table 79	Fixed	Section B.3.5.1.3
Administration costs	Table 77	Fixed	Section B.3.5.1.2
HCRU	Table 80; Table 81	Fixed	Section B.3.5.2
AE costs	Table 82	Fixed	Section B.3.5.3

Abbreviations: AE, adverse event; BSA, body surface area; HCRU, healthcare resource use; HR, hazard ratio; loncastuximab, loncastuximab tesirine; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR; polatuzumab plus bendamustine plus rituximab ; TTD, time to discontinuation.

B.3.9.2. Assumptions

Assumption	Justification
The is no difference in efficacy between chemotherapy treatment options used at third-line-plus, and RGemOx is a representative choice.	The company sought clinical opinion on which chemotherapy regimens were most widely used at third line in R/R DLBCL. The most commonly mentioned regimen was RGemOX, however (R)GDP, DECC, PEPC, gemcitabine monotherapy and R+lenalidomide were also noted to be used. Clinical experts consulted by the company stated that that a wide range of chemotherapy treatments are used at third-line-plus due to a lack of differentiation between options, with the key driver behind treatment choice being toxicity rather than efficacy.
Outcomes from LOTIS-2 are generalisable to UK clinical practice	Clinical experts consulted by the company all considered the population included in LOTIS-2 to be a good reflection of the third-line-plus R/R DLBCL population in the UK.
Outcomes from the CORAL extension studies can be used to inform the chemotherapy arm of the model	The CORAL extension studies present data on patients following participation in the CORAL study, both for those who went on to receive ASCT per-protocol and those who did not proceed to ASCT and who were candidates for a third-line regimen. They present data for the correct line of treatment, however clinical experts consulted by the company considered the population to be fitter than the average patient, as they were all candidates for ASCT. This is reflected in the high number of SCTs observed during follow up, with 30% of patients going on to receive an SCT. As such, using CORAL extension data is a conservative approach for loncastuximab tesirine. The impact of this is tested in scenario analysis that reweights chemotherapy survival curves according to the proportion of patients expected to go on to receive an SCT.
The OS HR for chemotherapy vs loncastuximab tesirine is generalisable to PFS	No PFS outcomes for chemotherapy were available from the CORAL extension studies. Instead, the HR on OS has been applied to the modelled curves for loncastuximab tesirine. The impact of this assumption is tested in scenario analysis.
Outcomes from the GO29365 study are suitable for modelling Pola+BR	The study reports median data on outcomes for Pola+BR when used at third-line-plus, giving a median PFS of 6.1 months and median OS of 9.5 months. RWE from the UK suggests that median PFS in clinical practice is 4.8 months and OS is 8.2 months. These values are lower than observed in GO29365 and this population includes a significant number of second-line patients (33.8%), and 30% of patients were using Pola+BR as a bridge to CAR-T. As such, outcomes from the GO29365 study are considered to be optimistic for Pola+BR and represent a conservative comparison for loncastuximab tesirine.
There is no waning of the treatment effect	Patients enrolled in LOTIS-2 were treated for a maximum of 1 year, and so extrapolations of OS and PFS are based on follow-up that includes a significant proportion of patients off treatment. Clinical experts advised that the treatment effect would continue beyond the end of treatment. Data indicate that [redacted] following the use of loncastuximab tesirine with no further treatment (60).
CAR-T is not relevant subsequent treatments, and the rates of subsequent	There was no consensus between clinical experts on what subsequent therapies would be used after loncastuximab tesirine. Most stated that CAR-T was not likely subsequent therapies, however this was not unanimous. A small number of patients in LOTIS-2 did receive CAR-T

Assumption	Justification
treatment use does not differ between comparators.	therapy (11%), however scenarios removing the impact of this subsequent treatments on OS have been presented and there is minimal impact on results. Clinicians agreed that the rate of subsequent therapy use would not differ between comparators. The impact of CAR-T on OS outcomes for Pola+BR cannot be assessed, and so the costs are included in the comparison to Pola+BR. For the comparison to chemotherapy, the costs of CAR-T is excluded and the impact of CAR-T on OS curves is removed.
Resource use is dependent on health state and independent of treatment	In line with previous R/R DLBCL appraisals (TA559, TA649) resource use was assumed to be dependent on progression status only.

Abbreviations: ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T cells; DECC, dexamethasone, etoposide, chlorambucil, lomustine; GDP, cisplatin, gemcitabine, dexamethasone; HR, hazard ratio; OS, overall survival; PEPC, prednisone, etoposide, cyclophosphamide and procarbazine; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab ; R, rituximab; RGemOx, rituximab with gemcitabine and oxaliplatin; R/R DLBCL, relapsed or refractory diffuse large B-cell lymphoma; RWE, real-world evidence; SCT, stem cell transplant; UK, United Kingdom.

B.3.10. Base-case results

B.3.10.1. Base case incremental cost-effectiveness analysis results

Base-case results for the comparison with Pola+BR are provided in Table 87, with the net health benefit analysis presented in Table 88. Compared to SoC, Pola+BR, loncastuximab tesirine is less costly and more effective and dominates Pola+BR, with a positive net health benefit at any willingness-to-pay (WTP) threshold.

Base-case results for the comparison to chemotherapy are also presented in Table 89, with net health benefit analysis in Table 90. Compared to chemotherapy loncastuximab tesirine produces an additional [redacted] QALYs at an incremental cost of [redacted], giving an ICER of £48,986.

Table 87. Base-case results, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£871,751	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; LYG, life years gained; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine rituximab; QALYs, quality-adjusted life years; vs, versus

Table 88. Net health benefit, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	-2.12	-1.43

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine rituximab; QALYs, quality-adjusted life years; vs, versus

Table 89. Base-case results, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,986	£48,986

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; LYG, life years gained; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine rituximab; QALYs, quality-adjusted life years; vs, versus

Table 90. Net health benefit, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Chemotherapy	[redacted]	[redacted]	-	-	-	-
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	-1.25	-0.55

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine rituximab; QALYs, quality-adjusted life years; vs, versus

Estimates of clinical outcomes included in the cost-effectiveness analysis (and compare with the clinical trial results), and disaggregated results of the base-case incremental cost effectiveness analysis are provided in Appendix J.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 5,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

Table 91 presents the outputs of the PSA comparison loncastuixmab tesirine and Pola+BR. Results are aligned with the deterministic results. Figure 50 presents the incremental costs and QALYs from each simulation and Figure 51 presents the CEAC. Loncastuximab tesirine was dominant in [redacted]% of simulations, more effective in [redacted]% of simulations and cost saving in [redacted]% of simulations.

Table 91: Probabilistic cost-effectiveness results, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	-£706,009	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine rituximab; QAYs, quality-adjusted life years; vs, versus

Figure 50: Probabilistic cost-effectiveness results, loncastuximab tesirine vs Pola+BR: simulations (with PAS price for loncastuximab tesirine)

Abbreviations: PAS, patient access scheme ; Pola+BR, polatuzumab plus bendamustine rituximab; vs, versus

Figure 51: Cost-effectiveness acceptability curve, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Abbreviations: PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine rituximab ; vs, versus

Table 92 presents the outputs of the PSA comparison loncastuximab tesirine and chemotherapy. Results are aligned with the deterministic results. Figure 52 presents the incremental costs and QALYs from each simulation and Figure 53 presents the CEAC. Loncastuximab tesirine was cost-effective in [redacted]% of scenarios at a WTP threshold of £50,000.

Table 92: Probabilistic cost-effectiveness results, loncastuximab vs chemotherapy (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£51,009	£51,009

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; QALYs, quality-adjusted life years; vs, versus

Figure 52: Probabilistic cost-effectiveness results, loncastuximab vs chemotherapy: simulations (with PAS price for loncastuximab tesirine)

Abbreviations: PAS, patient access scheme; QALYs, quality adjusted life years; vs, versus

Figure 53: Cost-effectiveness acceptability curve, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

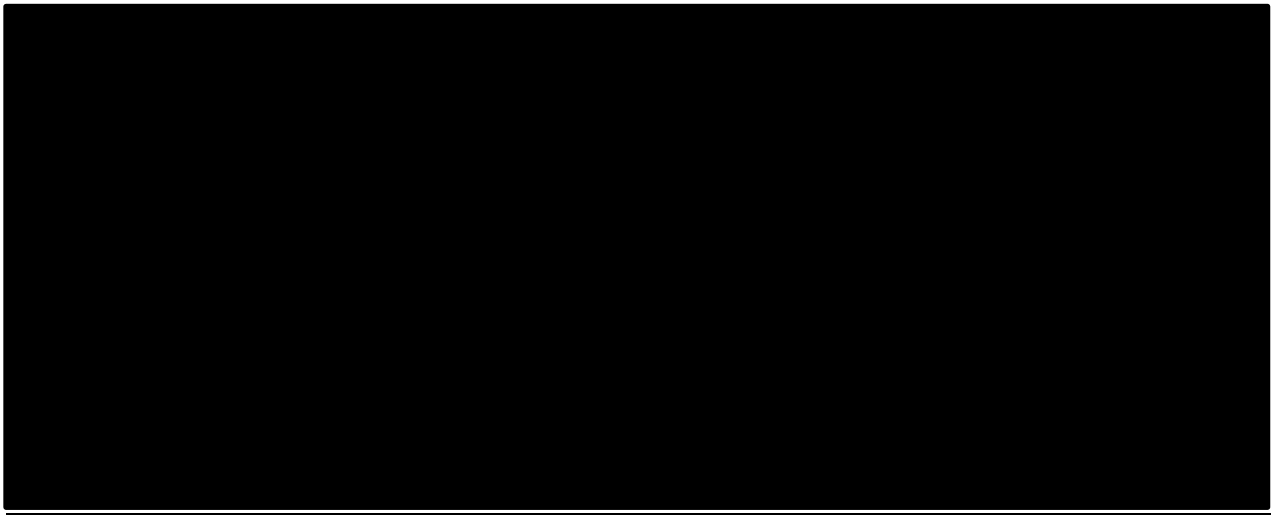
Abbreviations: PAS, patient access scheme ; vs, versus

B.3.11.2. Deterministic sensitivity analysis

Figure 54 and Figure 55 present the results of the deterministic sensitivity analyses comparing to Pola+BR and chemotherapy respectively. The most influential parameter for the comparison to pola+BR is the PD disutility. In both cases, the parameters related to survival models for OS and PFS are influential. In the comparison to Pola+BR, loncastuximab tesirine is either dominant or cost-effective in the south-west quadrant in all scenarios.

For the comparison to chemotherapy ICERs range from £38,000 to £83,000, with parameters linked to OS being the most influential.

Figure 54: Deterministic sensitivity analyses, loncastuximab tesirine vs Pola+BR: tornado diagram (with PAS price for loncastuximab tesirine)



*Denotes a south-west quadrant ICER, i.e. loncastuximab tesirine is less costly and less effective.
Abbreviations: 3L+ thirdline plus; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PD, progressed disease; PFS, progression free survival; Pola+BR, polatuzumab+bendamustin+rituximab ; TTD, time to discontinuation; vs, versus

Figure 55: Deterministic sensitivity analyses, loncastuximab tesirine vs chemotherapy: tornado diagram (with PAS price for loncastuximab tesirine)

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; TTD, time to discontinuation; vs, versus

B.3.11.3. Scenario analysis

Table 93 presents the outcomes of scenario analyses comparing to Pola+BR. In the majority of scenarios loncastuximab tesirine remains dominant, and there are only minor changes in costs or QALYs. The scenario that has the biggest impact on incremental QALYs is when COTA data are used to inform outcomes for Pola+BR. In this scenario, outcomes for Pola+BR are extrapolated from the COTA data, using a log-logistic curve for PFS and a gamma curve for OS. Outcomes for loncastuximab tesirine are extrapolated using weights from the MAIC comparing to the COTA data, with a generalised gamma curve used to extrapolate OS, PFS and TTD. In this scenario, the efficacy of Pola+BR is significantly reduced, with a median OS of 7.36 months and a total QALY gain of [redacted]. In this scenario, a severity multiplier of 1.2 could be applied to QALY gains.

When the Gompertz model is applied to model OS and the scenario modelling cure for patients that are progression-free at 2 years, a plateau in survival is seen at around [redacted]% for loncastuximab tesirine. Scenarios modelling cure reflect a return to near general population mortality for a proportion of patients, though the estimate of [redacted]% long-term survivors is at the top of what might be expected, based on clinical feedback, which put the figure between [redacted]% and [redacted]%. Scenarios modelling cure based on PFS at 5 and 10 years give plateaus of [redacted]% and [redacted]% respectively for loncastuximab tesirine.

The only scenario showing loncastuximab tesirine to be less effective than Pola+BR removes the impact of CAR-T on OS for loncastuximab tesirine. However, it was not possible to adjust at the Pola+BR curve in the same way, and this scenario is expected to be conservative.

Table 93: Scenario analyses, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Scenario	Incremental costs	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	Dominant
1.5% discount rates	[redacted]	[redacted]	Dominant
No discounting	[redacted]	[redacted]	Dominant
COTA data used to inform outcomes	[redacted]	[redacted]	Dominant
Gompertz distribution for extrapolating OS, loncastuximab tesirine only	[redacted]	[redacted]	Dominant
Gompertz distribution for extrapolating OS, loncastuximab tesirine and Pola+BR	[redacted]	[redacted]	Dominant

Scenario	Incremental costs	Incremental QALYs	ICER
Cure at 2 years	[redacted]	[redacted]	Dominant
Cure at 5 years	[redacted]	[redacted]	Dominant
Cure at 10 years	[redacted]	[redacted]	Dominant
ZUMA-1 progression decrement	[redacted]	[redacted]	Dominant
JULIET progression decrement	[redacted]	[redacted]	Dominant
AE disutility from the literature	[redacted]	[redacted]	Dominant
Excluding CAR-T	[redacted]	[redacted]	SW: £1,313,239
CAR-T at GO29365 rate	[redacted]	[redacted]	Dominant
100% RDI	[redacted]	[redacted]	Dominant
10-year time horizon	[redacted]	[redacted]	Dominant
20-year time horizon	[redacted]	[redacted]	Dominant

Abbreviations: CAR-T, chimeric antigen receptor T-cell; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; Pola+BR, polatuzumab+bendamustin+rituximab; QALYs, quality adjusted life years; RDI, relative dose intensity; SW, south-west

Table 94 presents the results of scenario analyses comparing to chemotherapy. The biggest changes in the ICER come from the scenario using a 10-year time horizon, which does not capture the full benefit of extended OS for loncastuximab tesirine, and the scenario assuming that patients who are progression free at two years are cured. In this scenario [redacted]% of loncastuximab tesirine patients and [redacted]% of chemotherapy patients would be considered cured. If cure is assumed at five years, this falls to [redacted]% and [redacted]%, which may be more aligned with clinical expectation.

In the scenarios extrapolating CORAL outcomes directly, the generalised gamma curve was used to extrapolate all outcomes, and the HR on OS was assumed to apply to PFS. Outcomes for loncastuximab tesirine were weighted using the MAIC weights.

Table 94: Scenario analyses, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	£48,986	
1.5% discount rates	[redacted]	[redacted]	£41,580	-15%
No discounting	[redacted]	[redacted]	£36,187	-26%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
10-year time horizon	[redacted]	[redacted]	£72,446	48%
20-year time horizon	[redacted]	[redacted]	£53,597	9%
Gompertz model for OS	[redacted]	[redacted]	£41,997	-14%
Direct extrapolation of CORAL extension outcomes	[redacted]	[redacted]	£40,103	-18%
Direct extrapolation of CORAL extension outcomes, no SCT only	[redacted]	[redacted]	£36,818	-25%
Cure at 2 years	[redacted]	[redacted]	£32,390	-34%
Cure at 5 years	[redacted]	[redacted]	£39,326	-20%
Cure at 10 years	[redacted]	[redacted]	£46,533	-5%
ZUMA-1 progression decrement	[redacted]	[redacted]	£48,995	0%
JULIET progression decrement	[redacted]	[redacted]	£49,028	0%
AE disutility from the literature	[redacted]	[redacted]	£48,868	0%

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALYs, quality adjusted life years; RDI, dose intensity; SCT, stem cell transplantation; vs, versus

B.3.11.4. Summary of uncertainty in the model

While there is uncertainty in the model, primarily driven by the requirement to use indirect comparison to generate comparator outcomes, the choice of data sources to inform the base-case means estimates of ICERs are likely to be conservative. The QALY gain with loncastuximab tesirine compared to Pola+BR was maintained in all but one of the scenario analyses and when alternate data sources were explored the scenarios show a decrease in efficacy for Pola+BR, indicating that the GO29365 data may overstate the efficacy of Pola+BR in third-line-plus. Similarly, by using the CORAL extension data to inform outcomes for chemotherapy, the model may overstate expected survival for these patients. Clinical input was that the population in the CORAL studies was fit, and this was reflected in the high number of SCTs performed. In an analysis excluding patients that had an SCT in the CORAL studies, the QALY gain for chemotherapy fell to [redacted].

Additionally, the base-case analyses do not make any assumptions about cure for patients in any arm of the model. While clinical feedback was that some patients would experience long-term remission, the proportion of patients this would apply to was unclear. Scenarios modelling cure led to an improvement in ICERs for loncastuximab tesirine. Thus, while there is uncertainty

in the modelled results, the outcomes from the model are expected to be conservative for loncastuximab tesirine.

B.3.12. Subgroup analysis

No subgroup analyses were considered.

B.3.13. Benefits not captured in the QALY evaluation

Not all benefits of loncastuximab tesirine have been captured in the economic analysis. Loncastuximab tesirine is simple to administer, with only a single 30-minute infusion required per cycle. This lessens the burden of administration on both healthcare practitioners and patients compared with other treatment options, with more frequent dosing or more and longer infusions required.

Further, utilities are not captured in the model with regards to the impact on carers and families of having to provide varying levels of care and attendance at hospital visits depending upon response to treatment. The level of care provided is expected to be reduced for patients treated with loncastuximab tesirine versus chemotherapies especially.

In addition, clinicians highlight that loncastuximab tesirine is a fast-acting, well tolerated, treatment for patients with few other options. The median time to response in LOTIS-2 was 41 days, which was highlighted as a key benefit of loncastuximab tesirine, as patients at third-line-plus often have quickly progressing disease.

B.3.14. Validation

B.3.14.1. Validation of cost-effectiveness analysis

B.3.14.1.1. Internal validation

Quality control of the economic model was performed by the model developers and by health economists not involved in the development of the model. This included cell-by-cell checks and logical checks.

The approach to modelling was validated with UK clinical and economic experts. Five clinical experts and two health economists were consulted. Expert input was sought on:

- The current treatment pathway and the positioning on loncastuximab tesirine
- Subsequent treatment use
- Sources of clinical evidence and approaches to analysing them
- Key prognostic factors
- Extrapolations of survival curves
- Key model assumptions

B.3.14.1.2. External validation

Table 95 presents a comparison of model outcomes for Pola+BR with different sources of clinical data. When using the COTA data to model Pola+BR, the model slightly over predicts median PFS, but understates median PFS when using the GO29365 data. In both cases, the model slight overstates OS. The table also includes median OS and PFS from Northend et al. 2022 (21), which presents data on 133 patients treated with Pola+BR from the early access to medicines scheme (EAMS) and the CDF. While this data was not suitable for modelling, as a third of patients were treated at second-line, and 40 were being treated as a bridge to CAR-T, it describes real-world clinical outcomes for Pola+BR.

Table 95: Comparison of model outcomes for Pola+BR with published sources

Outcome	GO29365 (third-line-plus)	COTA (third-line-plus)	Northend et al.	Model result – matched to GO29365	Model result – matched to COTA
Median PFS (months)	6.10	3.70	4.80	5.52	3.91
Median OS (months)	9.50	7.00	8.20	10.35	7.36

Abbreviations: OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab with bendamustine and rituximab.

Outcomes from the GO29365 study are higher than those seen in the Northend study, despite being in a solely third-line-plus population, which may indicate lower efficacy of Pola+BR in clinical practice than was observed in the clinical trial. Conversely, the outcomes for the COTA cohort are worse than observed by Northend et al., however this is expected, as the COTA population are solely third-line-plus.

Table 96 compares modelled outcomes for loncastuximab tesirine to the LOTIS-2. The median OS increases all comparisons; however, this may reflect that the populations in the comparator data sources were fitter than the LOTIS-2 population. The variation in median PFS is smaller.

Table 96: Comparison of model outcomes for loncastuximab tesirine with LOTIS-2

Outcome	LOTIS-2	Model result - unweighted	Model result – matched to COTA	Model result – matched to GO29365	Model results – matched to CORAL
Median PFS (months)	4.93	5.06	5.06	4.37	4.83
Median OS (months)	9.53	10.58	11.96	9.89	10.89

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 97 compares modelled OS with OS observed in the CORAL extension studies. The modelled value is closely matched to the value observed in the CORAL extension.

Table 97: Comparison of model outcomes for chemotherapy with published sources

Outcome	CORAL extension	Model result
Median OS (months)	5.85	5.98

Abbreviations: OS, overall survival.

A comparison of model outcomes with previous TAs in R/R DLBCL is challenging, as outcomes such as total costs, QALYs and life-years (LYs) have been redacted in previous submissions.

B.3.15. Interpretation and conclusions of economic evidence

Based on the proposed PAS price, this cost-effectiveness analysis estimates that loncastuximab tesirine is associated with a QALY gain of [redacted] and a cost saving of [redacted] when compared to Pola+BR, current SoC, making it the dominant treatment option.

When analysis is expanded to include comparison to chemotherapy, the model estimates a QALY gain of [redacted] for loncastuximab tesirine, with an incremental cost of [redacted], leading to an ICER of £48,986.

In both comparisons the data sources used to inform comparator outcomes are expected to be conservative for loncastuximab tesirine. The GO29365 study shows higher median OS and PFS for third-line-plus patients than was observed in a mixed second-line and third-line-plus population in UK clinical practice or in the third-line-plus population in the COTA EMR study. The CORAL extension studies used to inform chemotherapy outcomes were considered by clinicians to represent a fitter population than would be expected in clinical practice. Despite this, patients in the chemotherapy arm were only expected to receive [redacted] QALYs, a proportional QALY shortfall of [redacted].

The analysis has been conducted in line with the NICE reference case. The LOTIS-2 clinical trial provides mature data on loncastuximab tesirine in a population that is expected to be highly generalisable to UK clinical practice. As well as providing survival outcomes for loncastuximab tesirine, the trial also provides utility data on patients with R/R DLBCL that aligns with the reference case.

A key limitation of this analysis was the lack of clinical data available for Pola+BR and chemotherapy in third-line-plus R/R DLBCL are extremely limited. Data on Pola+BR is largely presented in the second-line-plus population, which clinicians stated was not generalisable to the population in this appraisal, as line of therapy is an important prognostic factor. Only two studies presenting relevant third-line-plus outcomes were identified. Similarly, only the CORAL extension studies were identified to provide data on chemotherapy. However, a wide range of sensitivity analyses have been presented to explore alternative approaches to extrapolating survival.

The results of this analysis have shown that, when using the proposed PAS price, loncastuximab tesirine dominates the key comparator, Pola+BR, and is also cost-effective at a WTP threshold of £50,000 compared to chemotherapy. Sensitivity analyses suggest that these results may be conservative, providing reassurance that loncastuximab tesirine is a cost-effective use of NHS resources.

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B.5. Appendices

The following appendices are provided in a standalone document:

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality of life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Price details of treatments included in the submission
- Appendix L: Checklist of confidential information
- Appendix M: LOTIS-2 supplementary data
- Appendix N: Fully incremental analysis
- Appendix O: Sensitivity analysis for survival analyses

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Loncastuximab tesirine (ZYNLONTA™)

1b) Population this treatment will be used by

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

'Relapsed' refers to a condition that returns after a period of remission, whilst 'refractory' is a condition that has not responded to an earlier line of treatment.

1c) Authorisation

Loncastuximab tesirine has been granted conditional marketing approval by the European Commission on December 20th 2022: https://www.ema.europa.eu/en/medicines/human/EPAR/zynlonta.

The UK's regulatory body – the Medicines and Healthcare products Regulatory Agency (MHRA) - recognised the conditional marketing authorisation in the UK in February 2023.

1d) Disclosures

Not applicable.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Lymphoma is a type of blood cancer which develops in lymphocytes, white blood cells that fight infection. Abnormal white blood cells can form a lump, usually found in lymph nodes in the neck, armpit, or groin. The two main types of lymphoma are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL) (1).

NHLs are classified as B cell or T cell lymphomas depending on the type of white blood cell they grow from. DLBCL is the most common type of high-grade (aggressive and fast-growing) NHL (2). The term 'high-grade B-cell lymphoma' (HGBL) refers to an aggressive type of B-cell lymphoma that is characterised by the genetic switching of chromosomes (2).

In general, these large B-cell lymphomas are curable with first-line (initial) treatment with chemoimmunotherapy in most patients (3). However, up to 40% of patients relapse or become refractory to initial treatment, and the prognosis for patients with relapse/refractory (R/R) DLBCL after two or more lines of treatment is particularly poor (4), with a median overall survival (OS) ranging from only four to 10 months (5-7).

There are approximately 5,510 new cases of DLBCL each year in the UK (8). DLBCL is more common in the elderly population, with a median age at diagnosis of 70 years and a slightly higher number of new cases in men (9).

The main symptom of DLBCL is having swollen glands in the neck, armpit, or groin. Symptom presentation in DLBCL is variable and dependent on where the swollen lymph nodes are, including abdominal or chest pain, bone pain, skin lumps, and coughing or breathlessness. Approximately 30% of patients experience what are known as 'B symptoms', which refers to symptoms such as fever, unintentional weight loss, and recurrent night sweats (10).

DLBCL is fatal without treatment. Untreated DLBCL patients have an estimated life expectancy of less than one year. Due to poor prognosis and the need for additional and intensive therapy, patients with R/R DLBCL have lower health-related quality of life (HRQoL) that general DLBCL patients, including physical, social, emotional and functional well-being (11).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

DLBCL is diagnosed by taking a piece of tissue from an affected lymph node (a biopsy) for analyses. A blood test can also be done to check on level of red blood cells, liver and kidney functions (10).

2c) Current treatment options:

Relapsed or refractory disease is treated using salvage chemotherapy followed by a haematopoietic stem cell transplant if the person is fit enough for intensive therapy. People who are not fit enough to have a transplant, or whose disease relapses after a transplant, are offered low-intensity chemotherapy regimens. There is a high unmet clinical need in this group of patients for regimens with improved outcomes or reduced toxicities.

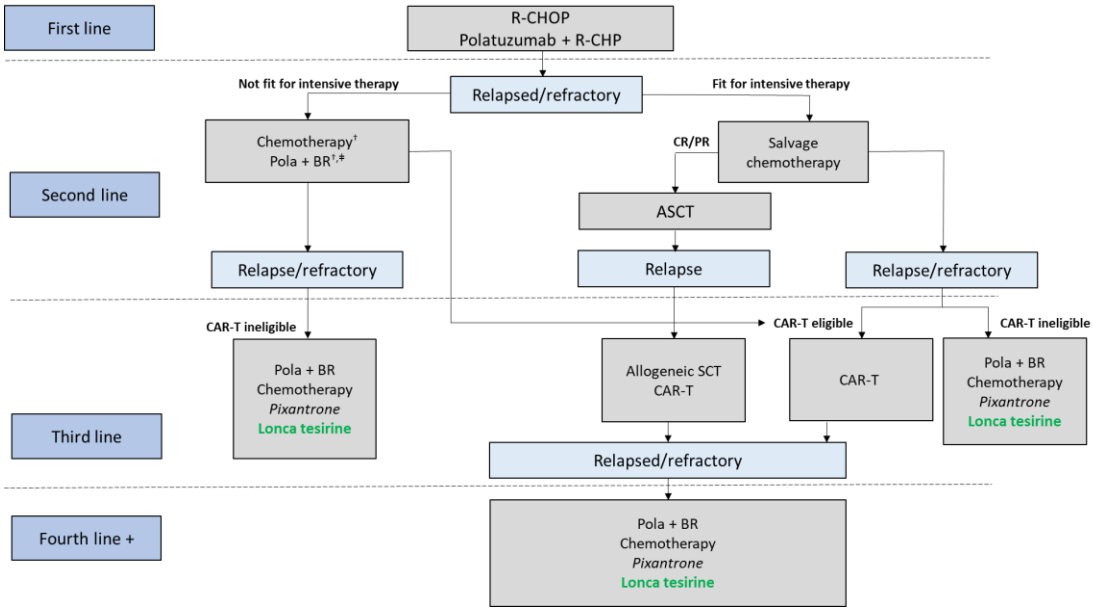
The pathway of care for patients with DLBCL in England is informed by NICE 2016 guidance NG52 (12) and more recent technology appraisals (13-15). In the third-line (3L) setting, polatuzumab plus bendamustine plus rituximab (Pola+BR) would be the main treatment option for patients (16). However, it is recognised that chemotherapy is also an option within this position in the treatment pathway, albeit less utilised due to its lower efficacy, therefore a comparative analysis of loncastuximab tesirine vs chemotherapies is also provided. Clinical experts stated that Pola+BR was more effective than chemotherapy, with one of the clinical experts saying they would use Pola+BR in all patients, provided they were willing to accept the additional toxicity. A second clinician said that the driver behind this decision was whether they had previously received treatment and that they would look for a trial or compassionate access to bispecifics rather than use chemotherapy (16). While Pola+BR can be used at second-line as well as third-line plus, data from a UK RWE study suggests that the majority of use is in third-line plus patients (17).

Additional therapies recommended by NICE in the third-line setting include a CAR T-cell therapy (18) and pixantrone monotherapy (19). Previous appraisals of interventions for R/R DLBCL including TA559 (13), TA567 (14), TA649 (15) and GID-TA10645 (20) removed pixantrone as a comparator either at the scoping stage or during the committee process. The respective committees were informed by clinical experts that pixantrone is rarely used in the UK; therefore, they concluded in each case that it was not a relevant comparator. The clinicians interviewed to inform this submission further confirmed that pixantrone is not used in clinical practice (16), and also noted the exclusion of pixantrone as a treatment option for patients with R/R DLBCL in the BSH guidelines (21). CAR T-cell therapies are considered as a major advance in DLBCL with some patients achieving durable responses. However, only 17.2% of DLBCL patients who received ≥3 prior lines of treatment were treated with CAR T-cell therapy due to its severe treatment burden and most patients have a rapid clinical disease course rendering them unsuitable for the treatment (22). Clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients that are not eligible for transplant or CAR-T therapy, or less commonly, in patients that are R/R to both therapies.

With no established SoC for patients with R/R DLBCL after ≥2 or more lines of systemic therapy, there is a significant unmet need for new and more effective treatments that extend survival with better tolerability profiles. Loncastuximab tesirine is a highly selective CD-19-targeted antibody drug conjugate (ADC), delivering a potent and mechanistically novel stable linker and cytotoxin which is different from other traditional therapies (16, 23). It is a monotherapy which is more easily accessible with a less burdensome dosing regimen compared with traditional chemotherapies and recently approved treatments (24). Given the benefits of its mechanism of action, it is fast acting with a quick response (two to four cycles), potentially offering a new therapeutic option for heavily pre-treated R/R DLBCL patients with fast-progressing disease. Data on long-term remission are available in Document B, Section B.2.6.

Loncastuximab tesirine is anticipated to be used as a third-line treatment for CAR-T ineligible patients, and as a fourth-line treatment for patients relapsing after CAR-T therapy (Figure 1). The evidence to support the use of loncastuximab tesirine for these patients is based on the phase 2 trial LOTIS-2 (NCT03589469).

Figure 1: Current NICE recommended treatment pathways for R/R DLBCL including proposed position of loncastuximab tesirine



Pixantrone is rarely used in UK clinical practice
†Clinicians indicated that some patients not previously fit for intensive therapy may respond to first-line treatment to a degree such that some may be considered eligible for CAR T-cell therapy.
‡If polatuzumab is given in first-line setting, it would not be given in the second-line setting
Abbreviations: ASCT, autologous stem cell transplant; BR, bendamustine with rituximab; CAR-T, chimeric antigen receptor T-cell; CR, complete response; Pola, polatuzumab vedotin; PR, partial response; R, rituximab; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP; rituximab, cyclophosphamide, doxorubicin and prednisone; R/R, relapsed/refractory; SCT, stem cell transplant; TA, technology appraisal.

2d) Patient-based evidence (PBE) about living with the condition

Sobi is not aware of any patient-based evidence that has been published to date on the patient population considered here.

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

In patients with B-cell lymphoma, B-cells (a type of white blood cell) have become cancerous. The active substance of loncastuximab tesirine is made up of a monoclonal antibody (a type of protein) combined with a cytotoxin (a substance that kills cells) called SG3199. The monoclonal antibody attaches to a protein called CD19 on the B-cells, including cancerous B-cells, and the medicine enters these cells. When loncastuximab tesirine is inside the B-cells, SG3199 is released and kills them.

A summary of product characteristics is available at the following link: https://www.ema.europa.eu/en/documents/product-information/zynlonta-epar-product-information_en.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐Yes

☒No

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable.

3c) Administration and dosing

Loncastuximab tesirine is given as an infusion (drip) into a vein over 30 minutes every 3 weeks. Treatment can continue for as long as the patient benefits from it and does not have intolerable side effects. The dose depends on the patient's body weight. If certain side effects develop, the doctor may decide to reduce the dose or to interrupt or stop treatment with loncastuximab tesirine.

The recommended dosage is:

- 0.15 mg/kg every 3 weeks for 2 cycles
- 0.075 mg/kg every 3 weeks for subsequent cycles

Before starting treatment, patients should be given dexamethasone (an anti-inflammatory medicine) to help reduce possible side effects of treatment.

3d) Current clinical trials

The clinical evidence used to support the marketing authorisation and reimbursement of loncastuximab tesirine for the treatment of R/R DLBCL comes from the Phase 2 pivotal

study LOTIS-2 (NCT03589469); results from LOTIS-2 formed the basis of the accelerated approval granted by the FDA in the United States of America and the granting of conditional marketing authorisation by the EMA (25) in Europe. LOTIS-2 was completed in August 2022.

LOTIS-2 is a large (n=145) Phase 2 multinational, single-arm clinical study of loncastuximab tesirine. The patients in the trial were chosen because the cancer either returned (relapsed cancer) or did not respond to past therapy (refractory) after two therapies. Eligibility criteria are summarised below.

Eligibility criteria in the pivotal study LOTIS-2 (NCT03589469)

Key inclusion criteria

- Male or female patients aged ≥18 years
- Pathologic diagnosis of DLBCL
- Relapsed or refractory disease following ≥2 multi-agent systemic treatment regimens
- ECOG performance status of 0 to 2
- Biopsy-proven CD19 expression for patients who received prior CD19-targeted therapy
- Adequate organ function

Key exclusion criteria

- Previous treatment with loncastuximab tesirine
- History of hypersensitivity to a CD19 antibody
- Pathological diagnosis of Burkitt lymphoma
- Bulky disease (defined as any tumour ≥10 cm in longest dimension)[1]
- Active CNS lymphoma
- ASCT ≤30 days or allogeneic SCT ≤60 days prior to start of treatment
- Significant medical comorbidities, including uncontrolled hypertension, unstable angina, congestive heart failure, acute ischemia, coronary angioplasty or myocardial infarction, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes or severe chronic pulmonary disease

Abbreviations: ASCT, autologous stem cell transplant; CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; SCT, stem cell transplant.

Loncastuximab tesirine continues to be evaluated both as monotherapy and as a combination treatment in a comprehensive clinical programme. Further data will be collected on the long-term safety and the safety and effectiveness of loncastuximab

[1] The exclusion criterion on bulky disease was implemented in Protocol amendment 2; with effect from this protocol amendment, patients with bulky disease were excluded due to low ORR in an interim analysis of the Phase 1 study.

tesirine in patients with B-cell lymphoma when used in combination with another cancer medicine (26-31).

3e) Efficacy

The effect of loncastuximab tesirine was investigated in a clinical trial (LOTIS-2) with 145 patients with relapsed or refractory B-cell lymphoma. In this trial, loncastuximab tesirine was not compared with any other treatment for B-cell lymphoma.

Participants included in the trial had R/R large B-cell lymphoma, most (88%) had a type of disease called DLBCL not otherwise specified (NOS), the remaining had types of lymphoma that are difficult to treat such as DLBCL arising from slow-growing lymphoma (20%), or fast-growing B-cell lymphoma (8%). The age range was from 23 to 94, 59% were male and 90% were Caucasian. Patients had at least two, and as many as seven treatments before loncastuximab tesirine. Some (17%) had a previous stem cell transplant, while some (9%) had received CAR T-cell therapy. More than half of patients (63%) did not respond to their previous treatment. A total of 68 people who received loncastuximab tesirine in the trial went on to be treated with other therapies. Some of these people did not respond to loncastuximab tesirine. Out of those 68: nine people were treated with SCT and 15 people were treated with CAR-T after their cancer worsened.

The study showed that 48.3% (70 out of 145) of the patients responded to treatment with loncastuximab tesirine, with about 25% (36 out of 145) of them showing no sign of cancer (complete response). Reponses to loncastuximab tesirine occurred quickly and were durable in some patients. The average time to first response was 41.0 days (range: 35 to 247 days) and the mean time was 51.5 days.

Data on the average progression-free survival, the length of time from the start of treatment until the cancer worsens or progresses to a more advanced stage, and the average overall survival (OS), the total length of time that patients lived following the start of treatment are available in Document B, Section B.2.6.

Clinical opinion suggests that it is reasonable to assume that patients who are progression free at two years following treatment can be discharged and regarded as ‘cured’ (16). Additionally, one clinician that was consulted noted a promisingly high number of observations of long-term remission free survival from loncastuximab tesirine without further treatment (16).

Patients’ quality of life was stable during treatment and a trend of improvement was seen as early as after two treatment cycles; these benefits were also seen in patients aged ≥65 years.

Loncastuximab tesirine produced durable responses in a variety of high-risk subgroups of patients including with double hit/triple hit genetics, advanced stage disease (Stage III/IV), transformed disease, primary refractory disease, and disease which was refractory to all prior therapies; and was also effective in elderly patients and in patients who had previous CD19-directed CAR-T therapy.

*Refer to Glossary of terms

3f) Quality of life impact of the medicine and patient preference information

Patients with R/R DLBCL treated with loncastuximab tesirine experienced improved HRQoL as early as after 2 treatment cycles and these benefits were also seen in patients aged ≥65 years.

The patient-reported outcome (PRO)/HRQoL were assessed using validated health related quality of life measurement questionnaires such as EQ-5D-5L and the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) questionnaires. These are used for evaluating response to treatment in patients in terms of their physical, social/family, emotional and functional well-being, as well as symptoms such as pain, lumps or swelling, fever, night sweat, weight loss, itching, trouble sleeping, fatigue, and loss of appetite (32). The results from the EQ-5D-5L questionnaire showed a trend of improvement on overall health over time. Mean changes in all FACT-Lym subscale and composite scores were generally stable over time.

The impact of loncastuximab tesirine treatment on symptoms was assessed using the LymS of FACT-Lym. During the course of treatment, more patients reported improvement compared with baseline for pain, lumps/swelling, and losing weight for a majority of the visits; differences in percentage of patients with improvement vs symptom worsening were >10 percentage points for a majority of the visits (32). A higher proportion of patients aged ≥65 reported an improvement for pain, lumps/swelling, and losing weight for the majority of visits comparing with the start of the study.

3g) Safety of the medicine and side effects

Overall loncastuximab tesirine was well-tolerated with low level of neuropathy and infections (even among more elderly patients). Toxicities were generally reversible and manageable in most patients with dose delays/reductions.

The most common side effects with loncastuximab tesirine (which may affect more than 1 in 5 people) are increased levels of gamma glutamyltransferase (GGT, a liver enzyme), neutropenia (low levels of neutrophils, a type of white blood cell), tiredness, anaemia (low levels of red blood cells), thrombocytopenia (low levels of blood platelets), nausea (feeling sick), peripheral oedema (swelling due to fluid retention, especially of the ankles and feet) and rash.

The most common serious adverse reaction (which may affect up to 1 in 20 people) are febrile neutropenia (low levels of white blood cells with fever), abdominal pain, dyspnoea (difficulty breathing), pleural effusion (fluid around the lungs) and lung infection.

For more details on the side effects of loncastuximab tesirine, please refer to the Summary of Product Characteristics (SmPC) (33) and the package leaflet.

3h) Summary of key benefits of treatment for patients

Summary of key clinical benefits of loncastuximab tesirine

Patients who relapsed after third-line therapy, including CAR T-cell therapy, have limited treatment options and represent a group that is considered difficult to treat. During LOTIS-2, outcomes among all the patients who received 3 or >3 prior lines of therapy were consistent, with 48.6% and 48.9% responded to treatment, respectively (34). In a small group of patients who had relapsed or progressed from prior CAR T-cell therapy, 46% responded to treatment (35). Clinical opinion suggests that it is reasonable to assume that patients who are progression free at two years following treatment can be discharged and regarded as 'cured' (16). Additionally, one clinician that was consulted noted a promisingly high number of observations of long-term remission free survival from loncastuximab tesirine without further treatment (16). These findings suggest loncastuximab tesirine as a treatment option for patients with R/R DLBCL who relapsed after multiple lines of treatments.

Loncastuximab tesirine as a monotherapy offers a lower patient burden compared with other third-line treatments for R/R DLBCL, which are administered as combination therapies and involve more extensive dosing schedules (such as Pola+BR), or those that can only be delivered in specialised centres (CAR-T therapies).

Patients treated with loncastuximab tesirine experienced improved HRQoL as early as after 2 treatment cycles (i.e. by 6 weeks) and these benefits were also observed in patient aged ≥65 years (32).

Loncastuximab tesirine was associated with a manageable safety profile, including patients aged ≥65 years (32). No new safety concerns were identified in the study (34). Adverse events such as oedema, effusion, and myelosuppression were generally reversible and manageable with dexamethasone premedication, diuretic therapy, dose delays, and/or dose modifications (36).

3i) Summary of key disadvantages of treatment for patients

While loncastuximab tesirine has the potential to satisfy an unmet need amongst patients with relapsed or refractory DLBCL and HGBCL after two or more systemic therapies, potential disadvantages could include the intravenous administration (33). However, in terms of administration, as a monotherapy loncastuximab tesirine offers a lower patient burden compared with other third-line treatments for R/R DLBCL: other third-line treatments are administered as combination therapies and involve more extensive dosing schedules (such as Pola+BR (37)), or those that can only be delivered in specialised centres (CAR-T therapies (38)). It is anticipated, however, that CAR-T therapy would be an option ahead of loncastuximab tesirine for eligible patients and is therefore not considered a relevant comparator in this appraisal.

As with all treatments there can be side-effects. Photosensitive skin rash may occur which can be minimised if patients wear factor 50 sun cream. Side-effects that patients taking this new drug might experience are listed above in Section 3g (33).

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The chosen model has been used in previous appraisals within the therapeutic area, it uses what is known as a 'partitioned survival' approach with three health states that are relevant to the condition:

1. Progression-free disease
2. Progressed disease
3. Death.

At the start of the model all patients are in the progression-free state, however over time patients disease may spread and they will move to the progressed disease state or death.

Modelling how much a treatment extends life

The treatment extends life by slowing the progression of disease. This is reflected in the model by using the progression-free survival (PFS) and overall survival (OS) curves reported in the clinical trial. The PFS curve is used to determine what proportion of patients are alive and progression free at each time point, and the OS curve is used to determine what proportion of patients are alive. The difference between these two curves tells us how many patients have progressed disease at each time point. As not all patients in the clinical trial were followed up until progression or death, models have been fit to the trial data to extrapolate OS and PFS data to accommodate a lifetime time horizon. The trial provides follow-up for approximately 3 years.

Modelling how much a treatment improves quality of life

The model assigns utility values (preference values that patients attach to their overall health status) to the progression-free disease and progressed disease health states, which have been estimated from the clinical trial. As patients in the progression-free health state have a higher quality of life than patients in the progressed disease state, by

slowing disease progression patients treated with loncastuximab tesirine have a higher quality of life.

Additionally, the model applies a reduction in quality of life for patients with an adverse reaction to treatment. As there was a lower rate of adverse reactions with loncastuximab tesirine relative to comparator treatments, there is an improvement in quality of life for patients treated with loncastuximab tesirine.

Modelling how the costs of treatment differ with the new treatment

Compared to Pola+BR, the model shows a cost saving, as loncastuximab tesirine is cheaper than Pola+BR when applying a confidential discount price, known as a Patient Access Scheme (PAS). However, the magnitude of this saving is unknown as the net costs of both loncastuximab tesirine and Pola+BR to the NHS are confidential.

When compared to chemotherapy, loncastuximab tesirine is associated with an increase in costs for the health service. This is due to both higher drug costs, as loncastuximab tesirine is more expensive than chemotherapy, and higher disease management costs, as patients survive longer.

All treatments included in the model are given by intravenous infusion in an outpatient setting.

Uncertainty

As not all patients were followed up until death in the trial, the OS and PFS curves have been extrapolated to predict outcomes beyond the trial period. These extrapolations are subject to uncertainty, and so different scenarios have been tested in sensitivity analysis.

A second source of uncertainty is in the outcomes for comparators. As LOTIS-2 was a single arm trial, there is no head-to-head efficacy data for loncastuximab tesirine vs either chemotherapy or Pola+BR. To generate outcomes for the comparators, data from the literature have been used to inform the model. Several different approaches and data sources have been used to make these comparisons.

Cost effectiveness results

In the company's base-case analysis, compared to Pola+BR, loncastuximab tesirine produces additional quality-adjusted life-years (QALYs) at a lower cost, with loncastuximab tesirine 'dominating' Pola+BR (list price). Compared to chemotherapy, loncastuximab tesirine produces a QALY gain at a higher cost. The incremental cost-effectiveness ratio (ICER) for loncastuximab tesirine is £48,986 (list price). These results do not take into account any confidential commercial discounts for the comparator treatments, any weighting to QALYs for severity (severity modifiers), or the committee's preferred assumptions which may differ to those applied in the base-case analysis.

Additional factors

In the chemotherapy arm, conditions for a severity modifier of 1.2 to be applied were met. This is based on the proportional shortfall, which is the QALYs lost due to disease, relative to that which a patient of the same age would expect.

Not all benefits of loncastuximab tesirine have been captured in the economic analysis. Loncastuximab tesirine is simple to administer, with only a single 30-minute infusion required per cycle. This lessens the burden of administration on both healthcare professionals and patients compared to other treatment options, with more frequent dosing or more and longer infusions required.

In addition, clinicians highlight that loncastuximab tesirine is a fast-acting, well tolerated, treatment for patients with few other options. The median time to response in LOTIS-2 was 41 days, which was highlighted as a key benefit of loncastuximab tesirine, as patients at 3L+ often have quickly progressing disease.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

With no established standard of care for patients with R/R DLBCL after ≥2 or more lines of systemic therapy, there is a significant unmet need for new and more effective treatments that extend survival with better tolerability profiles. Loncastuximab tesirine is a highly selective CD-19-targeted antibody drug conjugate (ADC), delivering a potent and mechanistically novel stable linker and cytotoxin which is different from other traditional therapies (16, 23). It is a monotherapy which is more easily accessible with a less burdensome dosing regimen compared with traditional chemotherapies and recently approved treatments (24). Given the benefits of its mechanism of action, it is fast acting with a quick response (two to four cycles), potentially offering a new therapeutic option for heavily pre-treated R/R DLBCL patients with fast-progressing disease.

Clinical opinion suggests that it is reasonable to assume that patients who are progression free at two years following treatment can be discharged and regarded as 'cured' (16). Additionally, one clinician that was consulted noted a promisingly high number of observations of long-term remission free survival from loncastuximab tesirine with no further treatment (16).

Based upon its improved efficacy and safety results produced from the analysis conducted by the Company, in addition to being fast acting, it could be the preferred treatment option, especially in the frail and elderly who may have limited options beyond palliative care.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No equality issues related to the use of loncastuximab tesirine in patients with R/R DLBCL have been identified.

SECTION 4: Further information, glossary and references

4a) Further information

- The results of study LOTIS-2 have been published in Lancet: Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial - The Lancet Oncology
- European Medicines Agency. Zynlonta - Summary of Product Characteristics: Zynlonta, INN-loncastuximab-tesirine (europa.eu)
- Lymphoma action: Lymphoma Action (lymphoma-action.org.uk)
- Blood cancer UK: Lymphoma - what is it, symptoms and treatment | Blood Cancer UK

Further information on NICE and the role of patients**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Adverse event: An unfavourable and unintended observation that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe

Antibody: A protein that plays an important role in the body's immune system. Each antibody is unique and recognises a specific part of foreign objects such as bacteria and viruses. Antibodies can be custom designed for use as drugs

Autologous: A stem cell transplant may be autologous (using a patient's own stem cells that were collected before treatment)

Biopsy: A process in which a very small part of tissue in the body is removed to look for presence, cause, or extent of a disease

Confidence interval (CI): A range of values that you can be 95% certain contains the true mean of the population

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease

Cytokine release syndrome: A condition that may occur after some types of immunotherapy caused by a large, rapid release of cytokines into the blood from immune cells

Cytotoxin: A chemical substance that can destroy infected cells

Effusion: An accumulation of fluid between the layers of tissue

Haematologic: Relating to blood and the body tissues that make it

Lines of treatment: The order in which different therapies are given to people as their disease progresses. For example, first-line treatment is the initial treatment and second-line treatment is given after the initial treatment has failed or stopped working

Myelosuppression: A condition in which bone marrow activity is decreased, resulting in a reduction of red blood cells, white blood cells, and platelets

NICE: The National Institute for Health and Care Excellence. It is an independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England

Oedema: An accumulation of fluid in the body which causes the affected tissue to become swollen

Prognosis: The likely or expected development of a disease

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living

Refractory: A disease that does not respond to treatment

Relapse: The return of a disease after a period of improvement

Salvage therapy: Treatment that is given after the standard treatments have failed

Standard-of-care: Treatment that is accepted and widely used by medical experts and healthcare professionals for a certain type of disease

Stem cell: A cell from which other types of cells develop

Treatment-emergent adverse event: An event that begins after the start of treatment, or any event already present that worsens following exposure to treatment

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Company responses to clarification questions

April 2023

File name	Version	Contains confidential information	Date
ID3943 lon-tes EAG Clarification letter v1.4 LE for company-fully redacted	1	Redacted	4 May 2023

Section A: Clarification on effectiveness data

Issues with indirect comparison

A1. Priority Question: The company claim to match to the whole PolaBR of GO29365 population in the absence of characteristics for the 3+ line population (39.6% of whole cohort had ≥3 lines of prior therapy → 60/152). But we know that 50 people had just 1 line of therapy from supplementary information. These people are excluded from the target population survival outcomes, and so should and can be excluded from this calculation, meaning the fraction becomes 60/ (152-50) = 60/102. Please repeat the MAIC using this proportion as the target for matching, and implement in the economic model.

Updated survival analyses with this correction are provided in Table 1 to Table 3. The greatest impact on the numerical values was in the comparison of overall survival (OS). However, the overall conclusions are unchanged, with no significant differences observed for OS and progression-free survival (PFS) when comparing loncastuximab tesirine with polatuzumab plus bendamustine plus rituximab (Pola+BR). As noted previously in the Company submission, these results are considered conservative for loncastuximab tesirine, due to the optimistic survival data available for Pola+BR from the GO29365 extension study, particularly when compared with the experience of patients receiving Pola+BR in third- or later line treatment from the real world COTA database study (3)(4), which indicates a more modest PFS and OS. The comparison presented is also likely subject to bias due to the lack of available Kaplan-Meier data for Pola+BR, resulting in only a crude calculation being possible for the hazard ratio (HR).

Table 1: Comparison of baseline characteristics loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study) – replacing Company submission, Table 20

Treatment (study)	N/ ESS	Prior lines ≥3 (%)	Primary refractory or progression / relapse <6 months (%)	IPI ≥3 (%)	HGBL (%)
Lonca unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	58.8	64.0	62.0	3.0

Abbreviations: ESS, effective sample size; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table 2: Summary of OS comparison – loncastuximab tesirine vs Pola+BR (GO29365 extension study) – replacing Company submission, Table 21

Treatment (study)	N/ ESS	Events	Median OS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	63	9.5 (7.6, 14.2)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table 3: Summary of PFS comparison – loncastuximab tesirine vs Pola+BR (GO29365 extension study) – replacing Company submission, Table 22

Treatment (study)	N/ ESS	Events	Median PFS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve comparison (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	79	6.1 (4.5, 8.0)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

The corrected MAIC results based on the EAG request have been implemented in the economic model and revised cost-effectiveness results have been generated for the comparison between loncastuximab and Pola+BR. A summary of the deterministic results from the updated economic model incorporating the corrected MAIC are presented in Table 4.

Table 4: Revised deterministic results including A1 MAIC correction, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	-
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	£204,040

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; LYs, life years; MAIC, matching-adjusted indirect comparison; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine plus rituximab; QALYs, quality-adjusted life years; vs, versus.

The results indicate that while the total QALYs for loncastuximab are reduced following the correction to the MAIC, loncastuximab remains cost-saving compared to Pola+BR with the ICER for loncastuximab lying in the south-west quadrant.

A2. Information for the pooled PolaBR population of the GO29365 extension is available for Male, Prior SCT and Refractory to last therapy, as are Age, Ann Arbor stage and ECOG. Please demonstrate exploration of including these variables in the MAIC analysis, and provide justification for your preferred set of variables.

The variables included in the model were based on discussion with clinical experts and review of subgroup data and variables included in previous comparative analyses. No evidence was identified to suggest that gender has a significant impact on outcome for this indication. Prior stem cell transplantation (SCT) was specifically ruled out as not relevant for the matching adjusted indirect comparison (MAIC) analyses by the clinical experts. In addition, age, Eastern Cooperative Oncology Group (ECOG) status and Ann Arbor stage are already accounted for in the population-adjustment by the inclusion of International Prognostic Index (IPI) status. Therefore, these variables were not included in the original MAIC analyses. However, their inclusion in the analyses are considered in detail in the revised base case response reported for Question A3.

A3. Priority Question: The EAG requests exploration specifically of a MAIC analysis for the comparison to GO29365 based on the following variables:

Age, ECOG, Refractory to last therapy, Prior lines therapy (corrected as above), HGBL, Male, Primary Refractory and IPI.

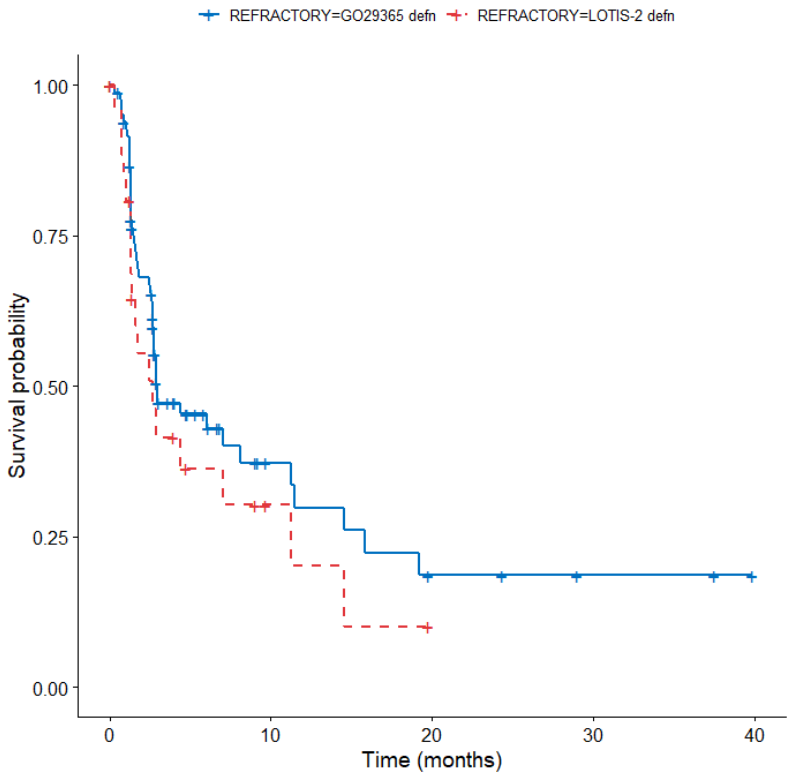
Exploration of a population-adjustment analysis including refractory to last therapy is not considered suitable by the company because there is a significant discrepancy between the definitions of refractory to last therapy across the two trials. In LOTIS-2 (loncastuximab tesirine trial), refractory to last therapy was defined as no response to therapy; in contrast, for the GO29365 extension, refractory was defined as no response or progression or relapse within 6 months of previous antilymphoma therapy end date. These definitions could not be matched as suitable data were not available from the LOTIS-2 individual patient dataset, thereby undermining the validity of a MAIC analysis based on matching this variable between the studies.

The difference the definition of this variable makes to the patient subgroup and their outcomes can be illustrated by considering the impact that a difference in the definition of primary refractory has on outcomes. Coiffier 2008 (1) identifies three groups of patients who fail primary treatment: refractory patients, not responding to first line therapy; partial remitters, with persisting lymphoma sites at the end of treatment; relapsing patients, with progressive disease after complete response. The author reports that “the outcome [between groups] is quite different” and that these patients should be looked at “separately and prospectively”. In private correspondence with the author, Kaplan-Meier curves for OS shared with the Company suggest that patients who do not respond following treatment have the worst OS, with those experiencing early relapse or partial response experiencing longer OS. Similarly, Bock et al. 2021 (2) concluded that patients with primary refractory disease with no response represent an “ultra-high risk group that has particularly poor survival outcomes” compared with patients who have early relapse experiencing longer OS.

Further supporting data was available from the LOTIS-2 dataset. Firstly, it was noted that there was a large difference between the number of patients defined as primary refractory using the LOTIS-2 definition (n=29/145, 20% in the total population) compared with those defined as primary refractory using the GO29365 extension

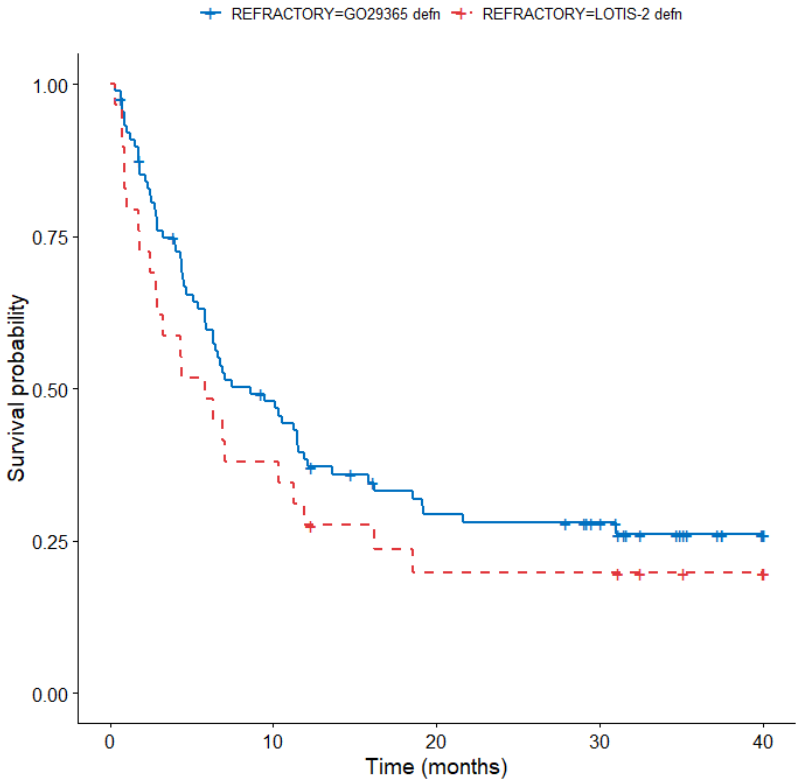
definition applied to the LOTIS-2 dataset (n=89/145, 61.4%). In addition, survival data for these two groups also differed. Kaplan-Meier curves for PFS (Figure 1) and OS (Figure 2) were generated for patients who were primary refractory according to the LOTIS-2 vs GO29365 extension definitions. In both cases, the curve for the GO29365 extension refractory definition sits above the curve for patients who are refractory based on the LOTIS-2 definition.

Figure 1: Kaplan-Meier curve for PFS using data from all patients in LOTIS-2 dataset, comparing alternative definitions of primary refractory (n=145)



Abbreviations: defn, definition; PFS, progression-free survival.

Figure 2: Kaplan-Meier curve for OS using data from patients in LOTIS-2 dataset, comparing alternative definitions of primary refractory (n=145)



Abbreviations: defn, definition; OS, overall survival.

Given the mismatch in definitions for refractory to previous line of therapy, more patients would be classified as refractory in LOTIS-2 if suitable data were available to enable a revised definition and classification of patients. Thus, when matching for refractory to prior line, the results would prove unreliable and should not be considered as an alternative result for the analyses presented in the tables that follow.

In response to the queries posed in the clarification questions, all characteristic data and patient inclusion criteria were re-considered and checked again for inclusion the indirect treatment comparison using the GO29365 extension study data. For the original Company submission, 14 patients with missing data with respect to primary relapse / refractory status and no response to first line treatment / time to progressive disease not available from LOTIS-2, were also excluded. These patients

were part of the “other” group whose refractory status after primary treatment was unknown, not evaluable, or missing. As the definition of refractory is of interest in the MAICs and these patients are considered relevant to decision making because they have received at least two prior lines of treatment and are relapsed or refractory to the prior line, thus the population of interest in clinical practice, they were reincluded for this comparison (see also response to Question A10). Including these patients and classifying them as non-refractory in the MAIC is considered a conservative approach, given the evidence that patients with no response to or early relapse following primary treatment have worse outcomes than those with longer initial response.

Finally, on the basis that clinical experts consulted as part of the original submission had advised not to correct for both IPI status and the individual components of the IPI (age, Ann Arbor stage, ECOG status, serum lactate dehydrogenase, extranodal sites) within the MAICs, due to the resulting double-adjustment of the population, age, ECOG and disease stage were included, whilst IPI was excluded.

Therefore, the additional MAIC analysis was run on the basis of:

- Correction outlined in Question A1
- Inclusion of LOTIS-2 patients described as “other” response to primary treatment (conservative assumption grouping these patients as non-refractory according to the GO29365 definition)
- Include age, ECOG status and disease stage variables
- Exclude IPI as a matching variable

Updated survival analysis results are provided in Table 5 to Table 7. No significant differences in survival were identified between the treatments, with the adjusted median survival and HR estimates being very close to those for the naïve data comparison.

Table 5: Comparison of baseline characteristics loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study) including "other" patients in LOTIS-2 dataset, with individual component adjustment replacing IPI

Treatment (study)	N/ ESS	HGBL (%)	Age <65 (%)	Male (%)	ECOG PS 0-1 (%)	Prior lines ≥3 (%)	Primary refractory or progression / relapse <6 months (%)	Disease stage ≥3 (%)
Lonca unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	3.0	32.0	55.0	87.0	58.8	64.0	80.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table 6: Summary of OS comparison – loncastuximab tesirine vs Pola+BR (GO29365 extension study) including "other" patients in LOTIS-2 dataset, with individual component adjustment for IPI

Treatment (study)	N/ ESS	Events	Median OS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	63	9.5 (7.6, 14.2)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Table 7: Summary of PFS comparison – loncastuximab tesirine vs Pola+BR (GO29365 extension study) including "other" patients in LOTIS-2 dataset, with individual component adjustment for IPI

Treatment (study)	N/ ESS	Events	Median PFS, months (95% CI)	Lonca vs Pola+BR HR (95% CI)
Lonca naïve comparison (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	79	6.1 (4.5, 8.0)	Comparator

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; Lonca, loncastuximab tesirine; N, sample size; OS, overall survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

The Company consider the updated MAIC analysis to be the most appropriate data from comparing loncastuximab and Pola+BR. Revised base-case results using the updated MAIC analysis for the comparison with Pola+BR have been presented in Table 8, with probabilistic results in Table 9.

Table 8: Revised deterministic base-case results, loncastuximab PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, QALY, quality adjusted life-years.

Table 9: Revised probabilistic base-case results, loncastuximab PAS price

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, QALY, quality adjusted life-years.

The results using the MAIC based on Question A3 generates show that loncastuximab is associate with a higher QALY gain than Pola+BR, at a lower cost and dominates Pola+BR, which is consistent across both deterministic and probabilistic results.

Additional results for this new base case, comprising probabilistic plots, univariate sensitivity analysis results, and scenario analysis results, are reported in Appendix A.

A4. For the MAIC to the PolaBR 3L+ COTA population, please clarify the source of the inputs. Some values appear inconsistent with reported values in Hamadani et al. 2022 as presented at ASH 2022 (e.g. 50% below 65, but median age reported to be 67, 60% vs 63% male), whilst other data on prior lines of therapy is not reported by Hamadani et al. Please explain these deviations and present a corrected MAIC analysis and updated Table 19 if necessary.

There is a discrepancy between the data presented in the conference abstract (3) and poster (4). This is due to different data cuts being available at the times these were written, with abstract data taken from a June 2022 COTA data delivery and the poster using a September 2022 data delivery. Demographics changed slightly between the two data cuts and the September data delivery included more robust death data. The data from the poster (September 2022 dataset) have been used for the MAIC analyses and this poster has been added to the reference pack.

A5. For the MAIC to the Chemotherapy CORAL population, the analysis appears very similar to the analysis performed by Hamadani et al. (Matching-adjusted Indirect Comparison of the Efficacy of Loncastuximab Tesirine Versus Treatment in the Chemoimmunotherapy Era for Relapsed/Refractory Diffuse Large B-cell Lymphoma, 2022). The same inputs are used however the sample size and results differ. Please explain these differences and state why the preferred analysis was chosen.

This discrepancy is due to a difference in the data cuts included in the two analyses. Data cut-off for the Hamadani analyses was 26 October 2020; in comparison, the Company submitted analyses included a data cut-off of 01 March 2022 (approximately 18 months longer follow-up).

Other clinical queries

A6. Please provide a detailed description of the two-stage adjustment applied to LOTIS 2 data in the chemotherapy comparison accounting for CAR T therapy, including covariate selection and full model output.

The two-stage adjustments made to OS data from LOTIS-2 are based on published methods to deal with treatment switching (5, 6), and have previously been used to adjust for the impact of retreatment (7).

The point of treatment discontinuation was considered as the secondary baseline, with post-discontinuation survival estimated from this point. In previous analyses, the point of disease progression has been used as the secondary baseline, however not all patients that received chimeric antigen receptor T cells (CAR-T) in LOTIS-2 had experienced disease progression. Accelerated failure time (AFT) models were then fit to the post-discontinuation survival curve, including covariates and an indicator for whether or not subsequent CAR-T therapy was received, providing an estimate of the treatment effect of subsequent CAR-T. This was then used to estimate counterfactual survival times for patients treated with CAR-T, using the formula:

$$U_i = T_{Ai} + \theta T_{Bi}$$

where T_{Ai} is time before CAR-T is received for the ith individual, T_{Bi} is their time post-CAR-T and θ is the acceleration factor associated subsequent CAR-T therapy.

The covariates included in the model were those that were identified as important during clinical interviews, and included age, number of prior lines of therapy, response to first and last treatment, ECOG score and disease stage at diagnosis. Time to disease progression was also included as a covariate, as an indicator of how well a patient had performed on loncastuximab. Models of post-discontinuation survival were fit using the Weibull, log-normal and log-logistic distributions and the log-logistic was selected as the best fitting model based on AIC and BIC, presented in Table 10. Full outputs of the log-logistic model are presented in Table 11.

Table 10: Model fits

Model	AIC	BIC
Weibull	398.2	454.8
Log-normal	395.1	451.7
Log-logistic	**393.0**	**449.6**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 11: Outputs of the log-logistic model of post-discontinuation survival

	Coefficient	S.E.	z	P>z	LCI	UCI
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy						
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responses to first line of therapy						
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response to last line of therapy						
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage at diagnosis						
Stage II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; LCI, lower confidence interval; PFS, progression-free survival; S.E., standard error; UCI, upper confidence interval.

For analyses using weights from the MAICs, the weights were applied prior to fitting the model of post-discontinuation survival, resulting in alternative acceleration factors for patients treated with CAR-T (Table 12).

Table 12: Summary of models for post-discontinuation survival for weighted analyses

Weights	CORAL extension		COTA		GO extension	
	Coefficient	S.E.	Coefficient	S.E.	Coefficient	S.E.
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy						
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responses to first line of therapy						
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response to last line of therapy						
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage at diagnosis						
Stage II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

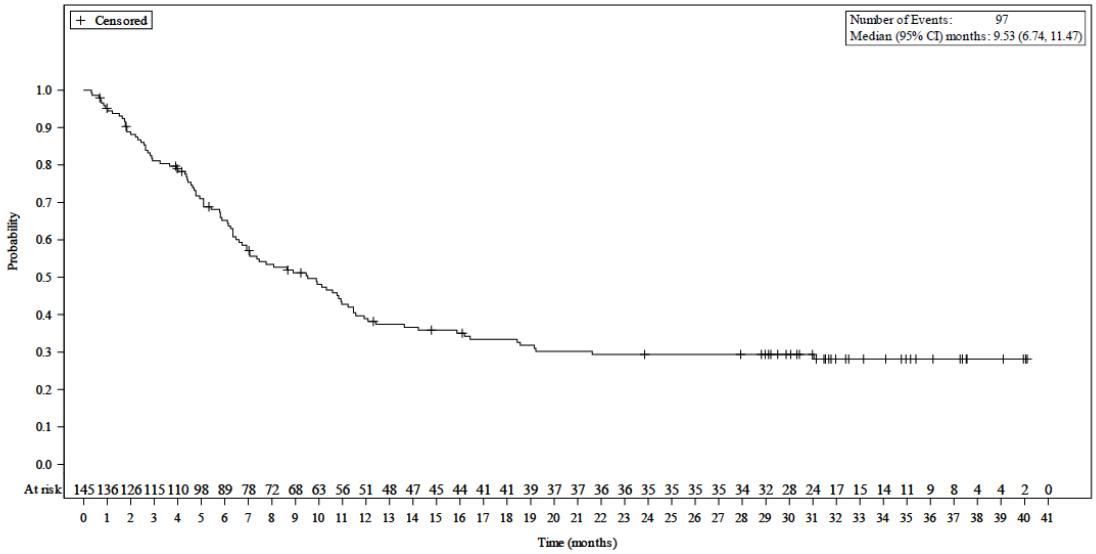
Abbreviations: CAR-T, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; S.E., standard error.

After counterfactual survival times have been generated for patients treated with CAR-T, standard parametric models have been used to analyse the adjusted survival curves, as per the analyses without two-stage adjustment.

A7. Please provide datasets for PFS and OS that the parametric survival models were fitted to (i.e. with and relevant weights where necessary)

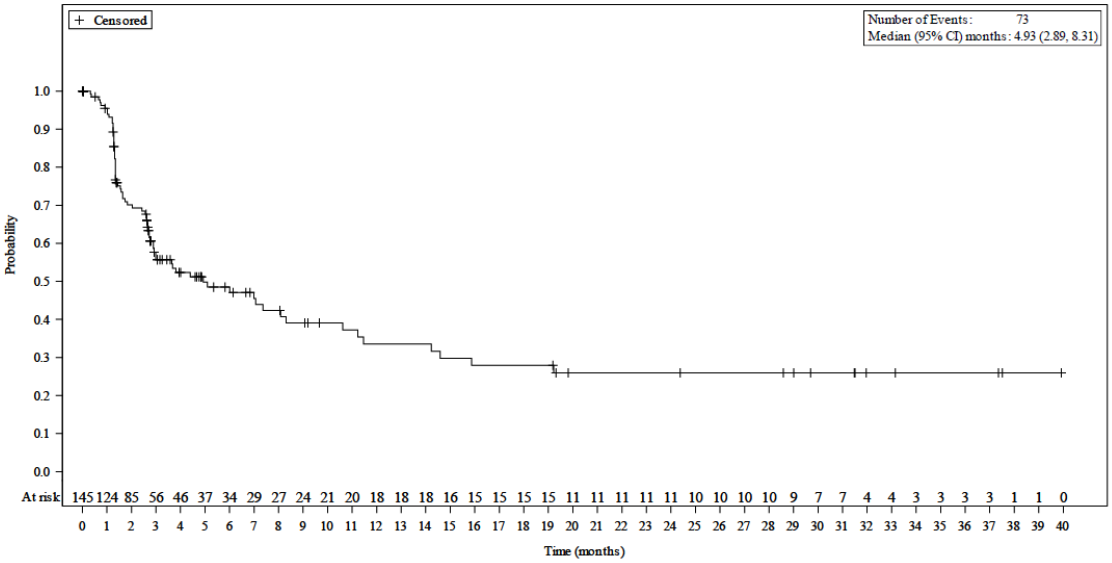
Kaplan-Meier data (including numbers of patients at risk) for OS and PFS from the March 2022 data set of LOTIS-2 are presented in Figure 3 and Figure 4, respectively.

Figure 3: OS K-M from LOTIS-2 (March 2022 data set)



Abbreviations: K-M, Kaplan-Meier; OS, overall survival.

Figure 4: PFS K-M from LOTIS-2 (March 2022 data set)



Abbreviations: K-M, Kaplan-Meier; PFS, progression-free survival.

A8. Priority Question: Please provide a comparison (graphical and statistical) of individual patients' duration of remission in LOTIS 2 with their respective durations of remission on their previous therapy.

Any analysis of duration of remission amongst patients who achieved remission to loncastuximab and their last line of therapy would be limited by sample size, as of the 36 patients with a CR to loncastuximab, only 13 had a CR to their last line of

treatment. Instead, the Company have considered a broader analysis of remission times at last line of treatment with remission times with loncastuximab.

The Company have attempted to produce this analysis; however, it has not been possible to define a consistent definition of remission across lines of treatment that would not lead to a biased analysis. Typically, duration of remission is defined as time from complete response (CR) to either progression or death, however time of response data is not available for prior lines of therapy. As an alternative approach, the Company have considered an analysis defining duration of remission as time from treatment initiation to progression or death amongst patients with a complete response.

However, the Company believe this analysis would remain biased, for the following reasons:

- In LOTIS-2, many patients with a CR go on to have consolidative treatment with transplant or CAR-T prior to disease relapsing and duration of remission is not followed up beyond this point. Censoring patients at this time point is likely to bias in favour of loncastuximab, as at the prior line patients must have progressed and gone on to receive loncastuximab without having consolidative treatment. Conversely, considering receipt of consolidative therapies as an event would artificially limit the durations for loncastuximab. Of the 36 patients achieving a CR, only 6 were observed to lose remission during LOTIS-2.

- Clinical experts consulted by the Company considered line of therapy to be one of the most important predictors of outcomes, making any comparison of response across lines of therapy biased.

- Patients entering LOTIS-2 cannot have died at their last line of therapy, and so the definition of duration of remission would not be consistent across the analysis.

As such, the Company does not feel that it is possible to produce a suitable analysis using the data available from LOTIS-2. However, if there is an alternative analysis that would help NICE and the EAG in their assessment of loncastuximab, Sobi will attempt to provide it.

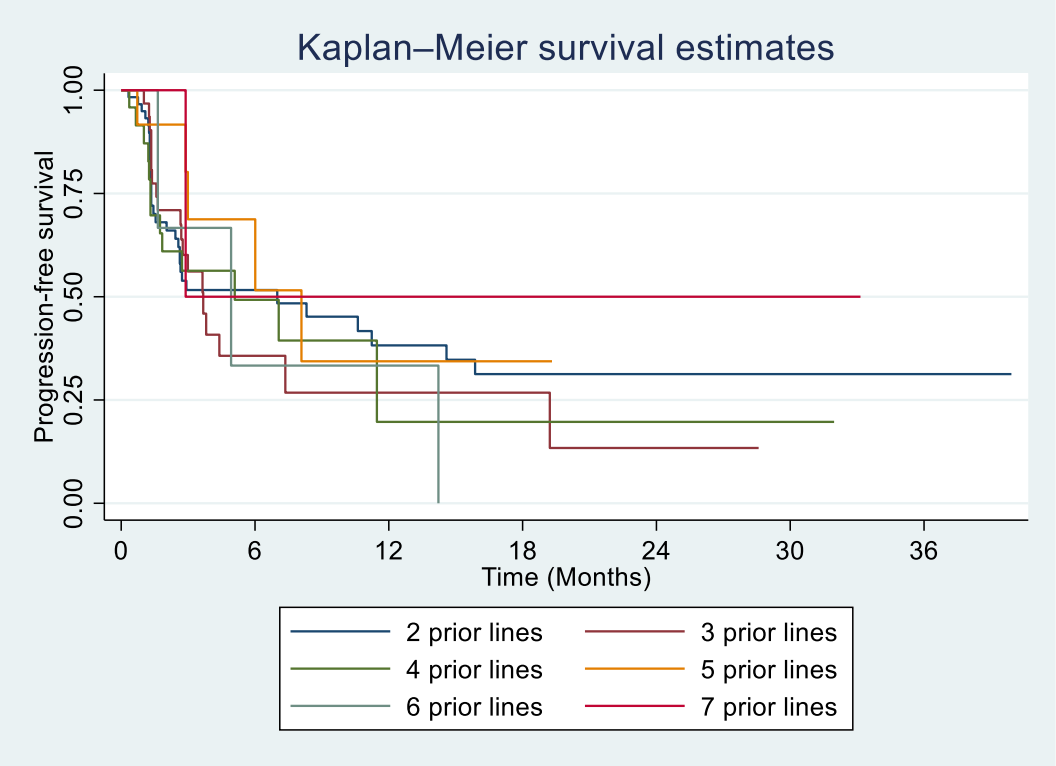
A9. Priority Question: Please explore the assumption of proportional hazards between subgroup populations of LOTIS-2 based on the number of prior therapies patients have received through fitting a time-varying hazard ratio, providing the output.

Table 13 presents the number of prior lines of therapy received in LOTIS-2. Figure 5 and Figure 6 present PFS and OS by number of prior lines of systemic treatment.

Table 13: Summary of prior lines of therapy

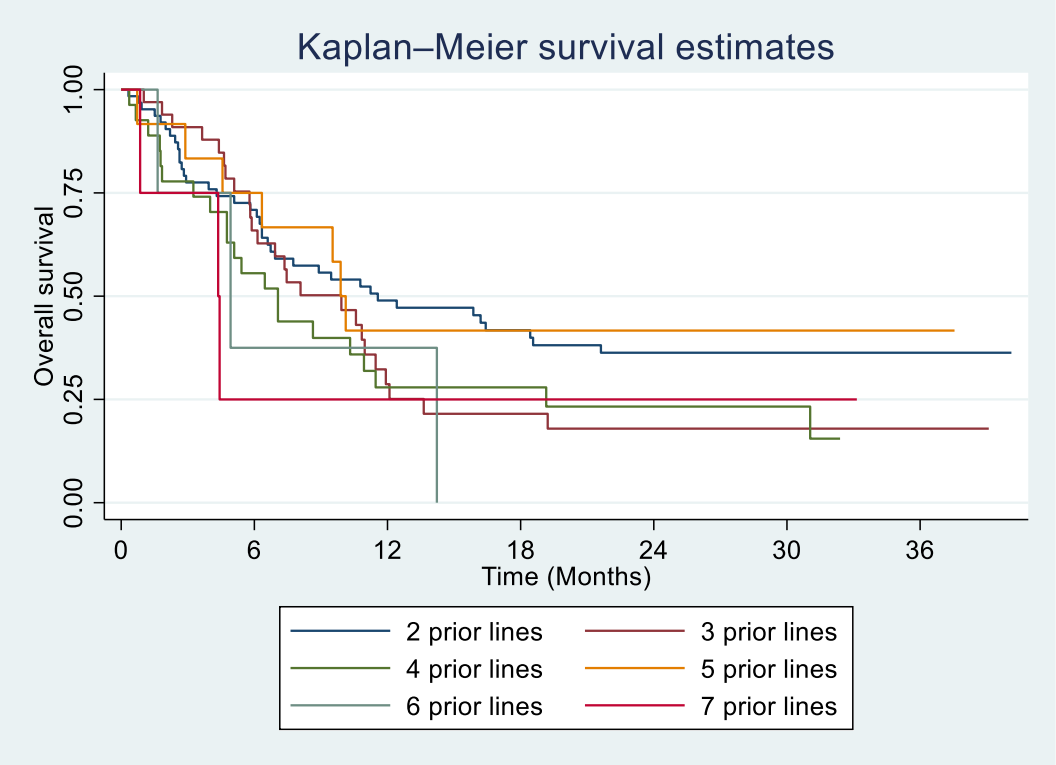
Number of prior lines of therapy	Frequency	Percent
2	63	43%
3	34	23%
4	27	19%
5	13	9%
6	4	3%
7	4	3%
Total	**145**	**100%**

Figure 5: PFS by number of lines of prior therapy in LOTIS-2



Abbreviations: PFS, progression-free survival.

Figure 6: OS by number of lines of prior therapy in LOTIS-2



Abbreviations: OS, overall survival.

As there are few patients with >4 prior lines of therapy, and for ease of interpretation, patients have been grouped into 2 prior lines vs 3+ prior lines.

PFS curves for 2 vs 3+ prior lines remain close up to 6 months, with patients who received 2 prior lines of therapy having higher PFS thereafter (Figure 7).

The smoothed hazard estimates (Figure 8) show a higher hazard for patients with 3+ prior lines of therapy up to 10 months, after which point the hazards cross. The log-cumulative hazards plots (Figure 9) are not parallel, however the global test of proportional hazards does not reject the proportional hazards (PH) assumption (p=0.2259).

Figure 7: PFS for 2 vs. 3+ prior lines of therapy in LOTIS-2

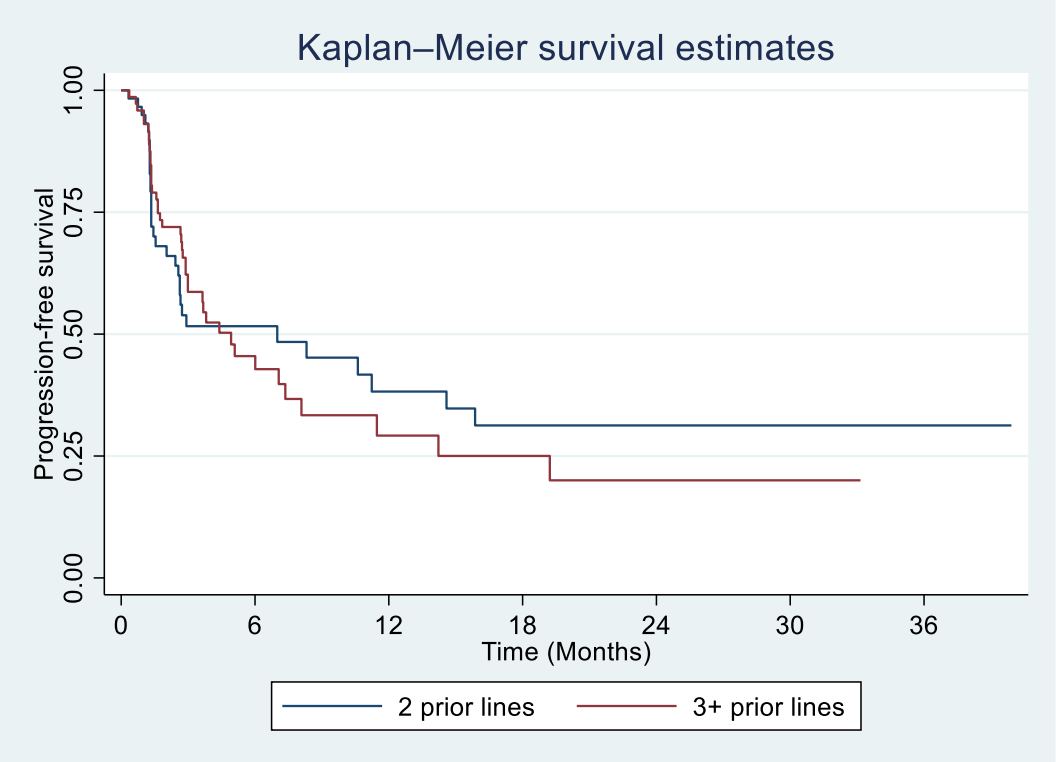


Figure 8: Smoothed hazard estimates – PFS for 2 vs. 3+ prior lines of therapy (LOTIS-2)

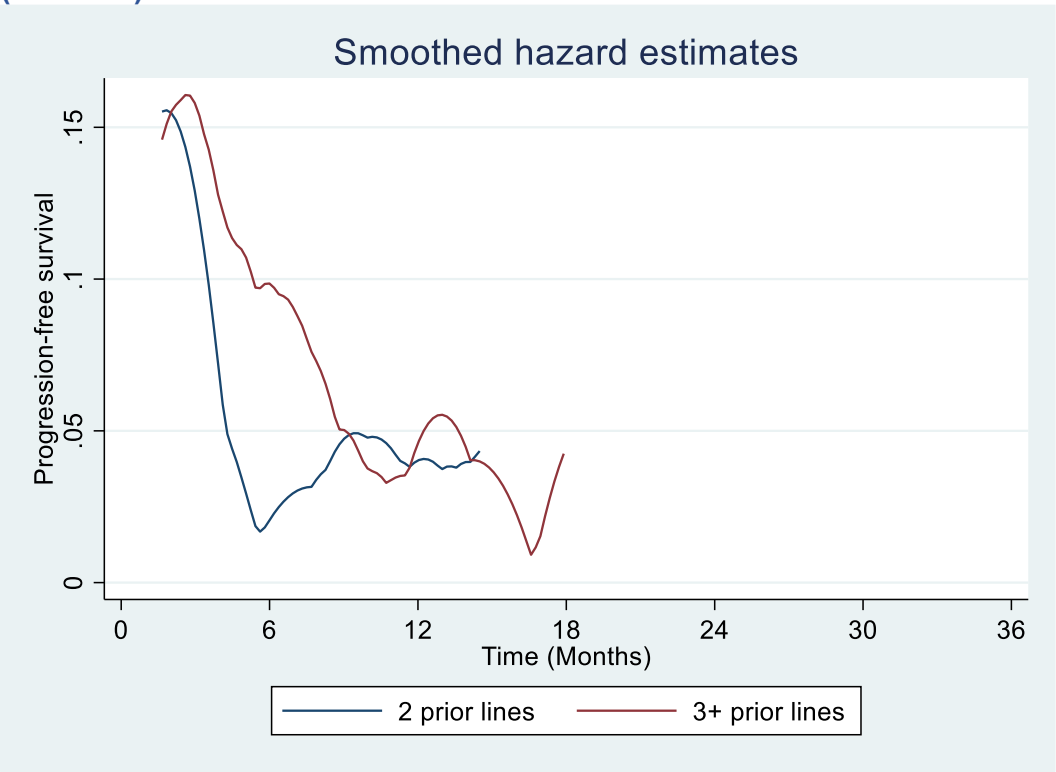


Figure 9: Log-cumulative hazards plot - PFS for 2 vs. 3+ prior lines of therapy (LOTIS-2)

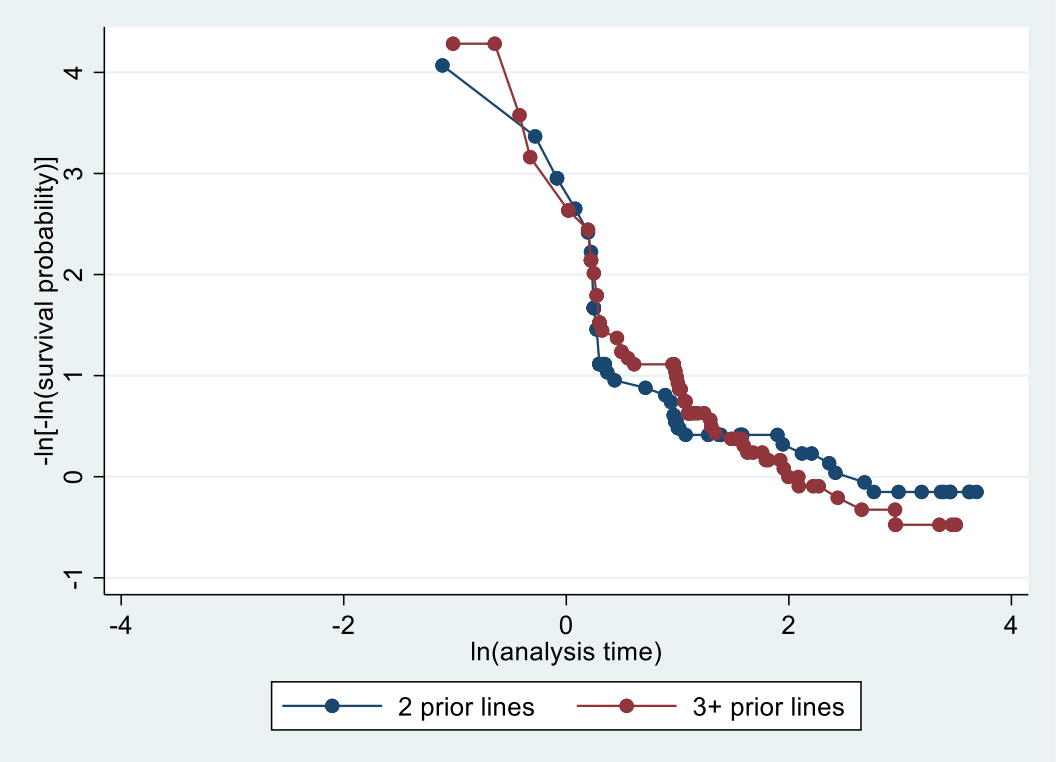
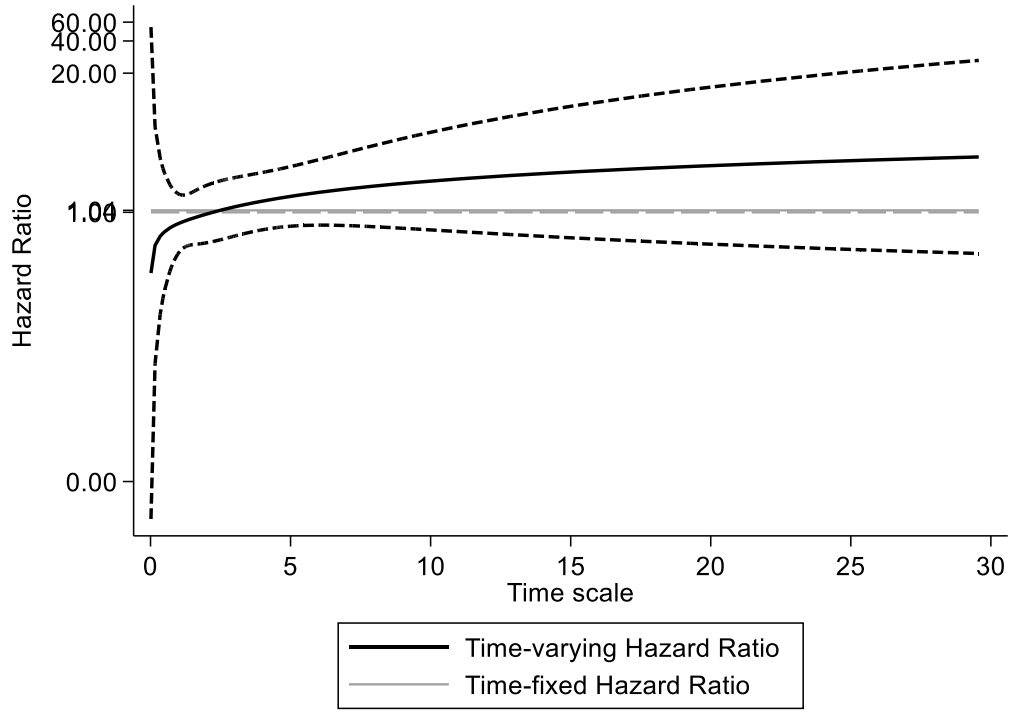


Figure 10 compares time-fixed and time-varying HRs for PFS, based on a restricted cubic spline model. This shows that the HR for being in the 3+ prior lines group versus 2+ lines increases over time.

Figure 10: Comparison of time-varying and time-fixed hazard ratios (PFS, LOTIS-2)



Results are similar for OS, with survival being similar in the first 6 months, but higher survival beyond this for patients with 2 prior lines of therapy (Figure 11).

The smoothed hazard plots show higher hazards for patients with 3+ lines of prior therapy up to 15 months (Figure 12). Again, the log-cumulative hazard plots are not parallel (Figure 13), although the global test of PH fails to reject the PH assumption (p=0.4400)

Figure 11: OS for 2 vs. 3+ prior lines of therapy in LOTIS-2

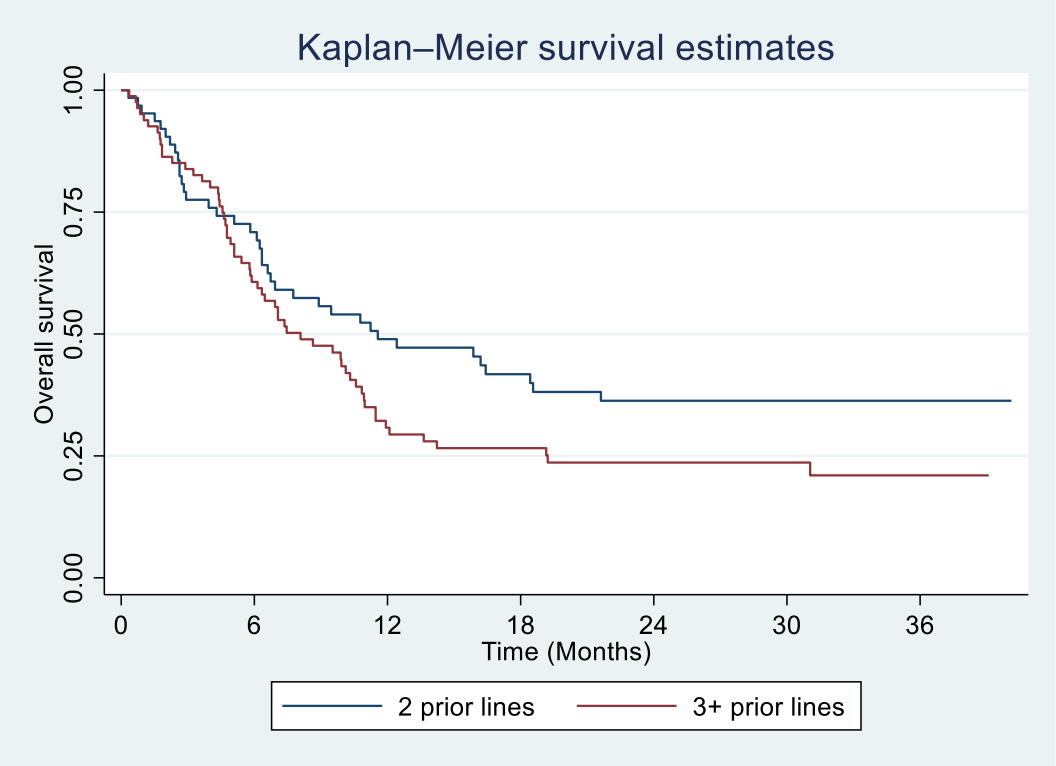


Figure 12: Smoothed hazard estimates – OS for 2 vs. 3+ prior lines of therapy (LOTIS-2)

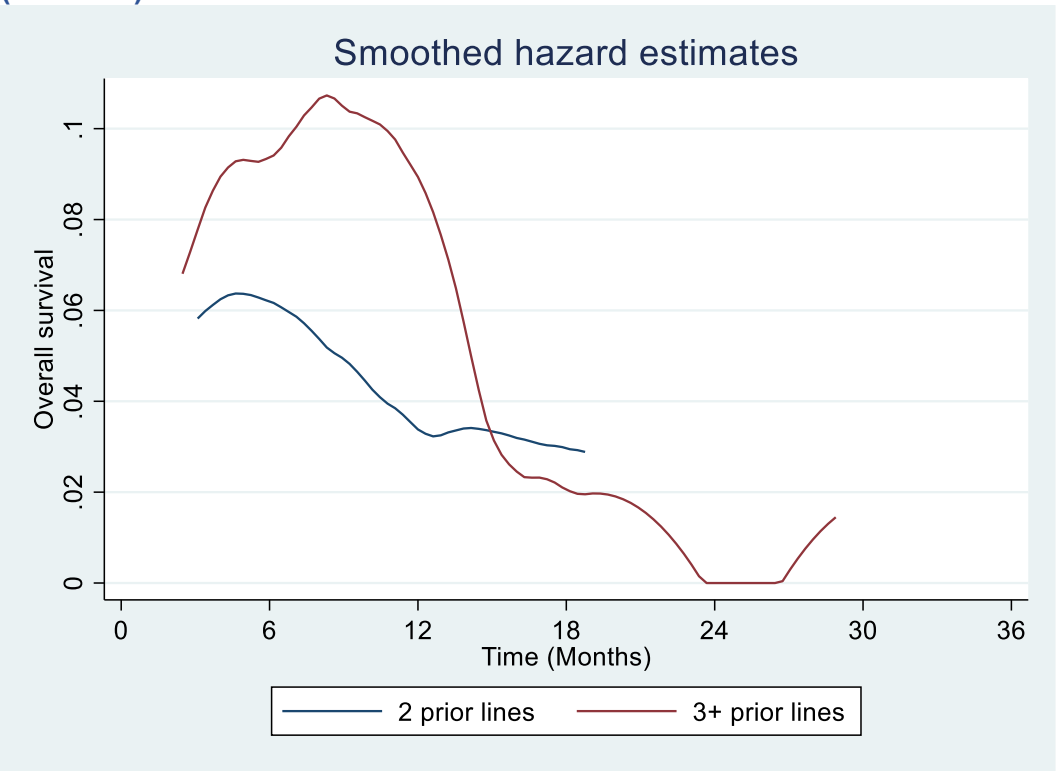


Figure 13: Log-cumulative hazards plot - OS for 2 vs. 3+ prior lines of therapy (LOTIS-2)

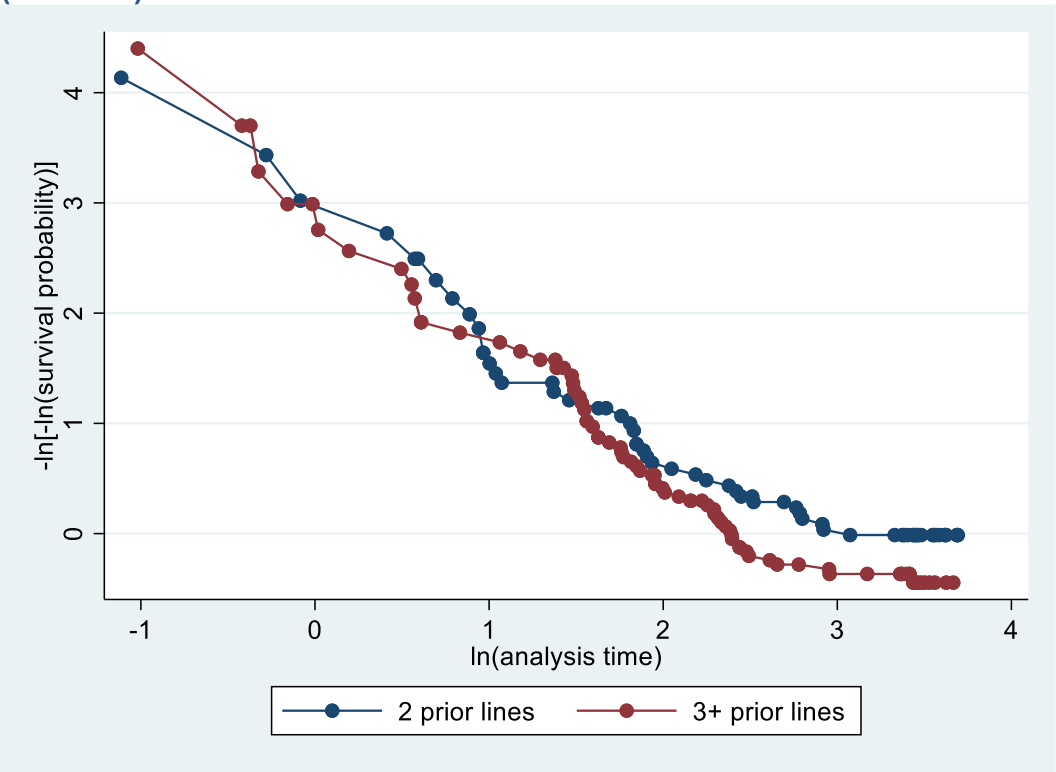
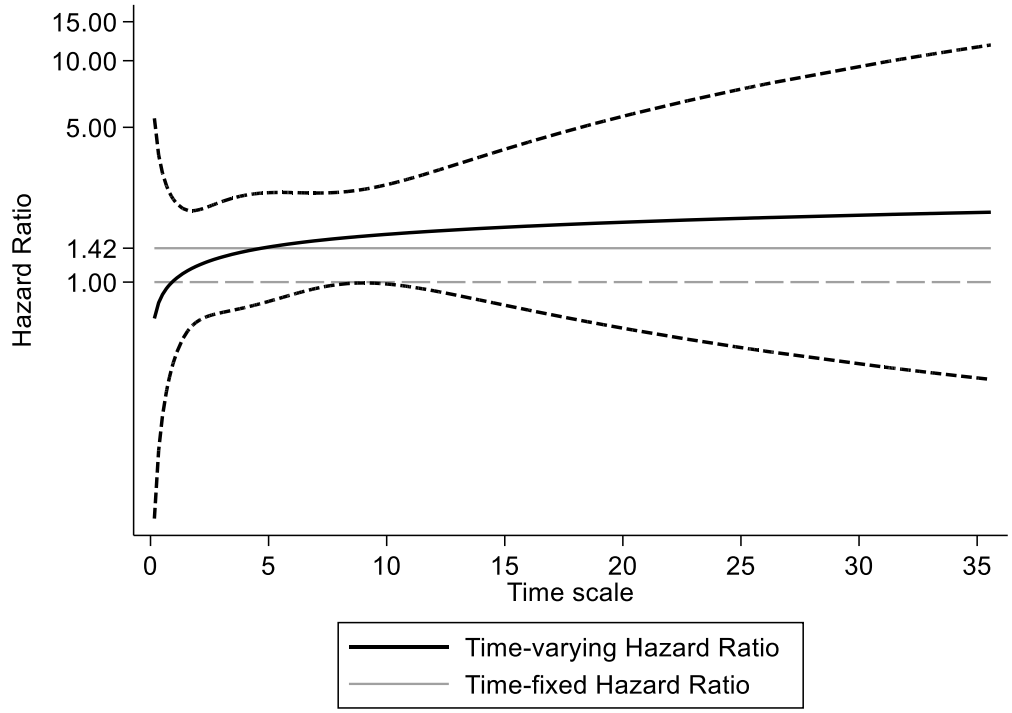


Figure 14 compares time-fixed and time-varying HRs for OS, based on a restricted cubic spline model. This shows that the HR for being in the 3+ prior lines group versus 2+ lines increases over time.

Figure 14: Comparison of time-varying and time-fixed hazard ratios (OS)



The same exercise has been conducted using the data for Pola+BR from the COTA data set.

PFS curves for 2 vs 3+ prior lines remain close throughout the observed period (Figure 15). The smoothed hazard estimates (Figure 16) show a similar hazard during the period in which PFS follow-up is available for both groups. The log-cumulative hazards plots (Figure 17) are not parallel, however the global test of proportional hazards does not reject the PH assumption (p=0.9433).

Figure 15: PFS for 2 vs. 3+ prior lines of therapy in COTA

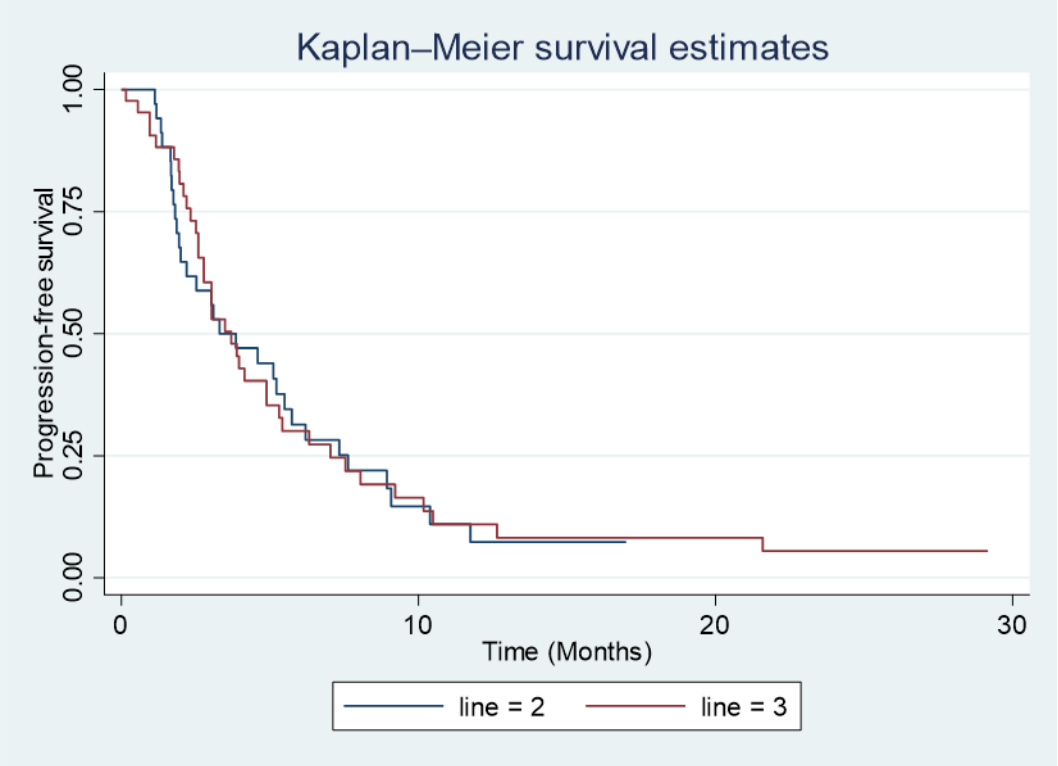


Figure 16: Smoothed hazard estimates – PFS for 2 vs. 3+ prior lines of therapy (COTA)

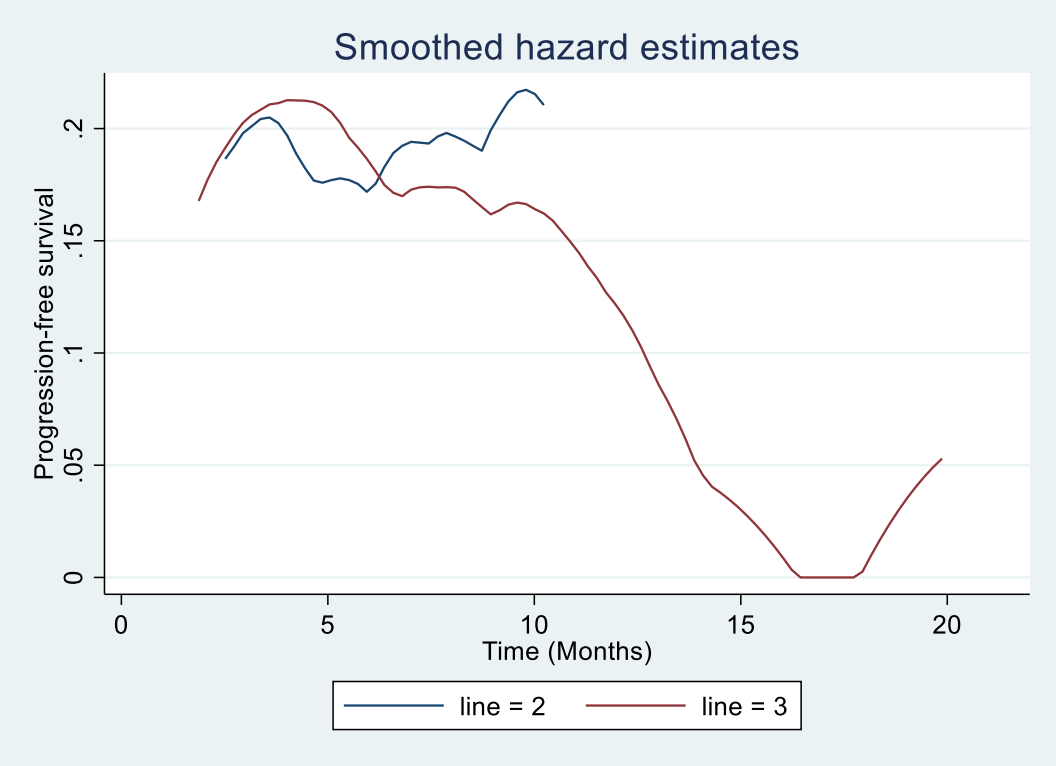


Figure 17: Log-cumulative hazards plot - PFS for 2 vs. 3+ prior lines of therapy (COTA)

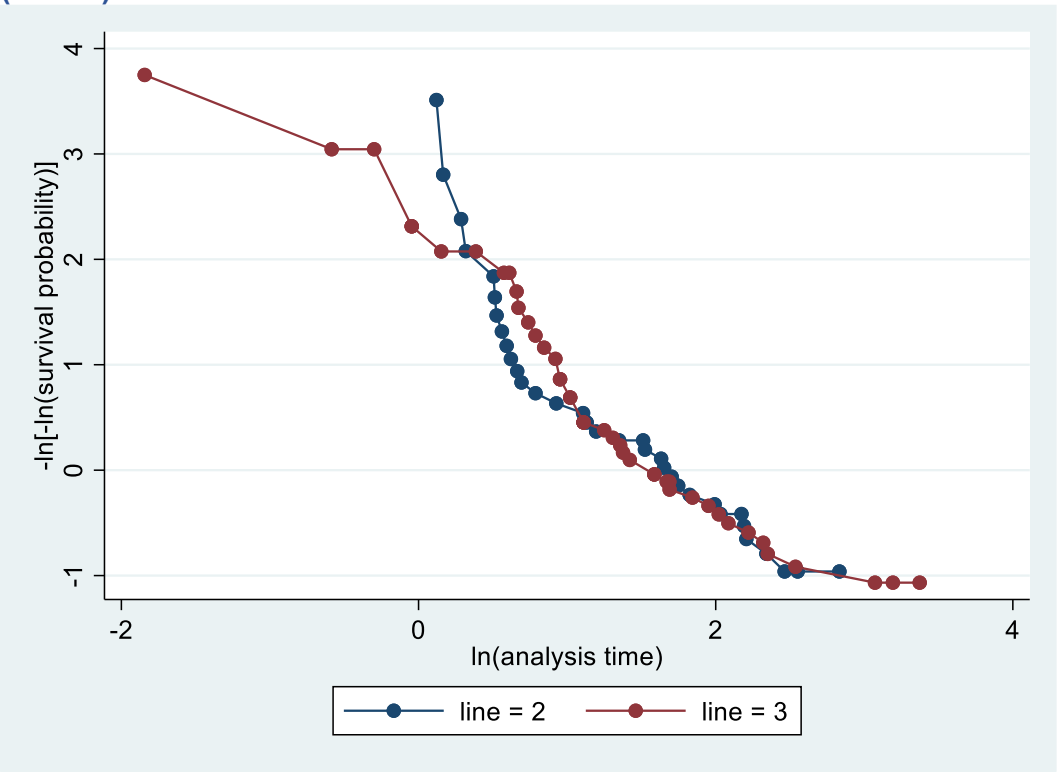
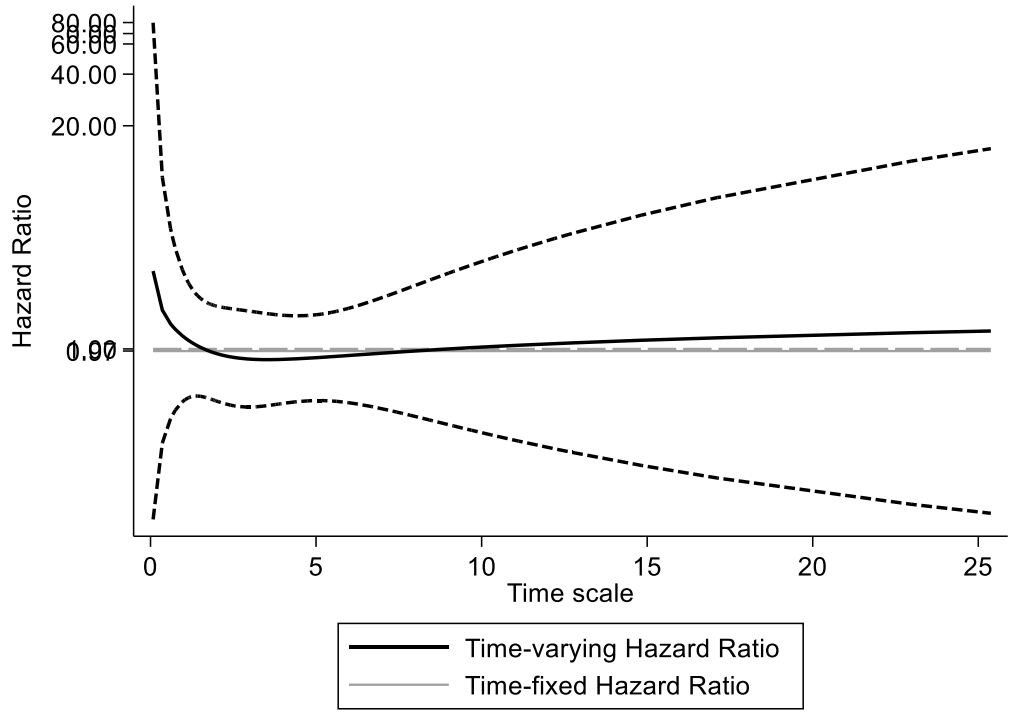


Figure 18 compares time-fixed and time-varying HRs for PFS, based on a restricted cubic spline model. This shows that the time-varying HR remains close to the time-fixed HR throughout the observed period. This suggests that the assumption of proportional hazards between the two groups may be reasonable.

Figure 18: Comparison of time-varying and time-fixed hazard ratios (PFS, COTA)



The OS curves for those with 2 and 3+ lines of prior therapy separate relatively early, with patients with 2 lines of prior therapy having improved OS (Figure 19). The smoothed hazard plots show that the hazard for patients with 3+ prior lines of therapy is initially higher than for those with 2 prior lines of therapy, but the smoothed hazard plots cross in two places (Figure 20). The log-cumulative hazard plots are not parallel, but the global test of PH fails to reject the PH assumption (p=0.9090).

Figure 19: OS for 2 vs. 3+ prior lines of therapy in COTA

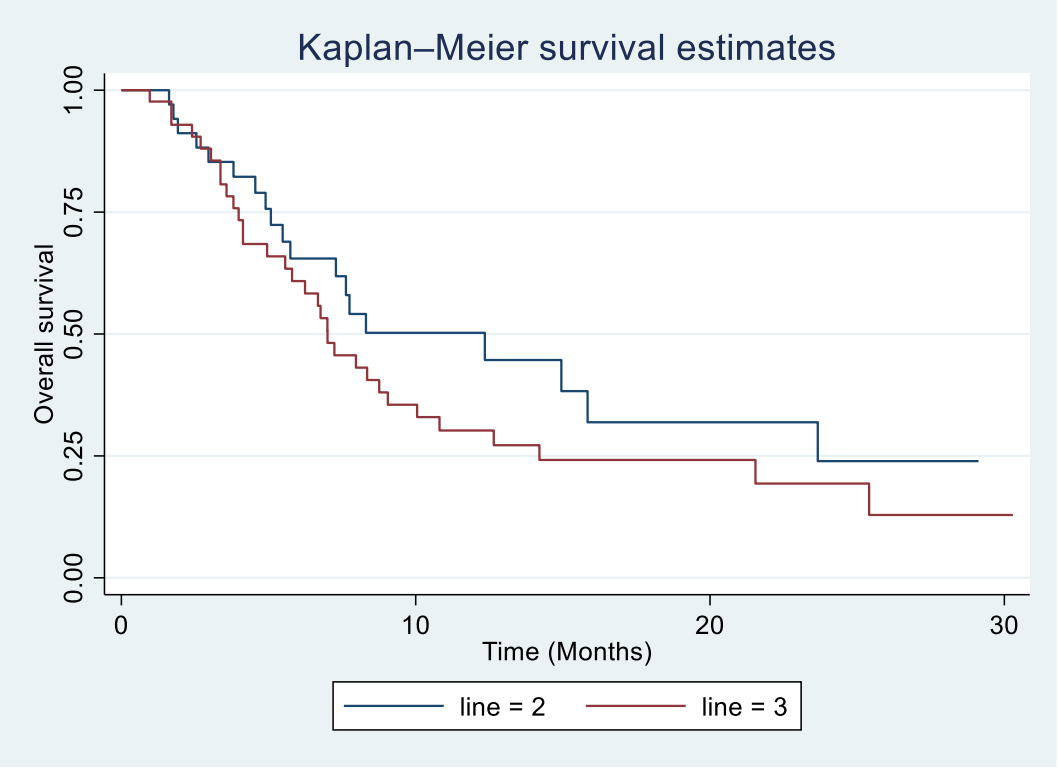


Figure 20: Smoothed hazard estimates – OS for 2 vs. 3+ prior lines of therapy (COTA)

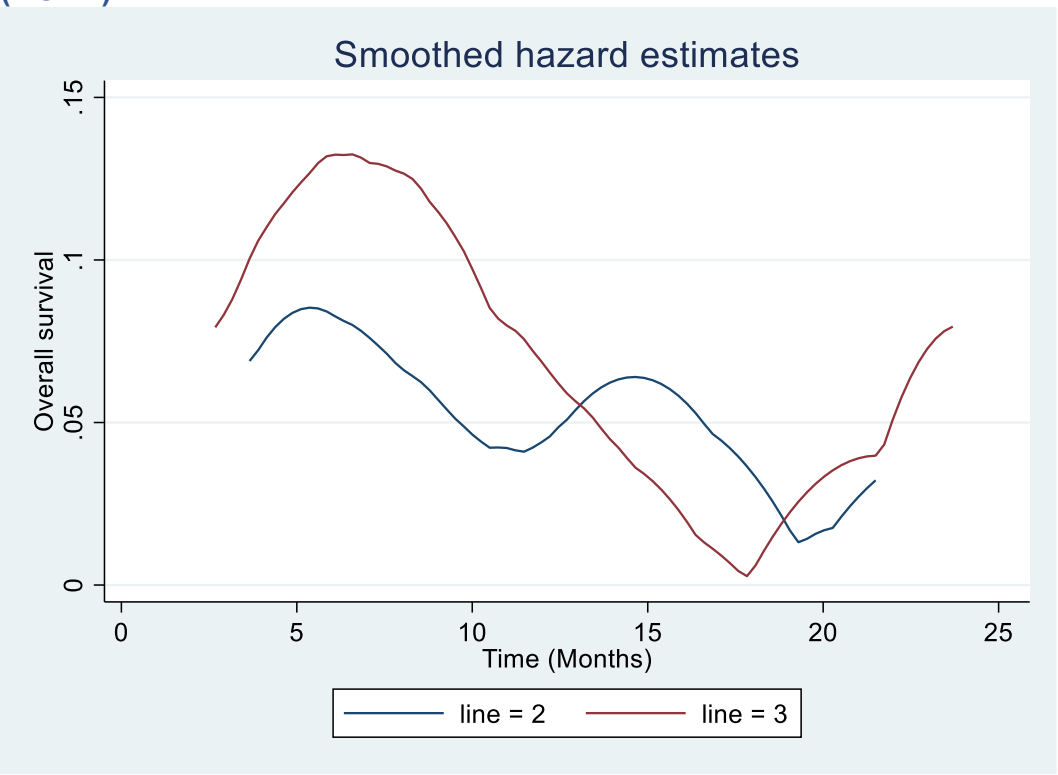


Figure 21: Log-cumulative hazards plot - OS for 2 vs. 3+ prior lines of therapy (COTA)

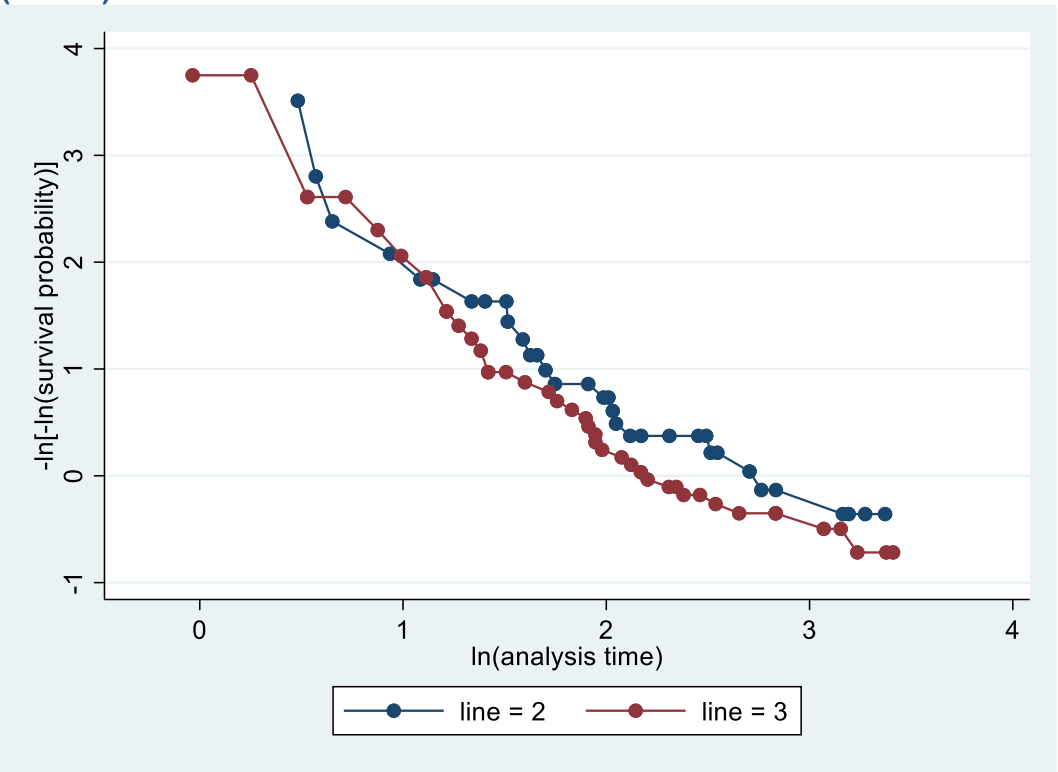
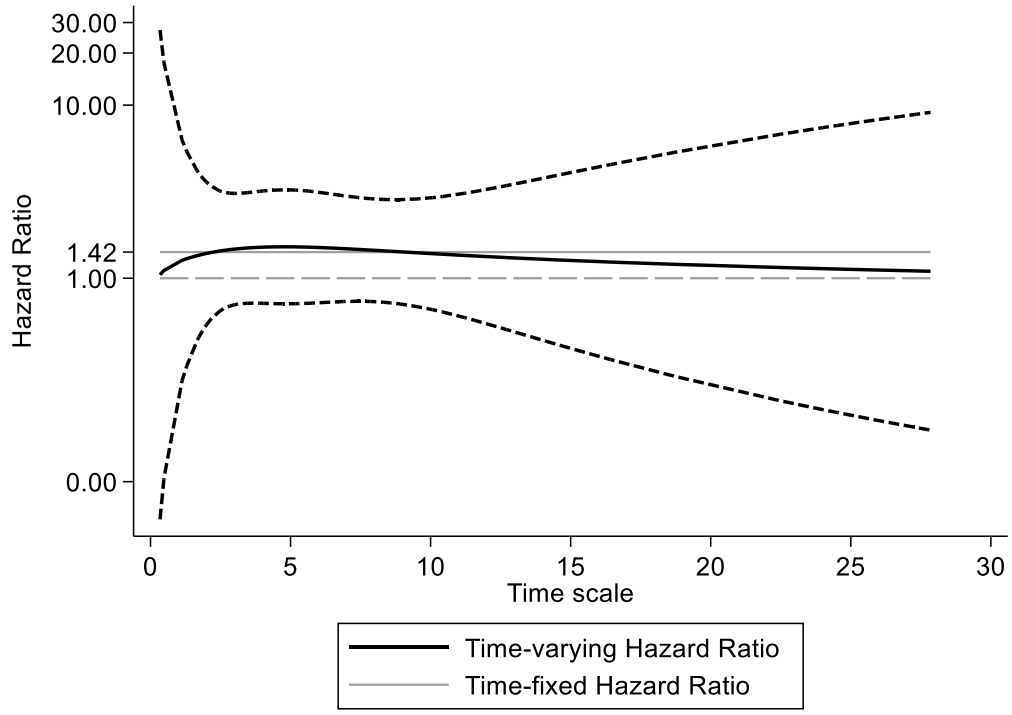


Figure 22 compares time-fixed and time-varying HRs for OS, based on a restricted cubic spline model. As for PFS, the time-varying HR remains relatively close to the time-fixed HR, suggesting that the assumption of proportional hazards between the two groups may be reasonable.

Figure 22: Comparison of time-varying and time-fixed hazard ratios (OS, COTA)



A10. Priority Question: Table 9 (page 44) of the company submission states that the population includes three groups in terms of Response to most recent systemic therapy: Relapse, Refractory and Other. Please justify the inclusion of the "Other" group to the population under consideration in this appraisal. If these patients are not relevant, please remove them from and update all necessary analyses.

If related to this response, please also justify the inclusion of "Other" responders to the Response for all previous therapies, and Response to first line systemic therapy variables.

The definition of 'Other' in terms of response includes unknown, not evaluable, or missing. In the most recent analysis, 17 patients were classified as 'Other' for response to first-line therapy, and 13 patients are classified as 'Other' for response to most recent line of therapy.

These patients are considered relevant to decision making because they have received at least two prior lines of treatment and are relapsed or refractory to the prior line, as per the clinical trial protocol. For these reasons they would be in the population of interest in clinical practice.

Sobi maintain that it would be inappropriate to exclude these patients from the analysis given their relevance to the decision problem and that they comprise a small number of patients.

A11. Please provide a breakdown and frequency of the previous therapies received by patients in the LOTIS-2 study, by line, indicating which are classed as systemic therapies.

Table 14 summarises previously received treatments by line of therapy. The definition of prior line of therapy includes stem cell transplant. For patients who received an autologous transplant, the mobilization regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment. All therapies except for stem cell transplants would be classed as systemic.

Table 14: Summary of frequency of prior therapies by line

Category	Line of treatment							
	1	2	3	4	5	6	7	Total
Allo SCT	0	0	0	2	1	0	0	3
Auto SCT	0	0	15	5	0	1	1	22
Auto SCT-Mob	0	1	2	0	1	0	0	4
CAR-T	1	0	4	4	3	2	0	14
CNS Tx/PPX	0	1	0	0	0	0	0	1
Chemotherapy	142	128	42	24	7	1	1	345
Targeted/Mab	1	12	13	6	6	2	1	41
Trial	1	3	6	7	3	2	1	23
Total	145	145	82	48	21	8	4	453

Abbreviations: Allo SCT, allogeneic stem cell transplant; Auto SCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; CNS Tx/PPX, central nervous system treatment/prophylaxis; Mab, monoclonal antibody; Mob, mobilisation.
ADCT402-201 - Cut off date 15Sep2022

Section B: Clarification on cost-effectiveness data

Model queries

B1. The economic model suggests that the two-stage adjustment was not applied alongside the weights for the comparison to chemotherapy. If this is the case, please apply the appropriate weights after the two-stage adjustment has been applied, and implement it in the economic model.

The Company base case uses unweighted OS (with two-stage adjustment), PFS and time-to-treatment discontinuation (TTD) data from LOTIS-2 and applies the HR for chemotherapy to these curves, assuming that the treatment effect for chemotherapy is generalisable to the LOTIS-2 population. This analysis was selected as the base case for comparison to chemotherapy, as the population of the LOTIS-2 trial was judged to be the most generalisable to UK clinical practice.

A scenario applying the weights for the comparison to the CORAL extension studies was provided in the Company submission. In this scenario, outcomes from the CORAL extension studies were directly extrapolated, and outcomes for loncastuximab were extrapolated applying the weights from the MAIC and including the two-stage adjustments for OS. This scenario resulted in an incremental cost of [redacted] and a quality-adjusted life year (QALY) gains of [redacted], leading to an incremental cost-effectiveness ratio (ICER) of £40,103. A second scenario analysis is presented in Table 15, which applies the weights from the MAIC when extrapolating loncastuximab data and applies the HR from the MAIC to generate outcomes for chemotherapy. This additional scenario gives an ICER of £43,654.

Table 15: Scenario analysis using weighted curves to extrapolate outcomes for loncastuximab, and HRs for chemotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,654

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, QALY, quality adjusted life-years.

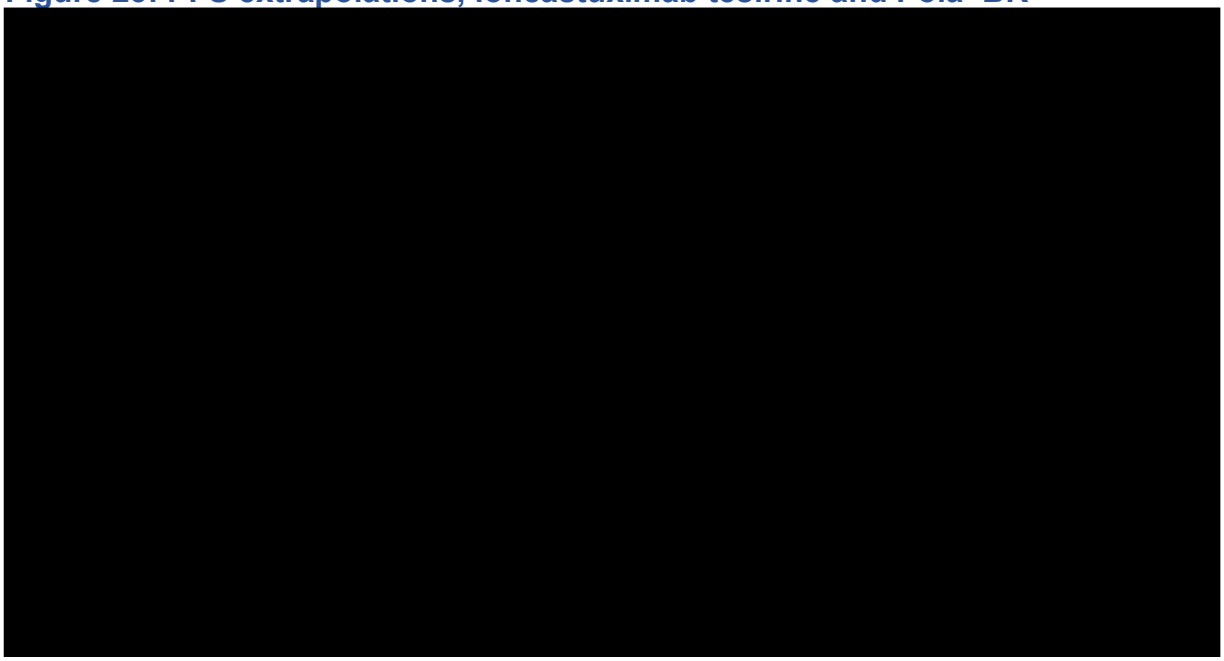
B2. Please clarify the following statement in Table 10 CS (Section B.2.4.1, page 46): "All patients in the all-treated population with baseline score (at least one instrument) and at least one postbaseline score (in at least one instrument)" were included in PRO analysis. For example, does this mean that if a patient had a baseline score on one instrument (e.g. EQ-5D-5L) but a post-baseline score in another instrument (e.g. Fact-Lym) they were included in the PRO evaluable population? Or were patients only included if they had a baseline score and post-baseline score from the same instrument (i.e. both in EQ-5D-5L)?

Patients were included if they had a baseline score and post-baseline score from the same instrument.

B3. Priority Question: In the company's base case, the table of disaggregated outcomes suggests a much-improved mean PFS for loncastuximab compared to Pola-BR despite a reduced median PFS. Can the company explain this discrepancy?

The mean PFS is higher for loncastuximab compared with Pola+BR due to a longer tail in the PFS curve for loncastuximab. Clinical experts highlighted that patients that are progression free after 2 years are often discharged from care and there is evidence of a plateau in survival for patients treated with loncastuximab, without the need for further therapies, indicating that a proportion of patients achieve long-term remission on loncastuximab (8). The longer tail for loncastuximab can be observed in the PFS survival extrapolations for loncastuximab and Pola+BR, which are presented in Figure 23.

Figure 23: PFS extrapolations, loncastuximab tesirine and Pola+BR



Abbreviations: PFS, progression-free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab.

B4. Please verify the algorithm used to map EQ-5D-5L to EQ-5D-3L utilities (page 122 CS)

EQ-5D-5L utility data was mapped to the EQ-5D-3L using the algorithm developed by the Decision Support Unit (DSU) (9), as specified in NICE guidelines. The mapping was carried out using the 'eq5dmap' command in Stata.

B5. Can the company clarify that except for CAR-T and SCT, no other data were collected in LOTIS-2 on actual subsequent treatments received by patients. The CS (page 174) states that, "Excluding CAR-T and SCT, 54% of patients in LOTIS-2 went on to receive subsequent treatment. This is assumed to be chemotherapy".

Additional data was collected on the type of subsequent treatment received in LOTIS-2; however, this data had not been analysed for the CSR and medicines were not categorised. The subsequent therapies used in LOTIS-2 were not aligned with UK clinical practice and included patients entering clinical trials. Clinical input provided to the Company indicated that there was no standard practice for patients that failed their third-line therapy, with clinicians stating that patients may receive palliative care, or be entered into a clinical trial. Subsequent anticancer therapy use

was recorded in 13 of 31 UK patients in LOTIS-2. 5 patients received subsequent CAR-T therapy and 1 patient received ASCT. Table 16 summarises the additional subsequent anticancer therapy used by UK patients.

Table 16: Subsequent therapy use amongst UK patients in LOTIS-2

Subsequent therapy	Frequency
[redacted]	[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T cell; pola+BR, polatuzumab plus bendamustine plus rituximab; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone.

B6. Please provide the regression model and coding used for the two models used to estimate PFS/Post-progression utilities (i.e., (i) adjusting for progression status and ongoing Grade ≥3 AEs and, (ii) adjusting for progression status only) alongside the detailed results.

The models for utility values were fit using the 'mixed' command in Stata, which fits linear mixed effects models (10). The code for the two models is presented below, with the model adjusting for progression status and ongoing adverse events (AEs) presented first, followed by the model adjusting for progression status only. Definitions for each variable are included in Table 17.

```
mixed eq5d3l_s eq5d3l_bc i.postprog2 i.aefl || subjid:

mixed eq5d3l_s eq5d3l_bc i.postprog2 || subjid:
```

Table 17: Variable definitions used in regression models for utility values

Variable	Definition
eq5d3l_s	The observed EQ-5D-3L score
eq5d3l_bc	The patient's baseline EQ-5D-3L score, centred on the mean baseline score
postprog2	A binary variable indicating that the patient had progressed disease at the time of completing the EQ-5D-5L questionnaire. This was defined as an observation date later than the patients PFS time, in a patient that was not censored in the PFS analysis
aefl	A binary variable indicating that the observation was taken during an AE

subjid	The unique patient identifier

Abbreviations: AE, adverse event; PFS, progression-free survival.

Both models were based on 772 observations in 138 patients, with an average of 5.6 observations per patient. The log-likelihood for the model including AEs was 385.8, compared to 381.7 for the model without. Outputs for each model, including random effects parameters, are presented in Table 18 and Table 19.

Table 18: Outputs of the utility model including progression status and ongoing AEs

	Coefficient	S.E	z	P>z	LCI	UCI
Baseline EQ-5D-3L†	0.739	0.039	18.730	0.000	0.662	0.817
Post-progression	-0.056	0.021	-2.660	0.008	-0.098	-0.015
AE	-0.045	0.016	-2.850	0.004	-0.076	-0.014
Constant	0.693	0.011	65.460	0.000	0.673	0.714
Random effects parameters						
	Coefficient	**S.E**	**z**	**P>z**	**LCI**	**UCI**
Subjid: Identity						
var(constant)	0.009	0.002	-	-	0.007	0.013
var(Residual)	0.017	0.001	-	-	0.016	0.019

†Centred on the mean.
Abbreviations: AE, adverse event; LCI, lower confidence interval; S.E., standard error; UCI, upper confidence interval.

Table 19: Outputs of the utility model including progression status only

	Coefficient	S.E	z	P>z	LCI	UCI
Baseline EQ-5D-3L†	0.739	0.039	18.730	0.000	0.662	0.817
Post-progression	-0.056	0.021	-2.660	0.008	-0.098	-0.015
AE	-0.045	0.016	-2.850	0.004	-0.076	-0.014
Constant	0.693	0.011	65.460	0.000	0.673	0.714
Random effects parameters						
	Coefficient	**S.E**	**z**	**P>z**	**LCI**	**UCI**
Subjid: Identity						
var(constant)	0.009	0.002	-	-	0.007	0.013
var(Residual)	0.017	0.001	-	-	0.016	0.019

†Centred on the mean.
Abbreviations: LCI, lower confidence interval; S.E., standard error; UCI, upper confidence interval.

B7. Please verify that incremental QALYs for loncastuximab tesirine vs chemotherapy are reported correctly on the bottom of page 184 (CS)

The incremental QALYs for loncastuximab vs chemotherapy have been incorrectly reported on Company submission, page 184. The correct figure is [redacted] incremental QALYs, in line with Table 89 of the Company submission.

B8. Priority Question: The QALY weighting for severity appears to have been applied to the willingness to pay (WTP) threshold, rather than to the QALY gain. Please provide updated ICERs with the modifier applied directly to the QALYs (alongside the QALYs and ICERs without the severity modifier applied).

The cost-effectiveness results have been updated with severity modifiers applied to the incremental QALYs. Deterministic results for the comparisons to Pola+BR and chemotherapy are presented in Table 20 and Table 21, respectively. Comparisons to Pola+BR are based on the new base case discussed in Question A3, while comparisons to chemotherapy are based on the submitted base case which remains unchanged. Probabilistic results for the comparisons to Pola+BR and chemotherapy are presented in Table 22 and Table 23, respectively.

Table 20: New base-case deterministic cost-effectiveness results, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Severity modifier	Comparator	Total costs	Total QALYs	ICER (£/QALY)
No severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated
1.2 severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated
1.7 severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine plus rituximab; QALYs, quality-adjusted life years; vs, versus.

Table 21: Submitted base-case deterministic cost-effectiveness results, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

Severity modifier	Comparator	Total costs	Total QALYs	ICER (£/QALY)
No severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£48,986
1.2 severity modifier	Chemotherapy	[redacted]	[redacted]	-

	Loncastuximab	[redacted]	[redacted]	£40,821
1.7 severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£28,815

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; QALYs, quality-adjusted life years; vs, versus.

Table 22: New base-case probabilistic cost-effectiveness results, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Severity modifier	Comparator	Total costs	Total QALYs	ICER (£/QALY)
No severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated
1.2 severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated
1.7 severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine plus rituximab; QALYs, quality-adjusted life years; vs, versus.

Table 23: Submitted base-case probabilistic cost-effectiveness results, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

Severity modifier	Comparator	Total costs	Total QALYs	ICER (£/QALY)
No severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£51,590
1.2 severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£42,991
1.7 severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£30,347

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; QALYs, quality-adjusted life years; vs, versus.

B9. The probability sensitivity analysis (CS, page 186-188), and the interpretation and conclusions of the economic evidence (CS, pg 197) refer to the use of a WTP threshold of £50,000. Please correct this to the appropriate WTP and, if necessary, update the results provided from the PSA (e.g. the percentage of scenarios in which loncastuximab tesirine is cost effective).

The probabilistic results based on cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained are presented in Table 24 and Table 25, for the comparisons against Pola+BR and chemotherapy, respectively.

Table 24: New base case, percentage of simulations cost-effective, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

WTP threshold	No severity multiplier		1.2 severity multiplier		1.7 severity multiplier	
	Lonca	Pola+BR	Lonca	Pola+BR	Lonca	Pola+BR
£20,000	98%	2%	98%	2%	99%	1%
£30,000	99%	1%	99%	1%	97%	3%

Abbreviations: lonca, loncastuximab tesirine; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine plus rituximab; vs, versus; WTP, willingness-to-pay.

Table 25: Submitted base case, percentage of simulations cost-effective, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

WTP threshold	No severity multiplier		1.2 severity multiplier		1.7 severity multiplier	
	Lonca	Chemo	Lonca	Chemo	Lonca	Chemo
£20,000	0%	100%	1%	99%	5%	95%
£30,000	2%	98%	8%	92%	49%	51%

Abbreviations: lonca, loncastuximab tesirine; PAS, patient access scheme; chemo, chemotherapy; vs, versus; WTP, willingness-to-pay.

Section C: Textual clarification and additional points

Literature Searches

C1. In the reference pack, we are unable to locate the document file for one of the 'data on file' references (Sobi. Data on file. Clinical overview - Loncastuximab tesirine October 2021), which is cited as a source in the CS Doc B (ref. 69) for tables 13 and 14 and figures 5, 8, 10, 12, 14, 16. Please supply the document or advise us of the filename.

Apologies, this reference was missing from the reference pack, submitted 17th March 2023. The reference has now been provided with these responses, with the filename 'DataOnFile-Sobi-Clinical overview-Loncastuximab tesirine October 2021.pdf'

C2. Please provide reference details and specify which SLRs and HTA documents' reference lists were screened in each of the SLRs. Please provide PDFs for any not already supplied in the reference pack.

The references for the systematic literature review (SLR)/network meta-analysis (NMA) hand searched can be found in Table 26 to Table 29 for each SLR. All references are now provided with these responses.

Table 26: Clinical SLR citation searching

Clinical SLR citation searching (n=9)
1. Aiman W, Ali MA, Ali R, Fatima FN, Mirza N, Javaid A, et al. Effiicacy and safety of lenalidomide based regimens in diffuse large B cell lymphoma: A systematic review and meta-analysis of clinical trials. Blood. 2020;136(SUPPL 1):13-4. 2. Galaznik A, Bell JA, Hoog MM, Stokes ME, Steenrod AW, Knopf KB, et al. Systematic review of therapy used in relapsed or refractory diffuse large B-cell lymphoma. Blood. 2016;128(22). 3. Galaznik A, Huelin R, Stokes M, Guo Y, Hoog M, Bhagnani T, et al. Systematic review of therapy used in relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. Future Science OA. 2018;4(7):FSO322. 4. Meng J, Wu X, Sun Z, Xun R, Liu M, Hu R, et al. Efficacy and Safety of CAR-T Cell Products Axicabtagene Ciloleucel, Tisagenlecleucel, and Lisocabtagene Maraleucel for the Treatment of Hematologic Malignancies: A Systematic Review and Meta-Analysis. Frontiers in Oncology. 2021;11: 698607. 5. Pasqui DM, Latorraca CDOC, Pacheco RL, Riera R. CAR-T cell therapy for patients with hematological malignancies. A systematic review. European Journal of Haematology. 2022((Pasqui, Riera) Discipline of Evidence-Based Medicine, Universidade Federal de Sao Paulo (Unifesp), Sao Paulo, Sao Paulo, Brazil(Latorraca, Pacheco, Riera) Centre of Health Technology Assessment, Hospital Sirio-Libanes, Sao Paulo, Sao Paulo, Brazil(Latorr). 6. Halford Z, Anderson MK, Bennett LL. Axicabtagene Ciloleucel: Clinical Data for the Use of CAR T-cell Therapy in Relapsed and Refractory Large B-cell Lymphoma. Annals of Pharmacotherapy. 2021;55(3):390-405. 7. Thuresson PO, Vander Velde N, Gupta P, Talbot J. A Systematic Review of the Clinical Efficacy of Treatments in Relapsed or Refractory Diffuse Large B Cell Lymphoma. Advances in Therapy. 2020;37(12):4877-93. 8. Ernst M, Oeser A, Besiroglu B, Caro-Valenzuela J, Abd El Aziz M, Monsef I, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. 2021;(9). 9. Colosia A, Njue A, Trask PC, Olivares R, Khan S, Abbe A, et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: A systematic literature review. Clinical Lymphoma, Myeloma and Leukemia. 2014;14(5):343-55.e6.

Table 27: HCRU SLR citation searching

HCRU SLR citation searching (n=4)
1. Petrou P. Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. Expert Review of Pharmacoeconomics and Outcomes Research. 2019;19(5):529-36. 2. Ho JK, Borle K, Dragojlovic N, Dhillon M, Kitchin V, Kopac N, et al. Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review. PharmacoEconomics. 2021;39(9):995-1019. 3. Harkins RA, Patel SP, Flowers CR. Cost burden of diffuse large B-cell lymphoma. Expert Review of Pharmacoeconomics and Outcomes Research. 2019;19(6):645-61. 4. Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. Health Technology Assessment. 2004;8(37).

Table 28: Economic SLR citation searching

Economic SLR citation searching (n=7)

1. Heine R, Thielen FW, Koopmanschap M, Kersten MJ, Einsele H, Jaeger U, et al. Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future. HemaSphere. 2021;5(2):e524.
2. Gye A, Goodall S, De Abreu Lourenco R. A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared With Older Patients. Value in Health. 2022;25(1):47-58.
3. Petrou P. Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. Expert Review of Pharmacoeconomics and Outcomes Research. 2019;19(5):529-36.
4. Harkins RA, Patel SP, Flowers CR. Cost burden of diffuse large B-cell lymphoma. Expert Review of Pharmacoeconomics and Outcomes Research. 2019;19(6):645-61.
5. Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. Health Technology Assessment. 2004;8(37).
6. Chen Z, Cheng Y, DeRemer D, Diaby V. Cost-effectiveness and drug wastage of immunotherapeutic agents for hematologic malignancies: a systematic review. Expert Review of Pharmacoeconomics and Outcomes Research. 2021;21(5):923-41.
7. Ho JK, Borle K, Dragojlovic N, Dhillon M, Kitchin V, Kopac N, et al. Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review. PharmacoEconomics. 2021;39(9):995-1019.

Table 29: HSUV SLR citation searching

HSUV SLR citation searching (n=3)
1. Ernst M, Oeser A, Besiroglu B, Caro-Valenzuela J, Abd El Aziz M, Monsef I, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database of Systematic Reviews. 2021;2021(9):CD013365. 2. Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. Health Technology Assessment. 2004;8(37). 3. Terasawa T, Dahabreh I, Nihashi T. Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography in Response Assessment Before High-Dose Chemotherapy for Lymphoma: A Systematic Review and Meta-Analysis. The Oncologist. 2010;15(7):750–759.

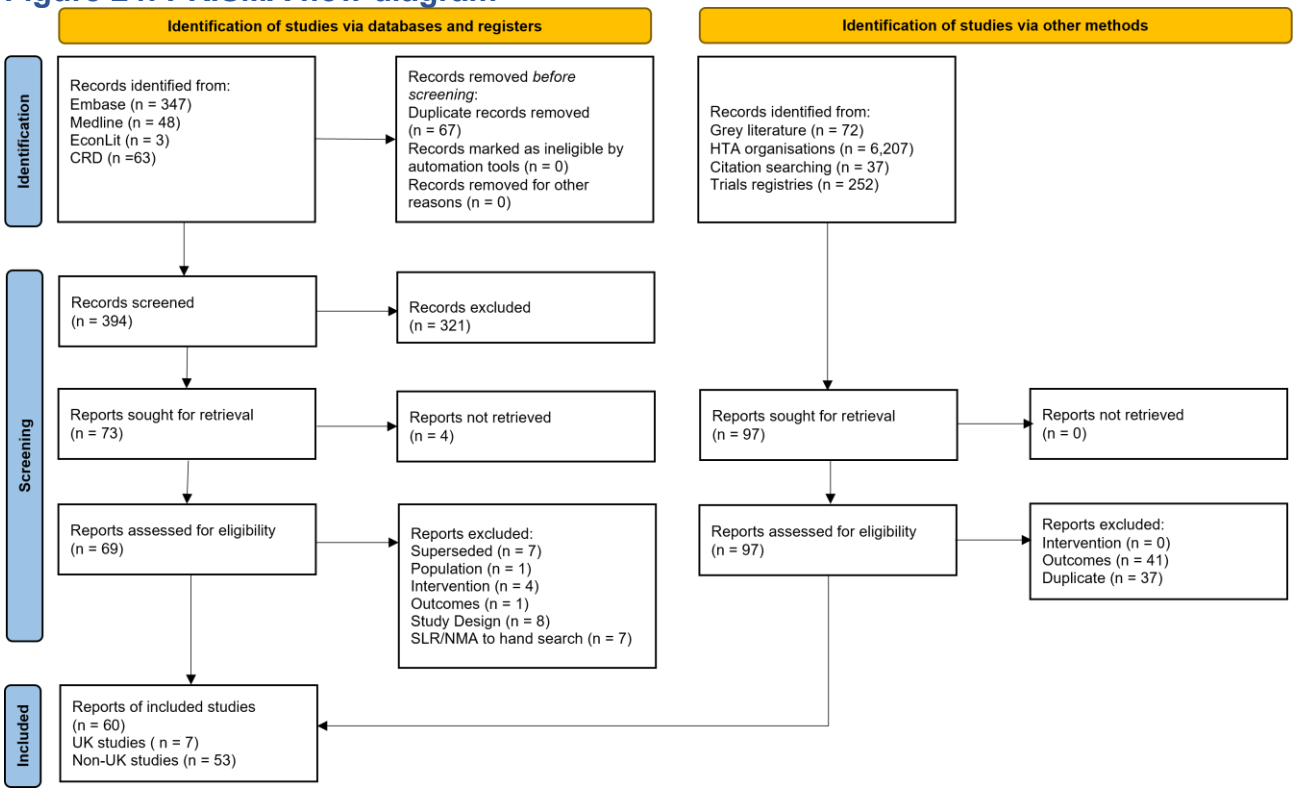
C3. Re. the SLR for published cost-effectiveness studies (CS Doc Section B.3.1 and Appendix G), CS Appendix G, section G.2 and the flow diagram report that 60 publications were included in the cost-effectiveness SLR (7 UK and 53 non-UK). However, only 7 and 44 references are provided in the list of included studies (CS Appendix G, section G.2.2). A list of 29 excluded studies with reasons for exclusion is provided (CS Appendix G, table 26), but this is slightly different to the 28 excluded records reported in the flow diagram for studies via databases and registers (CS Appendix G, figure 19). Please check and clarify these numbers and provide revised lists of included and excluded studies with missing references highlighted.

In total, 60 studies (7 UK and 53 non-UK) were included (detailed in Appendix B

Section 1: C3 supplementary material), with the nine missing references in the non-UK included studies list added and highlighted in green). The updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is presented Figure 24, with amended numbers for excluded reports. There were 32 reports not retrieved and excluded via databases and registers. The reasons for exclusion can be found in the excluded studies list table in Appendix B

Section 1: C3 supplementary material.

Figure 24: PRISMA flow diagram



Abbreviations: CRD, Centre for Reviews and Dissemination; HTA, health technology assessment; NMA, network meta-analysis; SLR, systematic literature review.

C4. Re. Cost and resource use SR (CS Doc B, section B.3.5 introductory sentence and Appendix I), a list of studies excluded at full text review, with reasons for exclusion, is provided in CS Appendix I, table 43, but there appears to be a discrepancy in numbers. 70 references are listed in 70 rows in table 43, although 109 is the number given in the title “List of studies excluded on full text review

(n=109)", but neither of those numbers match the numbers provided in the flow diagram (CS Appendix, figure 21), which reports 9 not retrieved + 77 excluded from the studies identified via databases and registers (total = 86) and a further 47 excluded from the studies identified via other sources. The lists of included studies provided in CS Appendix I, section I.2.2 also add up to a different number (7 UK studies and 50 non-UK studies = 50) to that given in the earlier text and flow diagram (64). Please check and clarify these numbers and provide revised lists of included and excluded studies with missing references highlighted.

There were a total of 86 studies excluded at full text review via databases and registers (9 papers not retrieved and 77 papers excluded at full text screening). The list of excluded studies has been updated and provided in Appendix B Section 2: C4 supplementary material. There were 57 non-UK studies included in total, in addition to the 7 UK studies. The reference list for the included non-UK specific studies has been updated, with the missing references highlighted in green, and is provided in Appendix B Section 2: C4 supplementary material.

C5. Re. the 'Identification of studies via other methods' section of the flow diagram for each SLR, please provide lists of excluded studies with reasons for the reports excluded.

The tables for each SLR detailing the excluded studies from hand searching, with exclusion reasons for each study are provided in Appendix B Section 3: C5 supplementary material.

References

1. Coiffier B. Diffuse large B-cell lymphoma: Which treatment for patients who failed first line treatment? Ann Oncol. 2008;19(iv81).
2. Bock AM, Mwangi R, Maurer MJ, Bennani N, Inwards DJ, Cerhan JR, et al. Time to Refractory Status Defines Subsets of Primary Refractory Diffuse Large B-Cell Lymphoma with Distinct Outcomes. Blood. 2021;138(23):2524.
3. Hamadani M, Liao L, Wilson L, Howarth A, Flores C, Chen L. Real-World Outcomes in Relapsed/Refractory DLBCL Patients Who Received Polatuzumab Vedotin PLUS Bendamustine and Rituximab or Tafasitamab Plus Lenalidomide By Line of Therapy (Poster abstract). Blood. 2022;140(Supplement 1):8058-60.
4. Hamadani M, Liao L, Wilson L, Howarth A, Flores C, Chen L. Real-World Outcomes in Relapsed/Refractory DLBCL Patients Who Received Polatuzumab Vedotin PLUS Bendamustine and Rituximab or Tafasitamab Plus Lenalidomide By Line of Therapy (Poster presented at ASH 2022). 2022.
5. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. NICE Decision Support Unit Technical Support Documents. London2014.
6. Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, et al. Adjusting for treatment switching in randomised controlled trials - A simulation study and a simplified two-stage method. Stat Methods Med Res. 2017;26(2):724-51.
7. Cranmer H, Trueman D, Evers E, Woodcock F, Podkonjak T. Brentuximab Vedotin Plus CHP in Frontline sALCL: Adjusted Estimates of Efficacy and Cost-Effectiveness Removing the Effects of Re-Treatment with Brentuximab Vedotin. PharmacoEconomics - Open. 2022;6(6):881-92.
8. DATA ON FILE:, Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, et al. LONG-TERM RESPONSES WITH LONCASTUXIMAB TESIRINE: UPDATED RESULTS FROM LOTIS-2, THE PIVOTAL PHASE 2 STUDY IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (EHA 2023). 2023.
9. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. PharmacoEconomics. 2022.
10. Stata. Stata multilevel mixed-effects reference manual (release 17). Available at: https://www.stata.com/manuals/me.pdf (last accessed 24th April 2023).

Appendices

Appendix A

A3 supplementary material

Additional probabilistic cost-effectiveness results from the new base case of the economic model are displayed in Figure 25 and Figure 26. Compared to Pola+BR, loncastuximab tesirine was dominant in 45% of simulations, more effective in 52% of simulations and cost saving in 93% of simulations.

Figure 25: New base case probabilistic cost-effectiveness results, loncastuximab tesirine vs Pola+BR: simulations (with PAS price for loncastuximab tesirine)

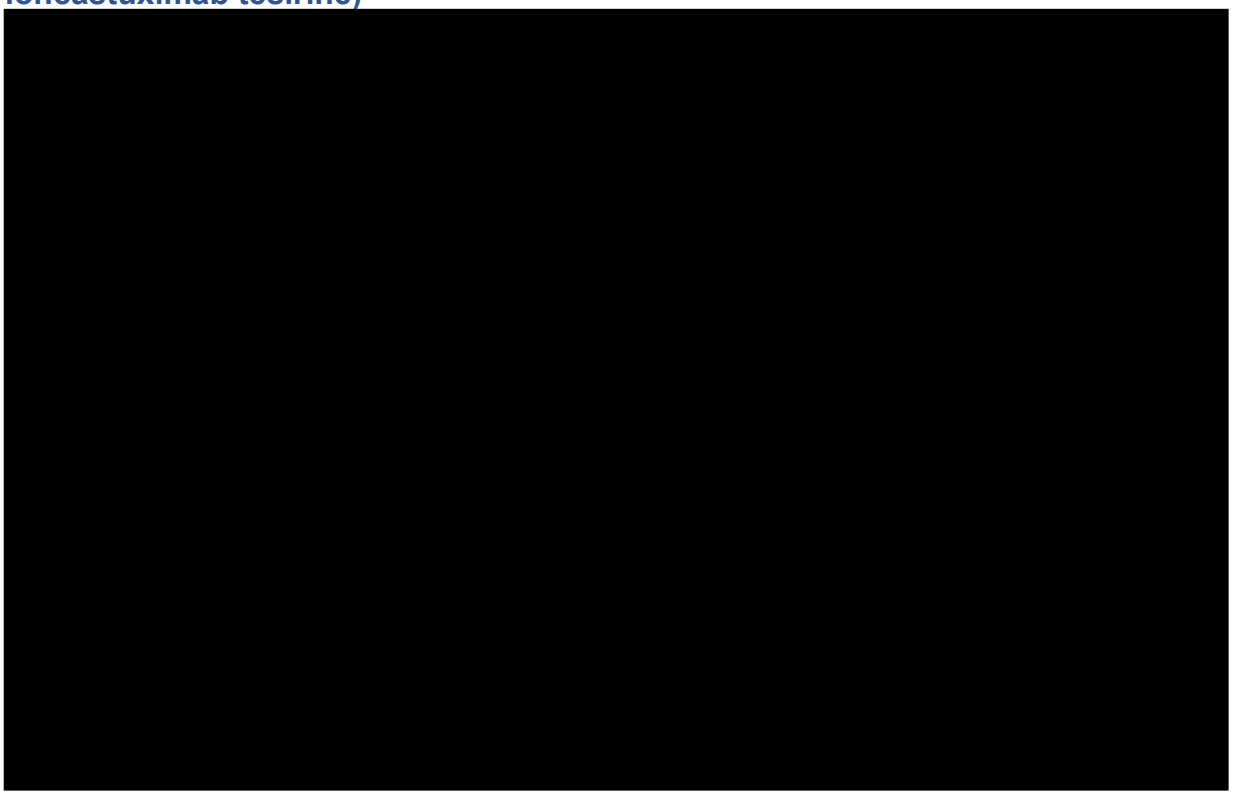
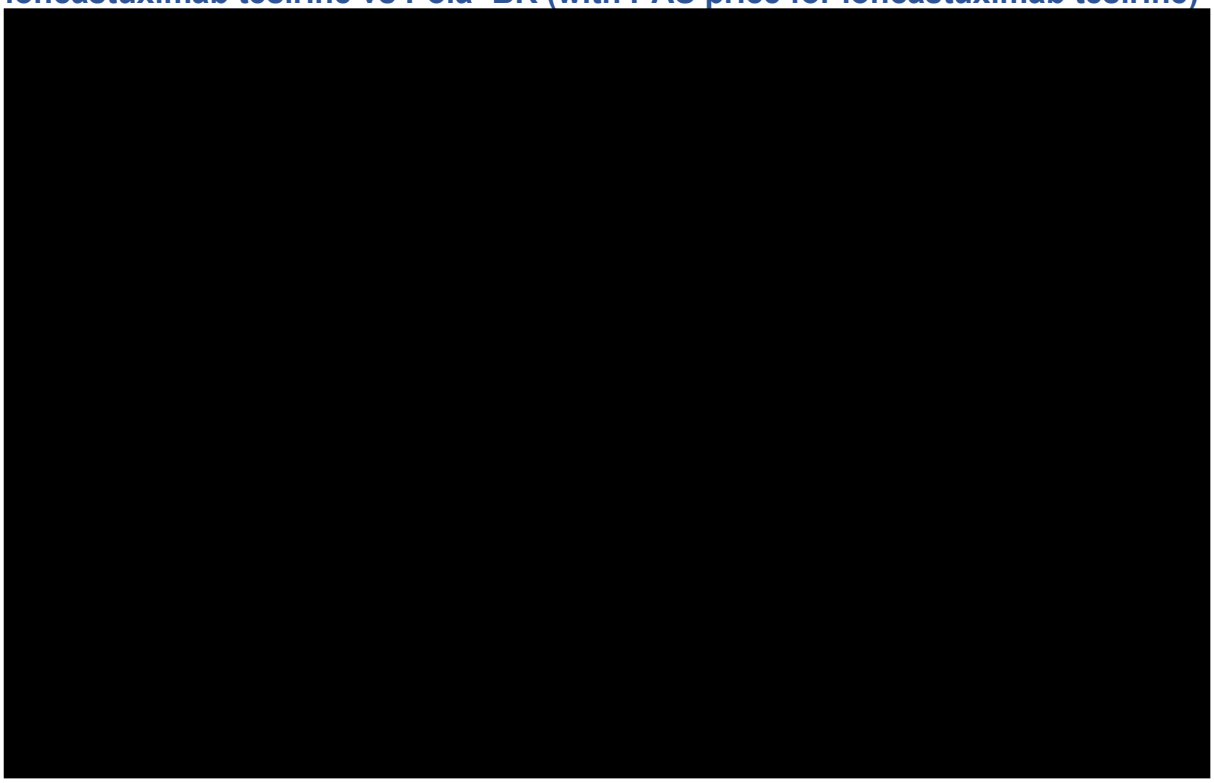


Figure 26: New base case cost-effectiveness acceptability curve, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)



The results of the revised univariate sensitivity analysis are presented in the form of a tornado diagram in Figure 27. The most influential parameters for the comparison to Pola+BR are parameters related to survival models for PFS. In the comparison to Pola+BR, loncastuximab tesirine is either cost-effective in the south-west quadrant or dominant in all scenarios.

Figure 27: New base case deterministic sensitivity analyses, loncastuximab tesirine vs Pola+BR: tornado diagram (with PAS price for loncastuximab tesirine)

*Denotes a south-west quadrant ICER, i.e. loncastuximab tesirine is less costly and less effective.
Abbreviations: 3L+, third-line plus; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPI, International Prognostic Index; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; TTD, time to discontinuation; vs, versus

The results of the revised scenario analyses are presented in Table 30. In all scenarios loncastuximab tesirine either becomes dominant or remains cost-effective in the south-west quadrant, and there are only minor changes in costs or QALYs. The scenario that has the biggest impact on incremental QALYs is when COTA data are used to inform outcomes for Pola+BR. In this scenario, outcomes for Pola+BR are extrapolated from the COTA data, using a log-logistic curve for PFS and a gamma curve for OS. Outcomes for loncastuximab tesirine are extrapolated using weights from the MAIC comparing to the COTA data, with a generalised gamma curve used to extrapolate OS, PFS and TTD. In this scenario, the efficacy of Pola+BR is significantly reduced, with a median OS of 7.36 months and a total QALY gain of 0.83. In this scenario, a severity multiplier of 1.2 could be applied to QALY gains.

The scenario giving the greatest reduction in QALYs for loncastuximab tesirine removes the impact of CAR-T on OS for loncastuximab tesirine. However, it was not possible to adjust at the Pola+BR curve in the same way, and this scenario is expected to be conservative.

Table 30: Revised scenario analyses, Pola+BR vs loncastuximab tesirine (with PAS price for loncastuximab tesirine)

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base-case	[redacted]	[redacted]	Dominant
1.5% discount rates	[redacted]	[redacted]	Dominant
No discounting	[redacted]	[redacted]	Dominant
COTA data used to inform outcomes	[redacted]	[redacted]	Dominant
Gompertz distribution for extrapolating OS, loncastuximab tesirine only	[redacted]	[redacted]	Dominant
Gompertz distribution for extrapolating OS, loncastuximab tesirine and Pola+BR	[redacted]	[redacted]	Dominant
Cure at 2 years	[redacted]	[redacted]	Dominant
Cure at 5 years	[redacted]	[redacted]	Dominant
Cure at 10 years	[redacted]	[redacted]	Dominant
ZUMA-1 progression decrement	[redacted]	[redacted]	Dominant
JULIET progression decrement	[redacted]	[redacted]	Dominant
AE disutility from the literature	[redacted]	[redacted]	Dominant
Excluding CAR-T	[redacted]	[redacted]	SW: £361,716
CAR-T at GO29365 rate	[redacted]	[redacted]	Dominant
100% RDI	[redacted]	[redacted]	Dominant
10-year time horizon	[redacted]	[redacted]	Dominant
20-year time horizon	[redacted]	[redacted]	Dominant

Abbreviations: CAR-T, chimeric antigen receptor T-cell; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine plus rituximab; QALYs, quality adjusted life years; RDI, relative dose intensity; SW, south-west

Appendix B

Section 1: C3 supplementary material

There were 60 studies (7 UK and 53 non-UK) included in the SLR of cost-effectiveness studies. The 60 included studies are listed in Table 31, and the nine missing references in the non-UK included studies list have been added and highlighted in green.

Table 31: List of included studies

Non-UK-specific studies
• Ball G, Kuruvilla J, Boodoo C, Jain MD. PCN108 Cost-Effectiveness of Axicabtagene Ciloleucel (axi-cel) and Tisagenlecleucel (tisa-cel) in Adult Patients with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL) in Canada. Value in Health. 2021;24(Supplement 1):S39. • Badaracco J, Gitlin M, Keating SJ. A Model to Estimate Cytokine Release Syndrome and Neurological Event Management Costs Associated With CAR T-Cell Therapy. Transplantation and cellular therapy. 2022(101774629). • Hillis C, Vicente C, Ball G. The Cost Effectiveness of Axicabtagene Ciloleucel Versus Best Supportive Care in the Treatment of Adult Patients with Relapsed or Refractory Large B-Cell Lymphoma (LBCL) After Two or More Lines of Systemic Therapy in Canada. PharmacoEconomics. 2022;40(9):917-28. • Li N, Zheng B, Cai H, Yang T, Hong Y, Liu M, et al. Cost-effectiveness analysis of axicabtagene ciloleucel vs. salvage chemotherapy for relapsed or refractory adult diffuse large B-cell lymphoma in China. Supportive Care in Cancer. 2022;30(7):6113-21. • Badaracco J, Ung B, Gitlin M, Keating SJ. EE181 An Economic Model to Estimate Costs of Cytokine Release Syndrome (CRS) and Neurological Events (NE) Among Patients Treated with Lisocabtagene Maraleucel (LISO-CEL) or Axicabtagene Ciloleucel (AXI-CEL) for Second-LINE (2L) Treatment of Large B-Cell L. Value in Health. 2022;25(7 Supplement):S368-S9. • Bellone M, Pradelli L, Caputo A, Ghislieri D, Launonen A, Ho R. POSB109 Cost-Effectiveness and Cost-Utility Analyses of Polatuzumab Vedotin with Bendamustine and Rituximab vs. Bendamustine and Rituximab for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma. Value in Health. 2022;25(1 Supplement):S82. • Betts KA, Thuresson PO, Du EX, Dieye I, Li J, Schulz M, et al. PCN238 Is polatuzumab vedotin plus bendamustine-rituximab cost-effective for patients in the United States with transplant-ineligible relapsed/refractory diffuse large B-cell lymphoma? Value in Health. 2019;22(Supplement 3):S482. • Calamia M, McBride A, Abraham I. Economic evaluation of polatuzumab-bendamustine-rituximab vs. tafasitamab-lenalidomide in transplant-ineligible R/R DLBCL. Journal of Medical Economics. 2021;24(S1):14-24. • Choe J, Abdel-Azim H, Abou-el-Enein M, Padula W. EE136 Cost-Effectiveness Analysis of Tisagenlecleucel Using Long-Term Survival Outcomes in Treating Adult Patients with Relapsed or Refractory Large B-Cell Lymphoma from US Societal Perspective. Value in Health. 2022;25(7 Supplement):S361. • Cummings Joyner AK, Snider J, Wade S, Wang ST, Buessing MG, Johnson S, et al. EE359 US Cost-Effectiveness of Chimeric Antigen Receptor T-Cell (CAR T) Therapy for Patients with Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL), Considering Infusion Setting and Payor Claims Data. Value in Health. 2022;25(7 Supplement):S405.

Non-UK-specific studies
• Dalal A, Yang H, Qi C, Zhang S, Zhang J, Ma Q. Cost-effectiveness of tisagenlecleucel for the treatment of relapsed or refractory diffuse large B-cell lymphoma in the United States. Journal of Managed Care and Specialty Pharmacy. 2020;26(10-A SUPPL.):S32. • Hathway J, Purdum A, Lin VW, Cyr P, Westin J, Jensen I. Budget impact model of axicabtagene ciloleucel (Axi-cel) in a us population of patients with relapsed or refractory large B-Cell lymphoma (R/R-LBCL). Bone Marrow Transplantation. 2019;53:878-9. • Qi CZ, Bollu V, Yang H, Dalal A, Zhang S, Zhang J. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the United Staytes. Clinical Therapeutics. 2021;43(8):1300-19.e8. • Roth J, Sullivan SD, Lin VW, Purdum A, Navale L, Cheng P, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large b-cell lymphoma in the United States. Bone Marrow Transplantation. 2019;53:874-5. • Skalt D, Moertl B, von Bergwelt-Baildon M, Schmidt C, Schoel W, Bucklein V, et al. Budget Impact Analysis of CAR T-cell Therapy for Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma in Germany. HemaSphere. 2022;6(7):e736. • Karampampa K, Stene E, Axelsen F, Lyngaa R, Vadgama S, Jerkeman M, et al. PPM3 Cost-Effectiveness of Axicabtagene Ciloleucel (axi-cel) VS Standard of Care for Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma in Sweden, Norway, Finland, and Denmark. Value in Health. 2020;23(Supplement 2):S687. • Lakhanpal S, Latour A, Wang J, Wang X. PCN24 Budget IMPACT Analysis (BIA) of Introducing Tisagenlecleucel for the Treatment of Patients with Relapsed and Refractory Diffuse Large B-CELL Lymphoma (R/R DLBCL) in Singapore (SG). Value in Health Regional Issues. 2020;22(Supplement):S8-S9. • Liao L, Yang C, Camardo J, Graden D, Kuntz C, Yang X, et al. Budget impact model for loncastuximab tesirine-lpyl in the treatment of relapsed/refractory diffuse large B-cell lymphoma. Journal of Managed Care and Specialty Pharmacy. 2021;27(10-B SUPPL):S33-S4. • Betts KA, Thuresson PO, Felizzi F, Du EX, Dieye I, Li J, et al. US cost-effectiveness of polatuzumab vedotin, bendamustine and rituximab in diffuse large B-cell lymphoma. Journal of Comparative Effectiveness Research. 2020;9(14):1003-15. • Roth JA, Sullivan SD, Lin VW, Bansal A, Purdum AG, Navale L, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. Journal of Medical Economics. 2018;21(12):1238-45. • Bastos-Oreiro M, de Las Heras A, Presa M, Casado MA, Pardo C, Martin-Escudero V, et al. Cost-Effectiveness Analysis of Axicabtagene Ciloleucel vs. Tisagenlecleucel for the Management of Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Spain. Cancers. 2022;14(3). • Cher BP, Gan KY, Aziz MIA, Lin L, Hwang WYK, Poon LM, et al. Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective. Journal of Medical Economics. 2020;23(11):1321-9. • Cummings Joyner AK, Snider JT, Wade SW, Wang ST, Buessing MG, Johnson S, et al. Cost-Effectiveness of Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed or Refractory Large B Cell Lymphoma: No Impact of Site of Care. Advances in Therapy. 2022;39(8):3560-77. • Moradi-Lakeh M, Yaghoubi M, Seitz P, Javanbakht M, Brock E. Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland. Advances in Therapy. 2021;38(6):3427-43. • Marchetti M, Martelli E, Zinzani PL. Cost-effectiveness of axicabtagene ciloleucel for relapsed or refractory dffuse large b-cell lymphoma in Italy. Blood. 2018;132(Suppl. 1).

Non-UK-specific studies
• Parker C, Liu FF, Deger K, Franco-Villalobos C, Proskorovsky I, Keating SJ, et al. Cost-effectiveness of lisocabtagene maraleucel (LISO-CEL) versus axicabtagene ciloleucel (AXI-CEL) for treatment of relapsed or refractory (r/r) large B-cell lymphoma (LBCL). Blood. 2021;138(SUPPL 1):3003. • Yang H, Qi C, Zhang J, El Ouagari K. Cost-effectiveness of tisagenlecleucel for adults with relapsed or refractory diffuse large B-cell lymphoma: A canadian societal perspective. Value in Health. 2018;21(Supplement 3):S44. • Yang H, Han S, Chai X, Wu E, Abikoff C, Hao Y, et al. Budget impact associated with the introduction of tisagenlecleucel for the treatment of relapsed or refractory diffuse large B-cell lymphoma. Journal of Managed Care and Specialty Pharmacy. 2018;24(10 A):S29-S30. • Tully S, Feng Z, Grindrod K, McFarlane T, Chan K, Wong WW. PCN439 Developing a discrete-event simulation to study the influence of waiting times on the effectiveness and cost-effectiveness of chimeric antigen receptor (CAR) T-cell therapy in large B-cell lymphoma. Value in Health. 2019;22(Supplement 3):S521. • Pinheiro B, Cardoso M, Borges M, Launonen A, Ho R, Silva Miguel L. POSA56 A Cost-Effectiveness Analysis of Polatuzumab in Combination with Bendamustine and Rituximab in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Portugal. Value in Health. 2022;25(1 Supplement):S43-S4. • Neubauer A, Minartz C, Schwenke C, Kurukulasuriya N, Boehnke A. PCN66 discrete event simulation model of MOR208 in combination with lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Value in Health. 2019;22(Supplement 2):S67-S8. • Liu R, Oluwole OO, Diakite I, Botteman MF, Snider JT, Locke FL. Cost effectiveness of axicabtagene ciloleucel versus tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the United States. Journal of Medical Economics. 2021;24(1):458-68. • Oluwole OO, Liu R, Diakite I, Feng C, Patel A, Nourhussein I, et al. Cost-effectiveness of axicabtagene ciloleucel versus lisocabtagene maraleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the US. Journal of Medical Economics. 2022;25(1):541-51. • Wang XJ, Wang YH, Li SCT, Gkitzia C, Lim ST, Koh LP, et al. Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective. Journal of Medical Economics. 2021;24(1):637-53. • Patel KK, Isufi I, Kothari S, Foss F, Huntington S. Cost-effectiveness of polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. Leukemia and Lymphoma. 2020;61(14):3387-94. • Whittington MD, McQueen RB, Ollendorf DA, Kumar VM, Chapman RH, Tice JA, et al. Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma. JAMA network open. 2019;2(2):e190035. • Wakase S, Teshima T, Zhang J, Ma Q, Fujita T, Yang H, et al. Cost Effectiveness Analysis of Tisagenlecleucel for the Treatment of Adult Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma in Japan. Transplantation and Cellular Therapy. 2021;27(6):506.e1-.e10. • Lin JK, Muffly LS, Spinner MA, Barnes JI, Owens DK, Goldhaber-Fiebert JD. Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma. Journal of Clinical Oncology. 2019;37(24):2105-19. • Perales MA, Kuruvilla J, Snider JT, Vadgama S, Blissett R, El-Moustaid F, et al. The Cost-Effectiveness of Axicabtagene Ciloleucel as Second-Line Therapy in Patients with Large B-Cell Lymphoma in the United States: An Economic Evaluation of the ZUMA-7 Trial. Transplant Cell Ther. 2022;28(11):750 e1- e6.

Non-UK-specific studies
• Kambhampati S, Saumoy M, Schneider Y, Serrao S, Solaimani P, Budde LE, et al. Cost-effectiveness of second-line axicabtagene ciloleucel in relapsed refractory diffuse large B-cell lymphoma. Blood. 2022;140(19):2024-36. • Institute for Clinical and Economic Review (ICER). Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. Available at https://icer.org/wp-content/uploads/2020/10/ICER_CAR_T_Final_Evidence_Report_032318.pdf (last accessed 25th January 2023). 2018. • Medical Services Advisory Committee (MSAC). Public Summary Document: Application No. 1519.1 – Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/content/A2B10F9A03293BC8CA2583CF001C7A4D/$File/1519.1%20Final%20updated%20PSD%20Nov%2019_redacted.pdf (last accessed 2nd February 2023). 2019. • Medical Services Advisory Committee (MSAC). Public Summary Document: Application No. 1587 – Axicabtagene ciloleucel (CAR-T therapy) for the treatment of refractory or relapsed CD19-positive lymphoma. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B5B780278B3A4B48CA2583C9001B80BB/$File/1587%20Final%20PSD%20Nov%2019_redacted.pdf (last accessed 18th April 2023). 2020. • National Centre for Pharmacoeconomics (NCPE). Cost-effectiveness of tisagenlecleucel (Kymriah®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Available from: https://www.ncpe.ie/tisagenlecleucel-kymriah-for-dlbcl/ (last accessed 18th April 2023). 2019. • National Centre for Pharmacoeconomics (NCPE). Cost effectiveness of axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. Available from: https://www.ncpe.ie/axicabtagene-ciloleucel-yescarta/ (last accessed 18th April 2023). 2020. • Canada's Drug and Health Technology Agency (CADTH). Axicabtagene Ciloleucel for Diffuse Large B-Cell Lymphoma. Available from: https://www.cadth.ca/axicabtagene-ciloleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma (last accessed 18th April 2023). 2019. • Canada's Drug and Health Technology Agency (CADTH). Polatuzumab vedotin for treatment of adult R/R DLBCL that are ineligible for autologous stem cell transplantation. Available from: https://www.cadth.ca/polatuzumab-vedotin-polivy-dlbcl-details (last accessed 18th April 2023). 2021. • Canada's Drug and Health Technology Agency (CADTH). Lisocabtagene Maraleucel (Breyanzi). Available from: https://www.cadth.ca/lisocabtagene-maraleucel (last accessed 18th April 2023). 2022. • Canada's Drug and Health Technology Agency (CADTH). Tisagenlecleucel (Kymriah) for Pediatric Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma. Available from: https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma (last accessed 18th April 2023). 2019. • Canada's Drug and Health Technology Agency (CADTH). Tafasitamab (Minjuvi). Available from: https://www.cadth.ca/tafasitamab (last accessed 18th April 2023). 2022. • Pharmaceutical Benefits Advisory Committee (PBAC). Polatuzumab vedotin. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-11/files/polatuzumab-vedotin-psd-november-2019.docx.pdf (last accessed 18th April 2023). 2019.

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• Norwegian Medicines Agency. Tisagenlecleucel (Kymriah) for the treatment of second or later relapsed/refractory diffuse large B cell lymphoma (DLBCL). Available from: https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/K/Kymriah_DLBCL_2019.pdf (last accessed 3rd February 2023). 2019. • Norwegian Medicines Agency. Axicabtagene ciloleucel (Yescarta) for the treatment of second or later relapsed/refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL). Available from: https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/K/Yescarta_DLBCL_2019.pdf (last accessed 3rd February 2023). 2018.

There 32 studies excluded via databases and registers are listed in Table 32.

Table 32: List of studies excluded on full text review (n=32)

Authors	Year	Title	Exclusion reason
Anonymous	2019	Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Clinical Report	Study design
Anonymous	2021	Erratum: US cost-effectiveness of polatuzumab vedotin, bendamustine and rituximab in diffuse large B-cell lymphoma	Study design
Badaracco J.; Keating S.; Gitlin M.	2021	Updates to an economic model to estimate costs of cytokine release syndrome (CRS) and neurological events (NE) with chimeric antigen receptor (CAR) T cell therapies in patients (pts) with relapsed or refractory (r/r) Large B-Cell Lymphoma (LBCL)	Superseded
Bastos-Oreiro M.; de las Heras A.; Presa M.; Casado M.A.; Pardo C.; Martin-Escudero V.; Sureda A.	2022	POSA57 Axicabtagene Ciloleucel and Tisagenlecleucel for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Spain: A Cost-Effectiveness Analysis	Superseded
Bastos-Oreiro M.; Presa M.; Heras A.D.L.; Casado M.A.; Pardo C.; Martin-Escudero V.; Sureda A.	2021	Cost-effectiveness analysis of axicabtagene ciloleucel vs tisagenlecleucel for the management of diffuse large b-cell lymphoma in Spain	Superseded
Betts K.A.; Felizzi F.;	2020	Cost-effectiveness of polatuzumab vedotin plus bendamustine-rituximab for transplant-ineligible	Superseded

Authors	Year	Title	Exclusion reason
Dieye I.; Li J.; Schulz M.; Hong S.J.; Masaquel A.S.		relapsed/refractory diffuse large B-cell lymphoma in the United States	
BlueCross BlueShield Association	2016	Off-label uses of monoclonal antibodies for treatment of B-cell lymphoid or myeloid malignancies (Structured abstract)	Unobtainable
BlueCross BlueShield Association	2016	Rituximab for treatment of intermediate and aggressive B-cell non-Hodgkin's lymphomas (Structured abstract)	Unobtainable
Calamia M.; McBride A.; Abraham I.	2021	Polatuzumab vedotinbendamustine-rituximab (PBR) versus tafasitamab-lenalidomide (TafaL) in ASCT-transplant ineligible relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL): Economic evaluation including novel metrics	Superseded
Catalan Agency for Health Technology Assessment and Research	2016	Diffuse large B-cell lymphoma OncoGuide (Structured abstract)	Unobtainable
Centre for Reviews and Dissemination	2015	Rituximab (MabThera) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation (Provisional abstract).	Intervention
Centre for Reviews and Dissemination	2014	Real world costs and cost-effectiveness of Rituximab for diffuse large B-Cell lymphoma patients: a population-based analysis (Provisional abstract)	Intervention
Centre for Reviews and Dissemination	2012	Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma (Provisional abstract)	Intervention
Chen Q.; Staton A.D.; Ayer T.; Goldstein D.A.; Koff J.L.; Flowers C.R.	2018	Exploring the potential cost-effectiveness of precision medicine treatment strategies for diffuse large B-cell lymphoma	Intervention
Chen Z.; Cheng Y.; DeRemer D.; Diaby V.	2021	Cost-effectiveness and drug wastage of immunotherapeutic agents for hematologic malignancies: a systematic review	SLR/NMA to hand search
Department of Science and Technology - Brazilian Health Technology Assessment	2016	Rapid HTA on the use of rituximabe in treating B-cell non-hodgkin's lymphoma, low-grade CD 20 (Structured abstract)	Unobtainable

Authors	Year	Title	Exclusion reason
General Coordination (DECIT-CGATS)			
Gye A.; Goodall S.; De Abreu Lourenco R.	2022	A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared With Older Patients	SLR/NMA to hand search
Harkins R.A.; Patel S.P.; Flowers C.R.	2019	Cost burden of diffuse large B-cell lymphoma	SLR/NMA to hand search
Heine R.; Thielen F.W.; Koopmanschap M.; Kersten M.J.; Einsele H.; Jaeger U.; Sonneveld P.; Sierra J.; Smand C.; Uyl-De Groot C.A.	2021	Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future	SLR/NMA to hand search
Ho J.K.; Borle K.; Dragojlovic N.; Dhillon M.; Kitchin V.; Kopac N.; Ross C.; Lynd L.D.	2021	Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review	SLR/NMA to hand search
Huguet M.; Raimond V.; Kaltenbach E.; Augusto V.; Perrier L.	2021	How much does the hospital stay for infusion of anti-CD19 CAR-T cells cost to the French National Health Insurance?	Study design
Knight, C; Hind, D; Brewer, N; Abbott, V	2016	Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation (Structured abstract)	SLR/NMA to hand search
Liu R.; Thornton Snider J.; Diakite I.; Tempelaar S.; Botteman M.	2020	Cost effectiveness of axicabtagene ciloleucel (Axi-cel) and tisagenlecleucel (Tisa-cel) for adult patients with relapsed or refractory large B-cell lymphoma (RR LBCL) in the US	Superseded
Ndegwa, S; Spry, C	2016	Rituximab for non-hodgkin's lymphoma: a review of the clinical and cost- effectiveness and guidelines (Structured abstract)	Study design
Petrou P.	2019	Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy	SLR/NMA to hand search

Authors	Year	Title	Exclusion reason
Porteous A.; Gregori D.; Hilton B.	2022	P49 Accuracy of Life Year Gains Predictions for CAR-T Therapy in the Long Term: An Analysis for Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma	Outcomes
Raymakers A.J.N.; Regier D.A.; Peacock S.J.	2019	Modelling uncertainty in survival and cost-effectiveness is vital in the era of gene therapies: the case of axicabtagene ciloleucel	Study design
Rivolo S.; Xiao Y.; Litkiewicz M.; Saint-Laurent Thibault C.; Patel L.; Zhang Y.; Dorman E.; Liu F.F.; Kuruvilla J.	2020	Comparison of safety management costs across chimeric antigen receptor (CAR) T cell therapies in relapsed or refractory large B-cell lymphoma	Study design
Wang H.-I.; Smith A.; Aas E.; Roman E.; Crouch S.; Burton C.; Patmore R.	2017	Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort	Population
Yang H.; Hao Y.; Chai X.; Qi C.Z.; Wu E.Q.	2020	Estimation of total costs in patients with relapsed or refractory diffuse large B-cell lymphoma receiving tisagenlecleucel from a US hospital's perspective	Study design
Yang H.; Hao Y.; Chai X.; Qi C.Z.; Wu E.Q.	2019	Estimation of Total Costs in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Receiving Tisagenlecleucel from a US Hospital's Perspective	Superseded
Yang H.; Ma Q.; Chai X.; Zhang J.; Wu E.Q.; Jousseaume E.; Kuzan D.; Hao Y.; Duteil E.; Jewitt K.	2019	PBI18 Estimation of the healthcare resource utilization (HCRU) costs in patients with relapsed or refractory Diffuse Large B-Cell Lymphoma Receiving Tisagenlecleucel: A micro-costing study in the UK and France	Study design

Section 2: C4 supplementary material

An updated list of included and excluded studies from the cost and resource use SLRs are provided in Table 33 and Table 34, respectively, with missing references highlighted in green.

The reference list for the included non-UK specific studies is provided in Table 33.

Table 33: List of included studies

Non-UK-specific studies
• Abramson JS, Siddiqi T, Garcia J, Dehner C, Kim Y, Nguyen A, et al. Cytokine release syndrome and neurological event costs in lisocabtagene maraleucel-treated patients in the TRANSCEND NHL 001 trial. Blood Advances. 2021;5(6):1695-705. • Acheampong T, Keating S. Treatment patterns, health care resource utilization, and total cost of care among US patients with diffuse large B-cell lymphoma not receiving hematopoietic stem cell transplant as second-line therapy. Journal of Managed Care and Specialty Pharmacy. 2022;28(3-A Supplement):S22-S3. • Bachier CR, Palomba ML, Abramson JS, Andreadis C, Sehgal AR, Godwin J, et al. Outpatient Treatment with Lisocabtagene Maraleucel (liso-cel) in Three Ongoing Clinical Studies in Relapsed/Refractory (R/R) B Cell Non-Hodgkin Lymphoma (NHL), Including Second-Line Transplant Ineligible Patients: Transcend NHL 001, Outreach, and PILOT. Blood. 2019;134(Supplement 1):2868. • Broder MS, Ma Q, Yan T, Zhang J, Chang E, Kuzan D, et al. Economic burden of neurologic toxicities associated with treatment of patients with relapsed or refractory diffuse large b-cell lymphoma in the United States. American Health and Drug Benefits. 2020;13(5):192-9. • Burke JM, Wang R, Hossain F, Li J, Masaquel A, Zhou SQ, et al. ABCL-102 A SEER-Medicare Analysis of the Cost of Disease Progression After Frontline R-CHOP in Diffuse Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma and Leukemia. 2022;22(Supplement 2):S360. • Canada's Drug and Health Technology Agency (CADTH). Axicabtagene Ciloleucel for Diffuse Large B-Cell Lymphoma. Available from: https://www.cadth.ca/axicabtagene-ciloleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma (last accessed 18th April 2023). 2019. • Canada's Drug and Health Technology Agency (CADTH). Polatuzumab vedotin for treatment of adult R/R DLBCL that are ineligible for autologous stem cell transplantation. Available from: https://www.cadth.ca/polatuzumab-vedotin-polivy-dlbcl-details (last accessed 18th April 2023). 2021. • Canada's Drug and Health Technology Agency (CADTH). Lisocabtagene Maraleucel (Breyanzi). Available from: https://www.cadth.ca/lisocabtagene-maraleucel (last accessed 18th April 2023). 2022. • Canada's Drug and Health Technology Agency (CADTH). Tisagenlecleucel (Kymriah) for Pediatric Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma. Available from: https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma (last accessed 18th April 2023). 2019. • Canada's Drug and Health Technology Agency (CADTH). Tafasitamab (Minjuvi). Available from: https://www.cadth.ca/tafasitamab (last accessed 18th April 2023). 2022. • Chacim S, Monjardino T, Cunha JL, Medeiros P, Redondo P, Bento MJ, et al. Costs Analysis, Effectiveness and Safety Associated with Chimeric Antigen Receptor (CAR)-T Cell Therapy: Results from a Portuguese Comprehensive Cancer Center. Value in Health. 2022;25(7 Supplement):S307-S8. • Chen L, Xie J, Wu A, Liao L, Du EX, Noman A, et al. Resource use and costs in patients with relapsed/refractory diffuse large C-cell lymphoma who initiated a third-line therapy in the post CAR-T era: A longitudinal outlook. Journal of Clinical Oncology. 2021;39(15 SUPPL). • Cher BP, Gan KY, Aziz MIA, Lin L, Hwang WYK, Poon LM, et al. Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective. Journal of Medical Economics. 2020;23(11):1321-9. • Danese MD, Griffiths RI, Gleeson ML, Dalvi T, Li J, Mikhael JR, et al. Second-line therapy in diffuse large B-cell lymphoma (DLBCL): treatment patterns and outcomes in older

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patients receiving outpatient chemotherapy. Leukemia and Lymphoma. 2017;58(5):1094-104. • Davies K, Kamalakar R, Huang Y, Wang A, Sail K, Doerr T, et al. EE458 Health Care Resource Utilization and Costs of CAR T-Cell Therapy in Patients with Diffuse Large B-Cell Lymphoma: A Retrospective Claims Database Analysis in the US. Value in Health. 2022;25(7 Supplement):S424-S5. • Duteil E, Lafon T, Blein C, Affinito S, Duco J, Oprea C, et al. DIRECT COST OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT) FOR RELAPSED/REFRACTORY (RR) DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS FROM THE FRENCH HOSPITAL PERSPECTIVE. Value in Health. 2018;21(Supplement 3):S35. • Feinberg B, Klink A, Balanean MA, Schuler T, McAllister L, Liassou D, et al. CO5 Completeness of Real-World Data (RWD) in Chimeric Antigen Receptor T-Cell Therapy (CAR-T) for Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) in United States (US) Community Oncology/Hematology Practices (CH/OS). Value in Health. 2022;25(7 Supplement):S304. • Flowers C, Chastek B, Becker L, Mahmoud D, Dulac E. The burden of healthcare cost among relapsed diffuse large B-cell lymphoma (DLBCL) patients: (A seer medicare dataset examination). Haematologica. 2014;99(SUPPL. 1):784-5. • Garcia J, Gitlin M, Snyder S, McMorrow D, Bonafede MM, Tkacz J. Treatment patterns and costs associated with diffuse large B-cell lymphoma-A retrospective analysis of claims. Value in Health. 2018;21(Supplement 1):S26-S7. • Godwin JE, Freytes CO, Maris M, Stevens DA, Hoda D, Mattar B, et al. Outcomes of Treatment with the Chimeric Antigen Receptor (CAR) T Cell Therapy Lisocabtagene Maraleucel (liso-cel) in the Nonuniversity Setting: Initial Results from the Outreach Study. Blood. 2020;136(Supplement 1):50-2. • Huntington S, Keshishian A, McGuire M, Xie L, Baser O. Costs of relapsed diffuse large B-cell lymphoma among Medicare patients. Leukemia and Lymphoma. 2018;59(12):2880-7. • Huntington SF, Keshishian A, Xie L, Baser O, McGuire M. Evaluating the economic burden and health care utilization following first-line therapy for diffuse large B-cell lymphoma patients in the US medicare population. Blood. 2016;128(22). • Hutchings M, Sureda A, Terol MJ, Bosch Albareda F, Corradini P, Larsen TS, et al. Glofitamab (Glofit) in Combination with Polatuzumab Vedotin (Pola): Phase Ib/II Preliminary Data Support Manageable Safety and Encouraging Efficacy in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL). Blood. 2021;138(Supplement 1):525. • Keating SJ, Gu T, Jun MP, McBride A. Health Care Resource Utilization and Total Costs of Care Among Patients with Diffuse Large B Cell Lymphoma Treated with Chimeric Antigen Receptor T Cell Therapy in the United States. Transplantation and Cellular Therapy. 2022;28(7):404.e1-.e6. • Kwon M, Iacoboni G, Reguera JL, Lopez Corral L, Hernani R, Guerreiro M, et al. Axicabtagene Ciloleucel Compared to Tisagenlecleucel for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma in the Real World Setting in Spain. Blood. 2021;138(Supplement 1):1742. • Liu R, Oluwole OO, Diakite I, Botteman MF, Snider JT, Locke FL. Cost effectiveness of axicabtagene ciloleucel versus tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the United States. Journal of Medical Economics. 2021;24(1):458-68. • Lynch RC, Chow VA, Maloney DG, Turtle CJ, Shadman M, Ujjani CS, et al. Low Achievement of End of Life Quality Measures in Large B-Cell Lymphoma Patients Who Progressed after CD19-Specific CAR-T Cell Therapy. Blood. 2019;134(Supplement 1):413.

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• Maziarz RT, Yang H, Liu Q, Wang T, Zhao J, Lim S, et al. Real-world healthcare resource utilization and costs associated with tisagenlecleucel and axicabtagene ciloleucel among patients with diffuse large B-cell lymphoma: an analysis of hospital data in the United States. Leukemia and Lymphoma. 2022;63(9):2052-62. • McGarvey N, Vaidya N, Gitlin M, Lee A, Keating S. A micro-costing estimation of health care resource utilization and costs for management of cytokine release syndrome and neurological events observed among patients treated with lisocabtagene maraleucel in the transform study. Journal of Managed Care and Specialty Pharmacy. 2022;28(3-A Supplement):S22. • McGarvey N, Vaidya N, Gitlin M, Lee A, Ung B, Carattini T, et al. EE286 Post-Infusion Monitoring Costs By Site of Care Among Patients with Relapsed or Refractory Large B-Cell Lymphoma (LBCL) Who Received Second-LINE Treatment with Lisocabtagene Maraleucel (LISO-CEL) in the Transform Study: A United States Subgroup Analy. Value in Health. 2022;25(7 Supplement):S389-S90. • Moertl B, Dreyling M, Schmidt C, Hoster E, Schoel W, Bergwelt-Baildon MV, et al. Inpatient treatment of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL): A health economic perspective. Clinical Lymphoma, Myeloma and Leukemia. 2022;22(7):474-82. • Mohammadi I, Purdum AG, Wong AC, Schroeder A, Kilgore KM, Shah GL. Cost and healthcare utilization in relapsed/refractory diffuse large B-cell lymphoma: A real-world analysis of medicare beneficiaries receiving chimeric antigen receptor T-cell vs. autologous and allogeneic hematopoietic cell transplants. Blood. 2020;136(SUPPL 1):4. • Mortl BA, Dreyling M, Hoster E, Schmidt C, Schoel W, Von Bergwelt M, et al. Economic Aspects of Stem Cell Transplantation by Patients with Relapsed Diffuse B-Cell Lymphoma (DLBCL) in A German Tertiary Hospital. Bone Marrow Transplantation. 2021;56((Mortl, Dreyling, Hoster, Schmidt, Schoel, Von Bergwelt, Berger) LMU Klinikum, Munich, Germany):124. • Mutebi A, Jun M, Flores C, Wang Z, Wang A, Elliot B, et al. EE308 Real-World Treatment Patterns and Costs in Relapsed and Refractory Diffuse Large B-Cell Lymphoma in the United States. Value in Health. 2022;25(7 Supplement):S394. • Nabhan C, Myerscough C, Kish J, Chung J, Chopra D. PCN140 TREATMENT PATTERNS AND COST ANALYSIS AMONG PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA. Value in Health. 2019;22(Supplement 2):S82. • Nasta SD, Hughes ME, Namoglu EC, Garfall A, DiFilippo H, Ballard HJ, et al. Outcomes of Tisagenlecleucel in Lymphoma Patients With Predominant Management in an Ambulatory Setting. Clinical Lymphoma, Myeloma and Leukemia. 2022;22(8):e730-e7. • Oluwole OO, Liu R, Diakite I, Feng C, Patel A, Nourhussein I, et al. Cost-effectiveness of axicabtagene ciloleucel versus lisocabtagene maraleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the US. Journal of Medical Economics. 2022;25(1):541-51. • Painschab MS, Kohler RE, Kasonkanji E, Zuze T, Kaimila B, Nyasosela R, et al. Microcosting Analysis of Diffuse Large B-Cell Lymphoma Treatment in Malawi. Journal of global oncology. 2019;5(101674751):1-10. • Palomba ML, Garcia J, Wang L, Dehner C, Chung KC, Maloney DG. Transcend: Lisocabtagene maraleucel (liso-cel; jcar017) healthcare resource utilization in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Blood. 2018;132(Suppl. 1). • Palomba ML, Jun MP, Lymp J, Nguyen A, McGarvey N, Gitlin M, et al. Postinfusion monitoring costs by site of care for patients with relapsed/refractory large B-cell lymphoma receiving third- or later-line treatment with lisocabtagene maraleucel in the TRANSCEND NHL 001 and OUTREACH trials. Leukemia and Lymphoma. 2021;62(9):2169-76. • Purdum A, Tieu R, Reddy SR, Broder MS. Direct Costs Associated with Relapsed Diffuse Large B-Cell Lymphoma Therapies. Oncologist. 2019;24(9):1229-36.

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• Purdum AG, Niecko T, Yang Y. Real world survival rates and healthcare utilization among SEER-Medicare patients treated with hematopoietic stem cell transplant (HSCT) for relapsed/refractory diffuse large b-cell lymphoma (RR-DLBCL). Journal of Clinical Oncology. 2018;36(15 Supplement 1). • Qi CZ, Bollu V, Yang H, Dalal A, Zhang S, Zhang J. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the United States. Clinical Therapeutics. 2021;43(8):1300-19.e8. • Rai MP, Bedi PS, Kasi A, Mehta K. In-hospital outcomes of CAR T-cell therapy in United States in 2018: A nationwide analysis. Journal of Clinical Oncology. 2021;39(15 SUPPL). • Riedell PA, Hwang WT, Nastoupil LJ, Pennisi M, McGuirk JP, Maziarz RT, et al. Patterns of Use, Outcomes, and Resource Utilization among Recipients of Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B Cell Lymphomas. Transplantation and Cellular Therapy. 2022;28(10):669-76. • Rivolo S, Xiao Y, Litkiewicz M, Saint-Laurent Thibault C, Patel L, Zhang Y, et al. Comparison of safety management costs across chimeric antigen receptor (CAR) T cell therapies in relapsed or refractory large B-cell lymphoma. HemaSphere. 2020;4(Supplement 1):805. • Rodriguez-Arocho C, Blue B, Mason N, Grajales-Cruz AF, Garcia F, Naqvi M, et al. Higher cost and no survival benefit with addition of rituximab to beam conditioning for autologous transplantation in patients with relapsed/refractory DLBCL. Bone Marrow Transplantation. 2020;55((Rodriguez-Arocho, Blue, Mason, Grajales-Cruz, Garcia, Naqvi, Bailey, Toska, Nieder, Pidala, Kharfan-Dabaja, Ayala, Bejanyan, Locke, Mishra, Elmariah, Khimani, Nishihori, Lazaryan) Moffitt Cancer Center, Tampa, FL, United States):414-5. • Shao YF, Modi D, Kin A, Alavi A, Ayash L, Ratanatharathorn V, et al. Feasibility of outpatient car t cell therapy: Experience of a single institution. Blood. 2021;138(SUPPL 1):4828. • Tkacz J, Garcia J, Gitlin M, McMorrow D, Snyder S, Bonafede M, et al. The economic burden to payers of patients with diffuse large B-cell lymphoma during the treatment period by line of therapy. Leukemia and Lymphoma. 2020;61(7):1601-9. • To TM, Gu J, Li J, Schulz M, Masaquel AS. PCN204 DO PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) RECEIVE TREATMENTS CONSISTENT WITH NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES AND WHAT ARE THE TOTAL COSTS OF CARE? Value in Health. 2019;22(Supplement 2):S94. • Tsutsue S, Makita S, Yi J, Crawford B. Cost drivers associated with diffuse large B-cell lymphoma (DLBCL) in Japan: A structural equation model (SEM) analysis. PLoS ONE. 2022;17(5 May):e0269169. • Tsutsue S, Makita S, Yi J, Crawford B. Economic burden in treated Japanese patients with relapsed/refractory large B-cell lymphoma. Future Oncology. 2021;17(33):4511-25. • Wang R, Roth J, Ng C, Hossain F, Li J, Masaquel A. Cost of disease progression after frontline (1l) R-chop in diffuse large B-cell lymphoma (DLBCL). Blood. 2021;138(SUPPL 1):3002. • Yang H, Hao Y, Chai X, Qi CZ, Wu EQ. Estimation of total costs in patients with relapsed or refractory diffuse large B-cell lymphoma receiving tisagenlecleucel from a US hospital's perspective. Journal of Medical Economics. 2020;23(9):1016-24. • Yang X, Laliberte F, Germain G, Raut M, Duh MS, Sen SS, et al. Real-World Characteristics, Treatment Patterns, Health Care Resource Use, and Costs of Patients with Diffuse Large B-Cell Lymphoma in the U.S. Oncologist. 2021;26(5):e817-e26. • Zhao J, Bollu V, Yang H, Dalal A, Tesfaye M, Ma Q, et al. Healthcare resource use (HRU) by infusion setting of chimeric antigen receptor T-cell (CAR-T) in patients with relapsed and refractory (r/r) diffuse large B-cell lymphoma (DLBCL): A retrospective cohort study using CMS 100% Medicare database. Journal of Clinical Oncology. 2021;39(15 SUPPL).

The 86 studies excluded at full text review via databases and registers are listed in Table 34.

Table 34: List of studies excluded on full text review (n=86)

Authors	Published Year	Title	Exclusion reason
Bastos-Oreiro, Mariana; de Las Heras, Ana; Presa, Maria; Casado, Miguel A; Pardo, Carlos; Martin-Escudero, Victoria; Sureda, Anna	2022	Cost-Effectiveness Analysis of Axicabtagene Ciloleucel vs. Tisagenlecleucel for the Management of Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Spain.	Outcomes
Betts K.A.; Thuresson P.-O.; Felizzi F.; Du E.X.; Dieye I.; Li J.; Schulz M.; Masaquel A.S.	2020	US cost-effectiveness of polatuzumab vedotin, bendamustine and rituximab in diffuse large B-cell lymphoma	Outcomes
Broder M.S.; Ma Q.; Yan T.; Chang E.; Eldjerou L.K.; Hao Y.; Kuzan D.; Zhang J.	2019	Economic Burden of Neurologic Toxicities Associated with Treating Relapsed Refractory Diffuse Large B-Cell Lymphoma in the United States	Superseded
Calamia M.; McBride A.; Abraham I.	2021	Economic evaluation of polatuzumab-bendamustine-rituximab vs. tafasitamab-lenalidomide in transplant-ineligible R/R DLBCL	Outcomes
Cummings Joyner A.K.; Snider J.T.; Wade S.W.; Wang S.-T.; Buessing M.G.; Johnson S.; Gergis U.	2022	Cost-Effectiveness of Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed or Refractory Large B Cell Lymphoma: No Impact of Site of Care	Outcomes
Hathway J.; Purdum A.; Lin V.W.; Cyr P.; Westin J.; Jensen I.	2019	Budget impact model of axicabtagene ciloleucel (Axi-cel) in a us population of patients with relapsed or refractory large B-Cell lymphoma (R/R-LBCL)	Outcomes
Huntington S.F.; Svoboda J.; Doshi J.A.	2015	Cost-effectiveness analysis of routine surveillance imaging of patients with diffuse large B-cell lymphoma in first remission	Outcomes
Lin J.K.; Muffly L.S.; Spinner M.A.; Barnes J.I.; Owens D.K.; Goldhaber-Fiebert J.D.	2019	Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma	Outcomes
Moradi-Lakeh M.; Yaghoubi M.; Seitz P.; Javanbakht M.; Brock E.	2021	Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland	Outcomes
Palomba M.L.; Jun M.P.; Garcia J.; Lymp J.; McGarvey N.; Gitlin M.; Pelletier C.; Nguyen A.	2020	Costs of postinfusion monitoring by site of care for patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) who	Outcomes

Authors	Published Year	Title	Exclusion reason
		received third-line or later treatment with lisocabtage nemaraleucel (LISO-CEL) in the transcend NHL 001 and outreach trials	
Patel K.K.; Isufi I.; Kothari S.; Foss F.; Huntington S.	2020	Cost-effectiveness of polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Perales M.-A.; Kuruvilla J.; Snider J.T.; Vadgama S.; Blissett R.; El-Moustaid F.; Smith N.J.; Patel A.R.; Johnston P.B.	2022	The Cost-Effectiveness of Axicabtagene Ciloleucel as Second-Line Therapy in Patients with Large B-Cell Lymphoma in the United States: An Economic Evaluation of the ZUMA-7 Trial	Outcomes
Purdum A.; Tieu R.; Reddy S.R.; Broder M.	2017	Total 1 -year cost of diffuse large B-cell lymphoma (DLBCL) beyond first line (1L) therapy: A retrospective cohort analysis	Outcomes
Riedell P.A.; Brower J.; Nastoupil L.; Perales M.-A.; Maziarz R.T.; McGuirk J.P.; Bachanova V.; Hwang W.-T.; Schuster S.J.; Bishop M.R.; Porter D.L.	2021	A multicenter analysis of outcomes, toxicities, and patterns of use with commercial axicabtagene ciloleucel and tisagenlecleucel for relapsed/refractory aggressive B-cell lymphomas	Outcomes
Skalt, Daniela; Moertl, Bernhard; von Bergwelt-Baildon, Michael; Schmidt, Christian; Schoel, Wolfgang; Bucklein, Veit; Weiglein, Tobias; Dreyling, Martin; Berger, Karin	2022	Budget Impact Analysis of CAR T-cell Therapy for Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma in Germany.	Outcomes
Whittington M.D.; McQueen R.B.; Ollendorf D.A.; Kumar V.M.; Chapman R.H.; Tice J.A.; Pearson S.D.; Campbell J.D.	2019	Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma	Outcomes
Hillis C.; Vicente C.; Ball G.	2022	The Cost Effectiveness of Axicabtagene Ciloleucel Versus Best Supportive Care in the Treatment of Adult Patients with Relapsed or Refractory Large B-Cell Lymphoma (LBCL) After Two or More Lines of Systemic Therapy in Canada	Outcomes
Valade S.; Darmon M.; Zafrani L.; Mariotte E.; Lemiale V.; Bredin S.; Dumas G.; Boissel N.; Rabian F.; Baruchel A.; Madelaine I.; Larghero J.; Brignier A.; Lengline E.; Harel S.; Arnulf B.; Di Blasi R.; Thieblemont C.; Azoulay E.	2022	The use of ICU resources in CAR-T cell recipients: a hospital-wide study	Population
Mian A.; Wei W.; Hill B.T.; Hamilton B.K.; Pohlman B.; Jagadeesh D.; Anwer F.; Kalaycio M.E.; Dean R.M.; Sobecks R.M.; Majhail N.S.	2021	Resource Utilization and Factors Prolonging Hospitalization for Patients with Refractory and Relapsed Large B-Cell Lymphoma	Population

Authors	Published Year	Title	Exclusion reason
		Receiving Tisagenlecleucel Versus Axicabtagene Ciloleucel	
Shah G.L.; Mohammadi I.; Purdum A.G.; Wong A.C.; Schroeder A.; Kilgore K.M.	2021	Cost and Healthcare Utilization in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Real-World Analysis of Medicare Beneficiaries Receiving Chimeric Antigen Receptor T-Cell Vs. Autologous and Allogeneic Hematopoietic Cell Transplants	Duplicate
Kambhampati S.; Saumoy M.; Schneider Y.; Serrao S.; Solaimani P.; Budde L.E.; Mei M.G.; Popplewell L.; Siddiqi T.; Zain J.; Forman S.J.; Kwak L.W.; Rosen S.T.; Danilov A.V.; Herrera A.F.; Thiruvengadam N.	2022	Cost Effectiveness of Second-Line Axicabtagene ciloleucel in Relapsed Refractory Diffuse Large B-cell Lymphoma	Outcomes
Ring A.; Grob B.; Aerts E.; Ritter K.; Volbracht J.; Schar B.; Greiling M.; Muller A.M.S.	2022	Resource utilization for chimeric antigen receptor T cell therapy versus autologous hematopoietic cell transplantation in patients with B cell lymphoma	Population
Li N.; Zheng B.; Cai H.; Yang T.; Hong Y.; Liu M.; Hu J.	2022	Cost-effectiveness analysis of axicabtagene ciloleucel vs. salvage chemotherapy for relapsed or refractory adult diffuse large B-cell lymphoma in China	Outcomes
Snider J.T.; McMorrow D.; Song X.; Diakun D.; Wade S.W.; Cheng P.	2022	Burden of Illness and Treatment Patterns in Second-line Large B-cell Lymphoma	Population
Law L.Y.; Dutia M.; Stevenson R.; Lau M.; Mok T.; Vu K.; Soe A.M.; Lopez A.R.; Thomas S.; Vempaty H.T.; Gavini A.; Nair B.	2021	Retrospective review of the safety and efficacy of high-dose methotrexate for prevention of cns relapse in diffuse large b-cell lymphoma at kaiser permanente-northern california (Jan 2015-june 2019)	Population
Liu J.; Zheng L.; Chuang L.-H.	2022	Cost-effectiveness of brentuximab vedotin for relapsed or refractory systemic anaplastic large-cell lymphoma in China	Population
Harvey M.J.; Zhong Y.; Morris E.; Beverage J.N.; Epstein R.S.; Chawla A.J.	2022	Assessing the transition from intravenous to subcutaneous delivery of rituximab: Benefits for payers, health care professionals, and patients with lymphoma	Population
Skalt D.; Berger K.; Von Bergwelt-Baildon M.; Schmidt C.; Schoel W.; Subklewe M.; Weiglein T.; Dreyling M.; Mortl B.	2021	Budget impact analysis of CAR-T-cell therapies for the inpatient treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in Germany	Superseded

Authors	Published Year	Title	Exclusion reason
Ho J.K.; Borle K.; Dragojlovic N.; Dhillon M.; Kitchin V.; Kopac N.; Ross C.; Lynd L.D.	2021	Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review	SLR/NMA to hand search
Kilgore K.M.; Mohammadi I.; Wong A.C.; Snider J.T.; Cheng P.; Schroeder A.; Patel A.R.	2021	Burden of illness and outcomes in second-line large B-cell lymphoma treatment: real-world analysis of Medicare beneficiaries	Population
Snyder S.; Albertson T.; Garcia J.; Gitlin M.; Jun M.P.	2021	Travel-Related Economic Burden of Chimeric Antigen Receptor T Cell Therapy Administration by Site of Care	Population
Wakase S.; Teshima T.; Zhang J.; Ma Q.; Fujita T.; Yang H.; Chai X.; Qi C.Z.; Liu Q.; Wu E.Q.; Igarashi A.	2021	Cost Effectiveness Analysis of Tisagenlecleucel for the Treatment of Adult Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma in Japan	Outcomes
Wang X.J.; Wang Y.-H.; Li S.C.T.; Gkitzia C.; Lim S.T.; Koh L.P.; Lim F.L.W.I.; Hwang W.Y.K.	2021	Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective	Outcomes
Moertl B.; Dreyling M.; Hoster E.; Schmidt C.; Schoel W.; Von Bergwelt-Baildon M.; Berger K.	2021	Inpatient care of patients with earlyrelapsed diffuse b-cell lymphoma (dlbcl): An economic perspective	Superseded
Yang H.; Qi C.Z.; Dalal A.; Bollu V.; Zhang J.; Zhang S.; Lim S.	2021	Estimating costs of adverse events (AEs) and healthcare resource use (HRU) in patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) receiving tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel): A summary of real-wor	Outcomes
Liao L.; Yang C.; Yang X.; Chen L.; Xie J.	2021	PCN71 Treatment-Related Costs of Pharmacologic Regimens for Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) Who Have Received Two or More Prior Lines of Therapies	Outcomes
Sampat D.; Goyal G.	2020	End of life healthcare and hospice utilization among patients with diffuse large B-cell lymphoma	Population
Purdum A.; Johnson J.; Bonagura A.; Nyamutswa L.; Elliott C.; Lal L.S.	2020	The first retrospective commercial claims-based analysis of CAR T treated patients with relapsed or refractory large B-cell lymphoma (R/R LBCL)	Population
Betts K.A.; Felizzi F.; Dieye I.; Li J.; Schulz M.; Hong S.J.; Masaquel A.S.	2020	Cost-effectiveness of polatuzumab vedotin plus bendamustine-rituximab for transplant-ineligible relapsed/refractory diffuse large B-cell lymphoma in the United States	Outcomes

Authors	Published Year	Title	Exclusion reason
Mian A.; Wei W.; Hill B.T.; Hamilton B.K.; Winter A.M.; Khouri J.; Pohlman B.; Jagadeesh D.; Mejia Garcia A.V.; Anwer F.; Gerds A.T.; Kalaycio M.; Dean R.M.; Sobecks R.; Majhail N.S.	2020	Resource utilization and factors prolonging hospitalization for patients with relapsed and refractory large B-cell lymphoma receiving tisagenlecleucel versus axicabtagene ciloleucel	Population
Lyman G.H.; Nguyen A.; Snyder S.; Gitlin M.; Chung K.C.	2020	Economic Evaluation of Chimeric Antigen Receptor T-Cell Therapy by Site of Care among Patients with Relapsed or Refractory Large B-Cell Lymphoma	Population
Gajra A.; Jeune-Smith Y.; Kish J.; Yeh T.-C.; Hime S.; Feinberg B.	2020	Perceptions of community hematologists/oncologists on barriers to chimeric antigen receptor T-cell therapy for the treatment of diffuse large B-cell lymphoma	Population
El-Galaly T.C.; Cheah C.Y.; Kristensen D.; Hutchison A.; Hay K.; Callreus T.; Villa D.	2020	Potentials, challenges and future of chimeric antigen receptor T-cell therapy in non-Hodgkin lymphomas	Outcomes
Kilgore K.M.; Mohammadi I.; Schroeder A.; Teigland C.; Purdum A.G.; Shah G.L.	2020	Medicare Patients Receiving Chimeric Antigen Receptor T-Cell Therapy for Non-Hodgkin Lymphoma: A Real-World Look at Patient Characteristics, Healthcare Utilization and Costs	Duplicate
Mian A.; Wei Wei; Hill B.T.; Hamilton B.K.; Pohlman B.; Jagadeesh D.; Anwer F.; Kalaycio M.E.; Dean R.M.; Sobecks R.M.; Majhail N.S.	2020	Resource Utilization and Factors Prolonging Hospitalization for Patients with Refractory and Relapsed B-Cell Lymphoma Receiving Axicabtagene Ciloleucel (Axi-cel)	Population
Harkins R.A.; Patel S.P.; Flowers C.R.	2019	Cost burden of diffuse large B-cell lymphoma	SLR/NMA to hand search
Snider J.T.; Brauer M.; Kee R.; Batt K.; Karaca-Mandic P.; Zhang J.; Goldman D.P.	2019	The potential impact of CAR T-cell treatment delays on society	Outcomes
Petrou P.	2019	Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy	SLR/NMA to hand search
Suh K.J.; Kim K.H.; Kim R.; Byun J.M.; Kim M.; Park J.H.; Keam B.; Kim T.M.; Kim J.-S.; Choi I.S.; Heo D.S.	2019	Costs and clinical outcomes of patients with diffuse large B-cell lymphoma in first remission: Role of PET/CT surveillance	Population
Yang H.; Hao Y.; Chai X.; Qi C.Z.; Wu E.Q.	2019	Estimation of Total Costs in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Receiving Tisagenlecleucel from a US Hospital's Perspective	Superseded
Kilgore K.M.; Mohammadi I.; Schroeder A.; Teigland C.; Purdum A.; Shah G.L.	2019	Medicare Patients Receiving Chimeric Antigen Receptor T-Cell Therapy for Non-Hodgkin Lymphoma: A First Real-World	Population

Authors	Published Year	Title	Exclusion reason
		Look at Patient Characteristics, Healthcare Utilization and Costs	
Kurukulasuriya N.; Menzler J.; Schwenke C.; Neubauer A.S.; Boehnke A.C.	2019	Treatment pathways of diffuse large B-cell lymphoma in german claims data	Population
Roth J.A.; Sullivan S.D.; Lin V.W.; Bansal A.; Purdum A.G.; Navale L.; Cheng P.; Ramsey S.D.	2018	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States	Outcomes
Landau D.; Wilds B.; Mouslly S.	2018	Cost consideration of second line therapy for relapsed diffuse large lymphoma in the community setting	Unobtainable
Garcia J.; Snyder S.; Gitlin M.	2018	Estimating the lifetime costs in adult patients with relapsed/refractory diffuse large B-cell lymphoma in the United States	Outcomes
Wang H.-I.; Smith A.; Aas E.; Roman E.; Crouch S.; Burton C.; Patmore R.	2017	Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort	Population
Kumar A.J.; Henzer T.; Rodday A.M.; Parsons S.K.	2017	Longer length of stay and no chemotherapy is associated with greater likelihood of death during hospitalization in patients with diffuse large B-cell lymphoma: An analysis from the national inpatient sample (NIS)	Population
Maziarz R.T.; Hao Y.; Guerin A.; Gauthier G.; Gauthier-Loiselle M.; Thomas S.K.; Eldjerou L.K.	2016	Short-term and long-term economic burden following allogeneic hematopoietic stem cell transplant (HSCT) in adult patients with diffuse large B-cell lymphoma (DLBCL)	Population
Chen W.; Xu X.	2016	Cost-effectiveness of rituximab in the treatment of diffuse large B-cell non-hodgkin's lyphoma patients (DLBCL) in China	Outcomes
Kim R.; Kim K.H.; Kim J.S.; Park J.H.; Choi I.S.	2015	Surveillance of relapse with 18F-flurodeoxyglucose positron emission to-mography/computed tomography in diffuse large B-cell lymphoma after achieving complete remission with rituximab containing regimen	Population
Hong J.; Kim J.; Yoo S.; Ahn J.; Park J.; Hoon Lee J.	2013	Clinical symptom or sign-directed surveillance can be more useful to detect relapse compared to routine imaging in patients with diffuse large B-cell lymphoma after complete remission	Duplicate

Authors	Published Year	Title	Exclusion reason
Danese M.; Griffiths R.; Gleeson M.; Dalvi T.; Li J.; Deeter R.G.; Mikhael J.R.; Dreyling M.	2013	Patterns of care, survival, and costs of second-line treatment in medicare beneficiaries with diffuse large b-cell lymphoma (DLBCL)	Outcomes
Hong J.; Kim J.H.; Park J.; Lee J.H.	2013	Clinical symptom or sign-directed surveillance can be more useful in detecting relapse compared to routine imaging in patients with diffuse large b-cell lymphoma in remission	Population
Kymes S.M.; Pusic I.; Lambert D.L.; Gregory M.; Carson K.R.; DiPersio J.F.	2012	Economic evaluation of plerixafor for stem cell mobilization	Outcomes
Crump M.; Kuruvilla J.; Couban S.; Macdonald D.; Kukreti V.; Kouroukis C.T.; Meyer R.M.; Rubinger M.; Buckstein R.; Imrie K.R.; Federico M.; Di Renzo N.; Howson-Jan K.; Baetz T.; Kaizer L.; Voralia M.; Olney H.J.; Turner A.R.; Sussman J.; Hay A.E.; Djurfeldt M.; Chen B.E.; Shepherd L.	2012	Gemcitabine, dexamethasone, cisplatin (GDP) compared to dexamethasone, cytarabine, cisplatin (DHAP) chemotherapy prior to autologous stem cell transplantation for relapsed and refractory aggressive lymphomas: Final results of the randomized phase III NCIC	Outcomes
Burke, John M; Wang, Rongrong; Hossain, Farah; Li, Jia; Masaquel, Anthony; Zhou, Summera Qiheng; Matasar, Matthew	2022	ABCL-102 A SEER-Medicare Analysis of the Cost of Disease Progression After Frontline R-CHOP in Diffuse Large B-Cell Lymphoma.	Duplicate
Zhu, Feng; Wei, Guoqing; Zhang, Mingming; Zhao, Houli; Wu, Wenjun; Yang, Luxin; Hu, Yongxian; Huang, He	2020	Factors Associated with Costs in Chimeric Antigen Receptor T-Cell Therapy for Patients with Relapsed/Refractory B-Cell Malignancies.	Population
Painschab, Matthew S; Kohler, Racquel E; Kasonkanji, Edwards; Zuze, Takondwa; Kaimila, Bongani; Nyasosela, Richard; Nyirenda, Ruth; Krysiak, Robert; Gopal, Satish	2019	Microcosting Analysis of Diffuse Large B-Cell Lymphoma Treatment in Malawi.	Duplicate
Centre for Reviews and Dissemination	2015	Rituximab (MabThera) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation (Provisional abstract).	Duplicate
Centre for Reviews and Dissemination	2015	Health care delivery in Canada and the United States: are there relevant differences in health care outcomes? (Structured abstract).	Population
Centre for Reviews and Dissemination	2015	Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review (Provisional abstract).	Study design

Authors	Published Year	Title	Exclusion reason
NHSC	2016	Rituximab for aggressive B-cell lymphoma - horizon scanning review (Structured abstract)	Unobtainable
BlueCross BlueShield Association	2016	Rituximab for treatment of intermediate and aggressive B-cell non-Hodgkin's lymphomas (Structured abstract)	Unobtainable
National Institute for Clinical Excellence	2016	Rituximab for aggressive non-Hodgkin's lymphoma (Structured abstract)	Unobtainable
Knight, C; Hind, D; Brewer, N; Abbott, V	2016	Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation (Structured abstract)	SLR/NMA to hand search
Catalan Agency for Health Technology Assessment and Research	2016	Diffuse large B-cell lymphoma OncoGuide (Structured abstract)	Unobtainable
Ndegwa, S; Spry, C	2016	Rituximab for non-hodgkin's lymphoma: a review of the clinical and cost- effectiveness and guidelines (Structured abstract)	Study design
Hintringer, K; Nachtnebel, A; Heyll, A	2016	Brentuximab (AdcetrisReg.) for the treatment of relapsed Hodgkin's lymphoma (HL) or relapsed systemic anaplastic large cell lymphoma (sALCL) (Structured abstract)	Population
NIHR, HSC	2016	Enzastaurin for diffuse large B-cell lymphoma - following complete remission (Structured abstract)	Unobtainable
NIHR, HSC	2016	Ofatumumab (Arzerra) for relapsed diffuse large B-cell lymphoma (Structured abstract)	Unobtainable
NIHR, HSC	2016	Pixantrone (Pixuvri) in combination with rituximab for diffuse large B-cell lymphoma or grade 3 follicular lymphoma - second and subsequent line (Structured abstract)	Unobtainable
NIHR, HSRIC	2016	Nivolumab (Opdivo) for diffuse large B cell lymphoma -second line (Structured abstract)	Unobtainable
Centre for Reviews and Dissemination	2014	Real world costs and cost-effectiveness of Rituximab for diffuse large B-Cell lymphoma patients: a population-based analysis (Provisional abstract)	Population
Centre for Reviews and Dissemination	2012	Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma (Provisional abstract)	Population

Authors	Published Year	Title	Exclusion reason
Centre for Reviews and Dissemination	2008	Cost-effectiveness analysis of the addition of rituximab to CHOP in young patients with good-prognosis diffuse large-B-cell lymphoma (Structured abstract)	Outcomes
Centre for Reviews and Dissemination	2005	Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma (Structured abstract)	Outcomes

Section 3: C5 supplementary material

The tables for each SLR detailing the excluded studies from hand searching, with exclusion reasons for each study are provided below.

Identification of studies via other methods

Table 35: List of excluded studies – Clinical SLR (n=62)

Source of hand searching	Authors	Published Year	Title	Exclusion reason
ClinicalTrials.gov website	ClinicalTrials.gov		Comparison of Pixantrone + Rituximab With Gemcitabine + Rituximab in Patients With Aggressive B-cell Non-Hodgkin Lymphoma or Follicular Grade 3 Lymphoma Who Have Relapsed After Therapy and Are Not Eligible for Stem Cell Transplant (PIX-R). (NCT01321541).	Duplicate – trial already found via database searches
ClinicalTrials.gov website	ClinicalTrials.gov		Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2). (NCT03589469).	Duplicate – trial already found via database searches
ClinicalTrials.gov website	ClinicalTrials.gov		A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL (L-MIND). (NCT02399085).	Duplicate – trial already found via database searches
ClinicalTrials.gov website	ClinicalTrials.gov		Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). (NCT02348216).	Duplicate – trial already found via database searches
Galaznik 2016	Ohmachi K.; Niitsu N.; Uchida T.; Kim S.J.; Ando K.; Takahashi N.; Uike N.; Eom H.S.; Chae Y.S.; Terauchi T.; Tateishi U.; Tatsumi M.; Kim W.S.; Tobinai K.; Suh C.; Ogura M.	2013	Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma	Duplicate – found via database searches
Halford 2021	Neelapu S.S.; Locke F.L.; Bartlett N.L.; Lekakis L.J.; Miklos D.B.; Jacobson C.A.; Braunschweig I.;	2017	Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma	Duplicate – found via database searches

	Oluwole O.O.; Siddiqi T.; Lin Y.; Timmerman J.M.; Stiff P.J.; Friedberg J.W.; Flinn I.W.; Goy A.; Hill B.T.; Smith M.R.; Deol A.; Farooq U.; McSweeney P.; Munoz J.; Avivi I.; Castro J.E.; Westin J.R.; Chavez J.C.; Ghobadi A.; Komanduri K.V.; Levy R.; Jacobsen E.D.; Witzig T.E.; Reagan P.; Bot A.; Rossi J.; Navale L.; Jiang Y.; Aycock J.; Elias M.; Chang D.; Wiezorek J.; Go W.Y.			
Thuresson 2020	Schuster S.J.; Bishop M.R.; Tam C.S.; Waller E.K.; Borchmann P.; McGuirk J.P.; Jager U.; Jaglowski S.; Andreadis C.; Westin J.R.; Fleury I.; Bachanova V.; Foley S.R.; Ho P.J.; Mielke S.; Magenau J.M.; Holte H.; Pantano S.; Pacaud L.B.; Awasthi R.; Chu J.; Anak O.; Salles G.; Maziarz R.T.	2019	Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma	Duplicate – found via database searches
Thuresson 2020	Pettengell R.; Sebban C.; Zinzani P.L.; Derigs H.G.; Kravchenko S.; Singer J.W.; Theocharous P.; Wang L.; Pavlyuk M.; Makhloufi K.M.; Coiffier B.	2016	Monotherapy with pixantrone in histologically confirmed relapsed or refractory aggressive B cell non-Hodgkin lymphoma: post-hoc analyses from a phase III trial	Duplicate – found via database searches
Ernst 2021	Locke F.L.; Ghobadi A.; Jacobson C.A.; Miklos D.B.; Lekakis L.J.; Oluwole O.O.; Lin Y.; Braunschweig I.; Hill B.T.; Timmerman J.M.; Deol A.; Reagan P.M.; Stiff P.; Flinn I.W.; Farooq U.; Goy A.; McSweeney P.A.; Munoz J.; Siddiqi T.; Chavez J.C.; Herrera	2019	Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial	Duplicate – found via database searches

	A.F.; Bartlett N.L.; Wiezorek J.S.; Navale L.; Xue A.; Jiang Y.; Bot A.; Rossi J.M.; Kim J.J.; Go W.Y.; Neelapu S.S.			
European Hematology Association (EHA), 2022 conference (keyword searched: DLBCL)	Dickinson M.; Carlo-Stella C.; Morschhauser F.; Bachy E.; Corradini P.; Iacoboni G.; Khan C.; Wrobel T.; Offner F.; Trneny M.; Wu S.-J.; Cartron G.; Hertzberg M.; Sureda Balari A.; Perez-Callejo D.; Lundberg L.; Relf J.; Clark E.; Humphrey K.; Hutchings M.	2022	Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥ 2 prior therapies: Pivotal phase II expansion results	Duplicate – found via database searches
European Hematology Association (EHA), 2022 conference (keyword searched: DLBCL)	Wu S.-J.; Liao C.-K.; Wang Y.-W.; Wang M.-C.	2022	Real-world experience of outcomes with glofitamab salvage therapy for relapse/refractory B-cell lymphoma in Taiwan: Minimal safety concern with hepatitis B reactivation	Duplicate – found via database searches
Society of Hematologic Oncology (SOHO), 2021 conference (keyword searched: DLBCL)	Solh M.; Alderuccio J.P.; Hess B.; Radford J.; Lunning M.; Ungar D.; Burke M.; Wang L.; Ardeshna K.	2021	ABCL-362: Incidence, Onset, and Management of Myelosuppression in Patients Treated with Ioncastuximab Tesirine for R/R DLBCL in a Pooled Safety Analysis	Duplicate – found via database searches
NICE (keyword searched: diffuse large B cell lymphoma)	National Institute for Health and Care Excellence (NICE)	2020	Polatuzumab vedotin with rituximab and bendamustine, (TA649).	Outcomes
NICE (keyword searched: diffuse	National Institute for Health and Care Excellence (NICE)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567)	Outcomes

large B cell lymphoma				
NICE (keyword searched: diffuse large B cell lymphoma	National Institute for Health and Care Excellence (NICE)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115] (TA559)	Outcomes
NICE (keyword searched: rituximab)	National Institute for Health and Care Excellence (NICE)	2020	Polatuzumab vedotin with rituximab and bendamustine, (TA649).	Outcomes
NICE (keyword searched: tisagenlecleucel)	National Institute for Health and Care Excellence (NICE)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567)	Outcomes
NICE (keyword searched: axicabtagene ciloleucel)	National Institute for Health and Care Excellence (NICE)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115] (TA559)	Outcomes
NICE (keyword searched: polatuzumab)	National Institute for Health and Care Excellence (NICE)	2020	Polatuzumab vedotin with rituximab and bendamustine, (TA649).	Outcomes
SMC (keyword searched: diffuse large B cell lymphoma)	Scottish Medicines Consortium (SMC)	2020	Polivy (SMC2282)	Outcomes
SMC (keyword searched: diffuse large B cell lymphoma)	Scottish Medicines Consortium (SMC)	2019	Axicabtagene ciloleucel (SMC2189)	Outcomes
SMC (keyword searched: diffuse	Scottish Medicines Consortium (SMC)	2019	Tisagenlecleucel (SMC2200), resubmission	Outcomes

large B cell lymphoma)				
SMC (keyword searched: rituximab)	Scottish Medicines Consortium (SMC)	2020	Polivy (SMC2282)	Outcomes
SMC (keyword searched: axicabtagene ciloleucel)	Scottish Medicines Consortium (SMC)	2019	Axicabtagene ciloleucel (SMC2189)	Outcomes
SMC (keyword searched: tisagenlecleucel)	Scottish Medicines Consortium (SMC)	2019	Tisagenlecleucel (SMC2129), full	Outcomes
SMC (keyword searched: tisagenlecleucel)	Scottish Medicines Consortium (SMC)	2019	Tisagenlecleucel (SMC2200), resubmission	Outcomes
SMC (keyword searched: polatuzumab)	Scottish Medicines Consortium (SMC)	2020	Polivy (SMC2282)	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2019	Kymriah (tisagenlecleucel), anti-CD19 CAR T	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Yescarta (axicabtagene ciloleucel)	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2020	Polivy, polatuzumab vedotin	Outcomes

HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Kymriah - LDGCB (tisagenlecleucel)	Outcomes
AWMSG (keyword searched: Polatuzumab)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes
AWMSG (keyword searched: tafasitamab)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes
AWMSG (keyword searched: axicabtagene ciloleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes
AWMSG (keyword searched: tisagenlecleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes
AWMSG (keyword searched: lenalidomide)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes
AWMSG (keyword searched: rituximab)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes
PBS (keyword searched: diffuse large B cell lymphoma)	The Pharmaceutical Benefits Scheme (PBS)	2019	Polatuzumab vedotin Powder for injection, 140 mg vial, Polivy®	Outcomes
PBS (keyword searched: DLBCL)	The Pharmaceutical Benefits Scheme (PBS)	2019	Polatuzumab vedotin Powder for injection, 140 mg vial, Polivy®	Outcomes

CADTH (keyword searched: diffuse large B cell lymphoma)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Axicabtagene Ciloleucel and Tisagenlecleucel for Diffuse Large B-cell Lymphoma	Outcomes
CADTH (keyword searched: diffuse large B cell lymphoma)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Lisocabtagene Maraleucel (Breyanzi)	Outcomes
CADTH (keyword searched: diffuse large B cell lymphoma)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes
CADTH (keyword searched: diffuse large B cell lymphoma)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Outcomes
CADTH (keyword searched: tafasitamab)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Tafasitamab (Minjuvi)	Outcomes
CADTH (keyword searched: tisagenlecleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Tisagenlecleucel for Diffuse Large B-Cell Lymphoma	Outcomes
CADTH (keyword searched: tisagenlecleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Outcomes
CADTH (keyword searched: tisagenlecleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes

CADTH (keyword searched: axicabtagene ciloleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Outcomes
CADTH (keyword searched: axicabtagene ciloleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Axicabtagene Ciloleucel and Tisagenlecleucel for Diffuse Large B-cell Lymphoma	Outcomes
CADTH (keyword searched: axicabtagene ciloleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes
CADTH (keyword searched: lisocabtagene maraleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Lisocabtagene Maraleucel (Breyanzi)	Outcomes
CADTH (keyword searched: lenalidomide	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes
CADTH (keyword searched: lenalidomide	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Tafasitamab (Minjuvi)	Outcomes
CADTH (keyword searched: polatuzumab	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes
CADTH (keyword searched: pixantrone	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes

CADTH (keyword searched: rituximab	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes
SBU (keyword searched: polatuzumab)	Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	2020	Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	Outcomes
G-BA (keyword searched: tafasitamab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2022	Tafasitamab (diffuse large B-cell lymphoma (DLBCL), combination with lenalidomide)	Outcomes
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Tisagenlecleucel (diffuse large B-cell lymphoma)	Outcomes
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Tisagenlecleucel (Reassessment after Expiry: Diffuse Large B-cell Lymphoma)	Outcomes
G-BA (keyword searched: polatuzumab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Polatuzumab Vedotin (Diffuse Large B-Cell Lymphoma, Combination with Bendamustine and Rituximab)	Outcomes
G-BA (keyword searched: axicabtagene ciloleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Axicabtagene ciloleucel	Outcomes

Table 36: List of excluded studies – Economic SLR (n=78)

Source of hand searching	Authors	Published Year	Title	Exclusion reason
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Moradi-Lakeh M.; Yaghoubi M.; Seitz P.; Javanbakht M.; Brock E.	2021	Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland.	Duplicate – found via database searches
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Calamia M.; McBride A.; Abraham I.	2021	Economic evaluation of polatuzumab-bendamustine-rituximab vs. tafasitamab-lenalidomide in transplant-ineligible R/R DLBCL	Duplicate – found via database searches
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Patel K.K.; Isufi I.; Kothari S.; Foss F.; Huntington S.	2020	Cost-effectiveness of polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma	Duplicate – found via database searches
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Wakase S.; Teshima T.; Zhang J.; Ma Q.; Fujita T.; Yang H.; Chai X.; Qi C.Z.; Liu Q.; Wu E.Q.; Igarashi A.	2021	Cost Effectiveness Analysis of Tisagenlecleucel for the Treatment of Adult Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma in Japan	Duplicate – found via database searches
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Qi C.Z.; Bollu V.; Yang H.; Dalal A.; Zhang S.; Zhang J.	2021	Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the United States	Duplicate – found via database searches
Cost Effectiveness Analysis (CEA)	Cher B.P.; Gan K.Y.; Aziz M.I.A.; Lin L.; Hwang W.Y.K.; Poon L.M.; Ng K.	2020	Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell	Duplicate – found via database searches

registry (keyword searched: DLBCL)			lymphoma from Singapore's healthcare system perspective	
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Wang X.J.; Wang Y.-H.; Li S.C.T.; Gkitzia C.; Lim S.T.; Koh L.P.; Lim F.L.W.I.; Hwang W.Y.K.	2021	Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective	Duplicate – found via database searches
Cost Effectiveness Analysis (CEA) registry (keyword searched: diffuse large B cell lymphoma)	Chen Q.; Staton A.D.; Ayer T.; Goldstein D.A.; Koff J.L.; Flowers C.R.	2018	Exploring the potential cost-effectiveness of precision medicine treatment strategies for diffuse large B-cell lymphoma	Outcomes
EQ-5D documents (keyword searched: DLBCL)	Ernst M, Oeser A, Besiroglu B, Caro-Valenzuela J, Abd El Aziz M, Monsef I, Borchmann P, Estcourt LJ, Skoetz N, Goldkuhle M.	2021	Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Petrou 2019	Roth J.A.; Sullivan S.D.; Lin V.W.; Bansal A.; Purdum A.G.; Navale L.; Cheng P.; Ramsey S.D.	2018	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States	Duplicate
Petrou 2019	Whittington M.D.; McQueen R.B.; Ollendorf D.A.; Kumar V.M.; Chapman R.H.; Tice J.A.; Pearson S.D.; Campbell J.D.	2019	Long-term survival and cost-effectiveness associated with axicabtagene ciloleucel vs chemotherapy for treatment of B-cell lymphoma	Duplicate – found via database searches

Petrou 2019	Lin J.K.; Muffly L.S.; Spinner M.A.; Barnes J.I.; Owens D.K.; Goldhaber-Fiebert J.D.	2019	Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma	Duplicate – found via database searches
Petrou 2019	Neelapu S.S.; Locke F.L.; Bartlett N.L.; Lekakis L.J.; Miklos D.B.; Jacobson C.A.; Braunschweig I.; Oluwole O.O.; Siddiqi T.; Lin Y.; Timmerman J.M.; Stiff P.J.; Friedberg J.W.; Flinn I.W.; Goy A.; Hill B.T.; Smith M.R.; Deol A.; Farooq U.; McSweeney P.; Munoz J.; Avivi I.; Castro J.E.; Westin J.R.; Chavez J.C.; Ghobadi A.; Komanduri K.V.; Levy R.; Jacobsen E.D.; Witzig T.E.; Reagan P.; Bot A.; Rossi J.; Navale L.; Jiang Y.; Aycock J.; Elias M.; Chang D.; Wiezorek J.; Go W.Y.	2017	Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma	Outcomes
Petrou 2019	Marchetti M, Martelli E, Zinzani PL.	2018	Cost-effectiveness of axicabtagene ciloleucel for relapsed or refractory dffuse large b-cell lymphoma in Italy	Outcomes
Petrou 2019	Hollmann S.; Painter C.; Hogan A.; Morten P.; Goyert N.; Vieira J.; Slowley A.; Jousseaume E.; El Ouagari K.; Zhang J.; Jewitt K.; Ma Q.	2018	Budget impact analysis of tisagenlecleucel for the treatment of paediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia in England	Outcomes

Petrou 2019	Yang H, Qi C, Zhang J, El Ouagari K.	2018	Cost-effectiveness of tisagenlecleucel for adults with relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Gye 2022	Schuster S.J.; Bishop M.R.; Tam C.S.; Waller E.K.; Borchmann P.; McGuirk J.P.; Jager U.; Jaglowski S.; Andreadis C.; Westin J.R.; Fleury I.; Bachanova V.; Foley S.R.; Ho P.J.; Mielke S.; Magenau J.M.; Holte H.; Pantano S.; Pacaud L.B.; Awasthi R.; Chu J.; Anak O.; Salles G.; Maziarz R.T.	2019	Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Gye 2022	Schuster, Stephen J; Svoboda, Jakub; Chong, Elise A; Nasta, Sunita D; Mato, Anthony R; Anak, Ozlem; Brogdon, Jennifer L; Pruteanu-Malinici, Iulian; Bhoj, Vijay; Landsburg, Daniel; Wasik, Mariusz; Levine, Bruce L; Lacey, Simon F; Melenhorst, Jan J; Porter, David L; June, Carl H	2017	Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas	Outcomes
Gye 2022	Locke F.L.; Ghobadi A.; Jacobson C.A.; Miklos D.B.; Lekakis L.J.; Oluwole O.O.; Lin Y.; Braunschweig I.; Hill B.T.; Timmerman J.M.; Deol A.; Reagan P.M.; Stiff P.; Flinn I.W.; Farooq U.; Goy A.; McSweeney P.A.; Munoz J.; Siddiqi T.;	2019	Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial	Outcomes

	Chavez J.C.; Herrera A.F.; Bartlett N.L.; Wiezorek J.S.; Navale L.; Xue A.; Jiang Y.; Bot A.; Rossi J.M.; Kim J.J.; Go W.Y.; Neelapu S.S.			
Gye 2022	National Institute for Health and Care Excellence (NICE)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115] (TA559)	Duplicate – found via HTA handsearching
Gye 2022	National Institute for Health and Care Excellence (NICE)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567)	Duplicate – found via HTA handsearching
Gye 2022	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Tisagenlecleucel for Diffuse Large B-Cell Lymphoma	Duplicate – found via HTA handsearching
Gye 2022	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Axicabtagene Ciloleucel and Tisagenlecleucel for Diffuse Large B-cell Lymphoma	Duplicate – found via HTA handsearching
Harkins 2019	Danese M.D.; Griffiths R.I.; Gleeson M.L.; Dalvi T.; Li J.; Mikhael J.R.; Deeter R.; Dreyling M.	2017	Second-line therapy in diffuse large B-cell lymphoma (DLBCL): treatment patterns and outcomes in older patients receiving outpatient chemotherapy	Outcomes
Harkins 2019	Huntington S.; Keshishian A.; McGuire M.; Xie L.; Baser O.	2018	Costs of relapsed diffuse large B-cell lymphoma among Medicare patients	Outcomes
Harkins 2019	Roth J.A.; Sullivan S.D.; Lin V.W.; Bansal A.; Purdum A.G.;	2018	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed	Duplicate – found via database searches

	Navale L.; Cheng P.; Ramsey S.D.		or refractory large B-cell lymphoma in the United States	
Harkins 2019	Neelapu S.S.; Locke F.L.; Bartlett N.L.; Lekakis L.J.; Miklos D.B.; Jacobson C.A.; Braunschweig I.; Oluwole O.O.; Siddiqi T.; Lin Y.; Timmerman J.M.; Stiff P.J.; Friedberg J.W.; Flinn I.W.; Goy A.; Hill B.T.; Smith M.R.; Deol A.; Farooq U.; McSweeney P.; Munoz J.; Avivi I.; Castro J.E.; Westin J.R.; Chavez J.C.; Ghobadi A.; Komanduri K.V.; Levy R.; Jacobsen E.D.; Witzig T.E.; Reagan P.; Bot A.; Rossi J.; Navale L.; Jiang Y.; Aycock J.; Elias M.; Chang D.; Wiezorek J.; Go W.Y.	2017	Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma	Outcome
Harkins 2019	Schuster S.J.; Bishop M.R.; Tam C.S.; Waller E.K.; Borchmann P.; McGuirk J.P.; Jager U.; Jaglowski S.; Andreadis C.; Westin J.R.; Fleury I.; Bachanova V.; Foley S.R.; Ho P.J.; Mielke S.; Magenau J.M.; Holte H.; Pantano S.; Pacaud L.B.; Awasthi R.; Chu J.; Anak O.; Salles G.; Maziarz R.T.	2019	Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma	Outcomes

Harkins 2019	Schuster, Stephen J; Svoboda, Jakub; Chong, Elise A; Nasta, Sunita D; Mato, Anthony R; Anak, Ozlem; Brogdon, Jennifer L; Pruteanu-Malinici, Iulian; Bhoj, Vijay; Landsburg, Daniel; Wasik, Mariusz; Levine, Bruce L; Lacey, Simon F; Melenhorst, Jan J; Porter, David L; June, Carl H	2017	Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas	Outcomes
Harkins 2019	Sehn L.H.; Herrera A.F.; Matasar M.J.; Kamdar M.K.; McMillan A.; Hertzberg M.; Assouline S.; Kim T.M.; Kim W.S.; Ozcan M.; Hirata J.; Penuel E.; Paulson J.N.; Cheng J.; Ku G.; Flowers C.R.	2018	Polatuzumab Vedotin (Pola) Plus Bendamustine (B) with Rituximab (R) or Obinutuzumab (G) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase (Ph) Ib/II Study	Outcomes
Harkins 2019	Maziarz R.T.; Hao Y.; Guerin A.; Gauthier G.; Gauthier-Loiselle M.; Thomas S.K.; Eldjerou L.	2018	Economic burden followingallogeneic hematopoietic stem cell transplant in patients withdiffuse large B-cell lymphoma	Outcomes
Ho 2021	Whittington M.D.; McQueen R.B.; Ollendorf D.A.; Kumar V.M.; Chapman R.H.; Tice J.A.; Pearson S.D.; Campbell J.D.	2019	Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma	Duplicate – found via database searches
Ho 2021	Lin J.K.; Muffly L.S.; Spinner M.A.; Barnes J.I.; Owens D.K.; Goldhaber-Fiebert J.D.	2019	Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma	Duplicate – found via database searches

Ho 2021	Cher B.P.; Gan K.Y.; Aziz M.I.A.; Lin L.; Hwang W.Y.K.; Poon L.M.; Ng K.	2020	Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective	Duplicate – found via database searches
Ho 2021	Petrou P.	2019	Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Comparison of Pixantrone + Rituximab With Gemcitabine + Rituximab in Patients With Aggressive B-cell Non-Hodgkin Lymphoma or Follicular Grade 3 Lymphoma Who Have Relapsed After Therapy and Are Not Eligible for Stem Cell Transplant (PIX-R). (NCT01321541).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2). (NCT03589469).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL (L-MIND). (NCT02399085).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). (NCT02348216).	Outcomes

SBU (keyword searched: polatuzumab)	Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	2020	Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	Outcome
G-BA (keyword searched: tafasitamab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2022	Tafasitamab (diffuse large B-cell lymphoma (DLBCL), combination with lenalidomide)	Outcome
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Tisagenlecleucel (diffuse large B-cell lymphoma)	Outcome
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Tisagenlecleucel (Reassessment after Expiry: Diffuse Large B-cell Lymphoma)	Outcome
G-BA (keyword searched: polatuzumab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Polatuzumab Vedotin (Diffuse Large B-Cell Lymphoma, Combination with Bendamustine and Rituximab)	Outcome
G-BA (keyword searched: axicabtagene ciloleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Axicabtagene ciloleucel	Outcome
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2019	Kymriah (tisagenlecleucel), anti-CD19 CAR T	Outcome

HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Yescarta (axicabtagene ciloleucel)	Outcome
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2020	Polivy, polatuzumab vedotin	Outcome
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Kymriah - LDGCB (tisagenlecleucel)	Outcome
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes – data not novel

AWMSG (keyword searched: Polatuzumab)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: tafasitamab)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: axicabtagene ciloleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: tisagenlecleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
NICE (keyword searched: rituximab)	National Institute for Health and Care Excellence (NICE)	2020	Polatuzumab vedotin with rituximab and bendamustine, (TA649).	Duplicate – already included from other keyword search
NICE (keyword searched: tisagenlecleucel)	National Institute for Health and Care Excellence (NICE)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567)	Duplicate – already included from other keyword search
NICE (keyword searched: axicabtagene ciloleucel)	National Institute for Health and Care Excellence (NICE)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115] (TA559)	Duplicate – already included from other keyword search
NICE (keyword searched: polatuzumab)	National Institute for Health and Care Excellence (NICE)	2020	Polatuzumab vedotin with rituximab and bendamustine, (TA649).	Duplicate – already included from other keyword search

SMC (keyword searched: rituximab)	Scottish Medicines Consortium (SMC)	2020	Polivy (SMC2282)	Duplicate – already included from other keyword search
SMC (keyword searched: axicabtagene ciloleucel)	Scottish Medicines Consortium (SMC)	2019	Axicabtagene ciloleucel (SMC2189)	Duplicate – already included from other keyword search
SMC (keyword searched: tisagenlecleucel)	Scottish Medicines Consortium (SMC)	2019	Tisagenlecleucel (SMC2129), full	Duplicate – already included from other keyword search
SMC (keyword searched: tisagenlecleucel)	Scottish Medicines Consortium (SMC)	2019	Tisagenlecleucel (SMC2200), resubmission	Duplicate – already included from other keyword search
SMC (keyword searched: polatuzumab)	Scottish Medicines Consortium (SMC)	2020	Polivy (SMC2282)	Duplicate – already included from other keyword search
CADTH (keyword searched: tisagenlecleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Tisagenlecleucel for Diffuse Large B-Cell Lymphoma	Duplicate – already included from other keyword search
CADTH (keyword searched: tisagenlecleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Duplicate – already included from other keyword search
CADTH (keyword searched: tisagenlecleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Duplicate – already included from other keyword search

CADTH (keyword searched: axicabtagene ciloleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Duplicate – already included from other keyword search
CADTH (keyword searched: axicabtagene ciloleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Axicabtagene Ciloleucel and Tisagenlecleucel for Diffuse Large B-cell Lymphoma	Duplicate – already included from other keyword search
CADTH (keyword searched: axicabtagene ciloleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Duplicate – already included from other keyword search
CADTH (keyword searched: lisocabtagene maraleucel)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Lisocabtagene Maraleucel (Breyanzi)	Duplicate – already included from other keyword search
CADTH (keyword searched: lenalidomide	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Duplicate – already included from other keyword search
CADTH (keyword searched: lenalidomide	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Tafasitamab (Minjuvi)	Duplicate – already included from other keyword search
CADTH (keyword searched: polatuzumab	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Duplicate – already included from other keyword search

CADTH (keyword searched: pixantrone	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Duplicate – already included from other keyword search
CADTH (keyword searched: rituximab	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Duplicate – already included from other keyword search

Table 37: List of excluded studies –HCRU (n=47)

Study	Authors	Published Year	Title	Exclusion reason
Ho 2021	Cher B.P.; Gan K.Y.; Aziz M.I.A.; Lin L.; Hwang W.Y.K.; Poon L.M.; Ng K.	2020	Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective	Duplicate – found via database searches
Ho 2021	Yang H.; Hao Y.; Chai X.; Qi C.Z.; Wu E.Q.	2020	Estimation of total costs in patients with relapsed or refractory diffuse large B-cell lymphoma receiving tisagenlecleucel from a US hospital's perspective	Duplicate – found via database searches
Ho 2021	Petrou P.	2019	Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy	Duplicate – found via database searches
Ho 2021	Lin J.K.; Muffly L.S.; Spinner M.A.; Barnes J.I.; Owens D.K.; Goldhaber-Fiebert J.D.	2019	Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma	Outcomes
Ho 2021	Roth J.A.; Sullivan S.D.; Lin V.W.; Bansal A.; Purdum A.G.; Navale L.; Cheng P.; Ramsey S.D.	2018	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
Ho 2021	Whittington M.D.; McQueen R.B.; Ollendorf D.A.; Kumar V.M.; Chapman R.H.; Tice J.A.; Pearson S.D.; Campbell J.D.	2019	Long-term survival and cost-effectiveness associated with axicabtagene ciloleucel vs chemotherapy for treatment of B-cell lymphoma	Outcomes
Harkins 2019	Maziarz R.T.; Hao Y.; Guerin A.; Gauthier G.; Gauthier-Loiselle M.; Thomas S.K.; Eldjerou L.	2018	Economic burden followingallogeneic hematopoietic stem cell transplant in patients withdiffuse large B-cell lymphoma	Outcomes
Harkins 2019	Danese M.D.; Griffiths R.I.; Gleeson M.L.; Dalvi T.; Li J.; Mikhael J.R.; Deeter R.; Dreyling M.	2017	Second-line therapy in diffuse large B-cell lymphoma (DLBCL): treatment patterns and outcomes in older patients receiving outpatient chemotherapy	Duplicate – found via database searches
Harkins 2019	Huntington S.; Keshishian A.; McGuire M.; Xie L.; Baser O.	2018	Costs of relapsed diffuse large B-cell lymphoma among Medicare patients	Duplicate – found via database searches
Harkins 2019	Roth J.A.; Sullivan S.D.; Lin V.W.; Bansal A.; Purdum A.G.; Navale L.; Cheng P.; Ramsey S.D.	2018	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States	Outcomes
Harkins 2019	Neelapu S.S.; Locke F.L.; Bartlett N.L.; Lekakis L.J.; Miklos D.B.; Jacobson C.A.; Braunschweig I.; Oluwole O.O.; Siddiqi T.; Lin Y.; Timmerman J.M.; Stiff P.J.; Friedberg J.W.; Flinn I.W.; Goy A.; Hill B.T.; Smith M.R.; Deol A.; Farooq U.; McSweeney P.; Munoz J.; Avivi I.; Castro J.E.; Westin J.R.; Chavez J.C.; Ghobadi A.; Komanduri K.V.; Levy R.;	2017	Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
	Jacobsen E.D.; Witzig T.E.; Reagan P.; Bot A.; Rossi J.; Navale L.; Jiang Y.; Aycock J.; Elias M.; Chang D.; Wiezorek J.; Go W.Y.			
Harkins 2019	Schuster S.J.; Bishop M.R.; Tam C.S.; Waller E.K.; Borchmann P.; McGuirk J.P.; Jager U.; Jaglowski S.; Andreadis C.; Westin J.R.; Fleury I.; Bachanova V.; Foley S.R.; Ho P.J.; Mielke S.; Magenau J.M.; Holte H.; Pantano S.; Pacaud L.B.; Awasthi R.; Chu J.; Anak O.; Salles G.; Maziarz R.T.	2019	Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Harkins 2019	Schuster, Stephen J; Svoboda, Jakub; Chong, Elise A; Nasta, Sunita D; Mato, Anthony R; Anak, Ozlem; Brogdon, Jennifer L; Pruteanu-Malinici, Iulian; Bhoj, Vijay; Landsburg, Daniel; Wasik, Mariusz; Levine, Bruce L; Lacey, Simon F; Melenhorst, Jan J; Porter, David L; June, Carl H	2017	Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas	Outcomes
Harkins 2019	Sehn L.H.; Herrera A.F.; Matasar M.J.; Kamdar M.K.; McMillan A.; Hertzberg M.; Assouline S.; Kim T.M.; Kim W.S.; Ozcan M.; Hirata J.;	2018	Polatuzumab Vedotin (Pola) Plus Bendamustine (B) with Rituximab (R) or Obinutuzumab (G) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase (Ph) Ib/II Study	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
	Penuel E.; Paulson J.N.; Cheng J.; Ku G.; Flowers C.R.			
Petrou 2019	Roth J.A.; Sullivan S.D.; Lin V.W.; Bansal A.; Purdum A.G.; Navale L.; Cheng P.; Ramsey S.D.	2018	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States	Outcomes
Petrou 2019	Whittington M.D.; McQueen R.B.; Ollendorf D.A.; Kumar V.M.; Chapman R.H.; Tice J.A.; Pearson S.D.; Campbell J.D.	2019	Long-term survival and cost-effectiveness associated with axicabtagene ciloleucel vs chemotherapy for treatment of B-cell lymphoma	Outcomes
Petrou 2019	Lin J.K.; Muffly L.S.; Spinner M.A.; Barnes J.I.; Owens D.K.; Goldhaber-Fiebert J.D.	2019	Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma	Outcomes
Petrou 2019	Neelapu S.S.; Locke F.L.; Bartlett N.L.; Lekakis L.J.; Miklos D.B.; Jacobson C.A.; Braunschweig I.; Oluwole O.O.; Siddiqi T.; Lin Y.; Timmerman J.M.; Stiff P.J.; Friedberg J.W.; Flinn I.W.; Goy A.; Hill B.T.; Smith M.R.; Deol A.; Farooq U.; McSweeney P.; Munoz J.; Avivi I.; Castro J.E.; Westin J.R.; Chavez J.C.; Ghobadi A.; Komanduri K.V.; Levy R.; Jacobsen E.D.; Witzig T.E.; Reagan P.; Bot A.; Rossi J.; Navale L.; Jiang Y.; Aycock J.; Elias M.; Chang D.; Wiezorek J.; Go W.Y.	2017	Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
Petrou 2019	Yang H, Qi C, Zhang J, El Ouagari K.	2018	Cost-effectiveness of tisagenlecleucel for adults with relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Petrou 2019	Marchetti M, Martelli E, Zinzani PL.	2018	Cost-effectiveness of axicabtagene ciloleucel for relapsed or refractory dffuse large b-cell lymphoma in Italy	Outcomes
Petrou 2019	Hollmann S.; Painter C.; Hogan A.; Morten P.; Goyert N.; Vieira J.; Slowley A.; Jousseaume E.; El Ouagari K.; Zhang J.; Jewitt K.; Ma Q.	2018	Budget impact analysis of tisagenlecleucel for the treatment of paediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia in England	Outcomes
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Moradi-Lakeh M.; Yaghoubi M.; Seitz P.; Javanbakht M.; Brock E.	2021	Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland	Outcomes
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Calamia M.; McBride A.; Abraham I.	2021	Economic evaluation of polatuzumab-bendamustine-rituximab vs. tafasitamab-lenalidomide in transplant-ineligible R/R DLBCL	Outcomes
Cost Effectiveness Analysis (CEA) registry (keyword	Patel K.K.; Isufi I.; Kothari S.; Foss F.; Huntington S.	2020	Cost-effectiveness of polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
searched: DLBCL)				
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Wang X.J.; Wang Y.-H.; Li S.C.T.; Gkitzia C.; Lim S.T.; Koh L.P.; Lim F.L.W.I.; Hwang W.Y.K.	2021	Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Comparison of Pixantrone + Rituximab With Gemcitabine + Rituximab in Patients With Aggressive B-cell Non-Hodgkin Lymphoma or Follicular Grade 3 Lymphoma Who Have Relapsed After Therapy and Are Not Eligible for Stem Cell Transplant (PIX-R). (NCT01321541).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2). (NCT03589469).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL (L-MIND). (NCT02399085).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). (NCT02348216).	Outcomes
SBU (keyword searched: polatuzumab)	Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	2020	Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
G-BA (keyword searched: tafasitamab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2022	Tafasitamab (diffuse large B-cell lymphoma (DLBCL), combination with lenalidomide)	Outcomes
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Tisagenlecleucel (diffuse large B-cell lymphoma)	Outcomes
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Tisagenlecleucel (Reassessment after Expiry: Diffuse Large B-cell Lymphoma)	Outcomes
G-BA (keyword searched: polatuzumab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Polatuzumab Vedotin (Diffuse Large B-Cell Lymphoma, Combination with Bendamustine and Rituximab)	Outcomes
G-BA (keyword searched: axicabtagene ciloleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Axicabtagene ciloleucel	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2019	Kymriah (tisagenlecleucel), anti-CD19 CAR T	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Yescarta (axicabtagene ciloleucel)	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2020	Polivy, polatuzumab vedotin	Outcomes

Study	Authors	Published Year	Title	Exclusion reason
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Kymriah - LDGCB (tisagenlecleucel)	Outcomes
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: Polatuzumab)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: tafasitamab)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel

Study	Authors	Published Year	Title	Exclusion reason
AWMSG (keyword searched: axicabtagene ciloleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: tisagenlecleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: lenalidomide)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel

Table 38: List of excluded studies – HSUV (n=48)

	Authors	Published Year	Title	Exclusion reason
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Moradi-Lakeh M.; Yaghoubi M.; Seitz P.; Javanbakht M.; Brock E.	2021	Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland	Outcomes
Cost Effectiveness Analysis (CEA)	Calamia M.; McBride A.; Abraham I.	2021	Economic evaluation of polatuzumab-bendamustine-rituximab vs. tafasitamab-	Outcomes

registry (keyword searched: DLBCL)			lenalidomide in transplant-ineligible R/R DLBCL	
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Patel K.K.; Isufi I.; Kothari S.; Foss F.; Huntington S.	2020	Cost-effectiveness of polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Cost Effectiveness Analysis (CEA) registry (keyword searched: DLBCL)	Wang X.J.; Wang Y.-H.; Li S.C.T.; Gkitzia C.; Lim S.T.; Koh L.P.; Lim F.L.W.I.; Hwang W.Y.K.	2021	Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Comparison of Pixantrone + Rituximab With Gemcitabine + Rituximab in Patients With Aggressive B-cell Non-Hodgkin Lymphoma or Follicular Grade 3 Lymphoma Who Have Relapsed After Therapy and Are Not Eligible for Stem Cell Transplant (PIX-R). (NCT01321541).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2). (NCT03589469).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL (L-MIND). (NCT02399085).	Outcomes
ClinicalTrials.gov website	ClinicalTrials.gov		Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). (NCT02348216).	Outcomes

CADTH (keyword searched: diffuse large B cell lymphoma)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2021	Polatuzumab Vedotin (Polivy) for DLBCL	Outcomes – data not novel
CADTH (keyword searched: diffuse large B cell lymphoma)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2019	Axicabtagene Ciloleucel for Adults With Relapsed or Refractory Large B-cell Lymphoma	Outcomes – data not novel
CADTH (keyword searched: tafasitamab)	Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)	2022	Tafasitamab (Minjuvi)	Outcomes – data not novel
SMC (keyword searched: tisagenlecleucel)	Scottish Medicines Consortium (SMC)	2019	Tisagenlecleucel (SMC2200), resubmission	Outcomes – data not novel
SMC (keyword searched: axicabtagene ciloleucel)	Scottish Medicines Consortium (SMC)	2019	Axicabtagene ciloleucel (SMC2189)	Outcomes – data not novel
SMC (keyword searched: rituximab)	Scottish Medicines Consortium (SMC)	2020	Polivy (SMC2282)	Outcomes – data not novel
SBU (keyword searched: polatuzumab)	Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	2020	Polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	Outcomes
G-BA (keyword searched: tafasitamab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2022	Tafasitamab (diffuse large B-cell lymphoma (DLBCL), combination with lenalidomide)	Outcomes

G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Tisagenlecleucel (diffuse large B-cell lymphoma)	Outcomes
G-BA (keyword searched: tisagenlecleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Tisagenlecleucel (Reassessment after Expiry: Diffuse Large B-cell Lymphoma)	Outcomes
G-BA (keyword searched: polatuzumab)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2020	Polatuzumab Vedotin (Diffuse Large B-Cell Lymphoma, Combination with Bendamustine and Rituximab)	Outcomes
G-BA (keyword searched: axicabtagene ciloleucel)	Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA])	2019	Axicabtagene ciloleucel	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2019	Kymriah (tisagenlecleucel), anti-CD19 CAR T	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Yescarta (axicabtagene ciloleucel)	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2020	Polivy, polatuzumab vedotin	Outcomes
HAS (keyword searched: diffuse large B cell lymphoma)	Haute Autorité de Santé (HAS)	2021	Kymriah - LDGCB (tisagenlecleucel)	Outcomes

AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: diffuse large B cell lymphoma)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: Polatuzumab)	All Wales Medicines Strategy Group (AWMSG)	2020	Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: tafasitamab)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel
AWMSG (keyword searched: axicabtagene ciloleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel
AWMSG (keyword searched: tisagenlecleucel)	All Wales Medicines Strategy Group (AWMSG)	2019	Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies	Outcomes – data not novel

AWMSG (keyword searched: lenalidomide)	All Wales Medicines Strategy Group (AWMSG)	2021	Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large b-cell lymphoma	Outcomes – data not novel
Ernst 2021	Locke F.L.; Ghobadi A.; Jacobson C.A.; Miklos D.B.; Lekakis L.J.; Oluwole O.O.; Lin Y.; Braunschweig I.; Hill B.T.; Timmerman J.M.; Deol A.; Reagan P.M.; Stiff P.; Flinn I.W.; Farooq U.; Goy A.; McSweeney P.A.; Munoz J.; Siddiqi T.; Chavez J.C.; Herrera A.F.; Bartlett N.L.; Wiezorek J.S.; Navale L.; Xue A.; Jiang Y.; Bot A.; Rossi J.M.; Kim J.J.; Go W.Y.; Neelapu S.S.	2019	Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial	Outcomes
Ernst 2021	Borchmann P.; Tam C.S.; Jäger U.; McGuirk J.P.; Holte H.; Waller E.K.; Jaglowski S.M.; Bishop M.R.; Andreadis C.; Foley S.R.; Westin J.R.; Fleury I.; Ho P.J.; Mielke S.; Salles G.; Maziarz R.T.; Anak O.; Pacaud L.B.; Corral C.; Awasthi R.; Agoulnik S.; Tai F.; Schuster S.J.	2018	An updated analysis of JULIET, a global pivotal phase 2 trial of tisagenlecleucel in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL)	Outcomes
Ernst 2021	Maziarz RT, Schuster SJ, Romanov VV, Rusch ES, Li J, Signorovitch JE, Maloney DG, Locke FL.	2020	Grading of neurological toxicity in patients treated with tisagenlecleucel in the JULIET trial	Outcomes
Ernst 2021	Maziarz RT, Waller EK, Jaeger U, Fleury I, McGuirk J, Holte H, Jaglowski S, Schuster SJ, Bishop MR, Westin JR, Mielke S, Teshima T, Bachanova V, Foley SR, Borchmann P, Salles GA, Zhang J,	2020	Patient-reported long-term quality of life aNer tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma	Outcomes

	Tiwari R, Pacaud LB, Ma Q, Tam CS.			
Ernst 2021	Schuster S.J.; Bishop M.R.; Tam C.S.; Waller E.K.; Borchmann P.; McGuirk J.P.; Jager U.; Jaglowski S.; Tobinai K.; Andreadis C.; Fleury I.; Mielke S.; Teshima T.; Westin J.R.; Bachanova V.; Foley S.R.; Ho P.J.; Magenau J.M.; Wagner-Johnston N.; Kato K.; Kersten M.J.; van Besien Ernst 2021K.; Chu J.; Anak O.; Salles G.; Maziarz R.T.	2019	Long-term follow-up of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma: updated analysis of Juliet study	Outcomes
Ernst 2021	Schuster S.J.; Bishop M.R.; Tam C.S.; Waller E.K.; Borchmann P.; McGuirk J.P.; Jager U.; Jaglowski S.; Andreadis C.; Westin J.R.; Fleury I.; Bachanova V.; Foley S.R.; Ho P.J.; Mielke S.; Magenau J.M.; Holte H.; Pantano S.; Pacaud L.B.; Awasthi R.; Chu J.; Anak O.; Salles G.; Maziarz R.T.	2019	Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma	Outcomes
Ernst 2021	Schuster SJ, Maziarz RT, Rusch ES, Li J, Signorovitch JE, Romanov VV, Locke FL, Maloney DG.	2020	Grading and management of cytokine release syndrome in patients treated with tisagenlecleucel in the JULIET trial	Outcomes
Ernst 2021	Schuster, Stephen J; Svoboda, Jakub; Chong, Elise A; Nasta, Sunita D; Mato, Anthony R; Anak, Ozlem; Brogdon, Jennifer L; Pruteanu-Malinici, Iulian; Bhoj, Vijay; Landsburg, Daniel; Wasik, Mariusz; Levine, Bruce L; Lacey,	2017	Chimeric antigen receptor t cells in refractory B-cell lymphomas	Outcomes

	Simon F; Melenhorst, Jan J; Porter, David L; June, Carl H			
Ernst 2021	Locke F.; Bartlett N.; Jacobson C.; Oluwole O.; Munoz J.; Lekakis L.; Topp M.; Avivi I.; Kim J.; Chu R.; Zheng L.; Rossi J.; Bot A.; Neelapu S.	2020	Retreatment of patients with refractory large B cell lymphoma with axicabtagene ciloleucel (Axi-cel) in ZUMA-1	Outcomes
Ernst 2021	Locke FL, Ghobadi A, Jacobson CA, Jacobsen ED, Miklos DB, Lekakis LJ, Braunschweig I, Oluwole O, Lin Y, Siddiqi T, Deol A, Reagan P.M, Farooq U, Bot A, Jiang A, Rossi J.M, Xue A, Go W.Y, Neelapu S.S.	2018	Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (pts) with refractory large B cell lymphoma	Outcomes
Ernst 2021	Locke FL, Ghobadi A, Lekakis LJ, Miklos DB, Jacobson CA, Jacobsen ED, Braunschweig I, Oluwole O, Siddiqi T, Lin Y, Reagan P.M, Farooq U, Deol A, Bot A, Rossi J.M, Jiang A, Xue A, Go W.Y, Neelapu S.S.	2018	Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: outcomes by prior lines of therapy in Zuma-1	Outcomes
Ernst 2021	Neelapu SS, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole O, Lin Y, Braunshweig I, Hill B, Timmerman J, Deol A, Reagan P, Flinn I, Farooq U, Goy A, McSweeney P, Munoz J, Saddiqi T, Chavez J, Herrera A, Xue A, Jiang Y, Bot A, Rossi J, Kim J.	2019	2-year follow-up and high-risk subset analysis of Zuma-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma	Outcomes

Ernst 2021	Locke F.L.; Bartlett N.L.; Braunschweig I.; Siddiqi T.; Lin Y.; Timmerman J.M.; Stiff P.J.; Friedberg J.W.; Flinn I.W.; Goy A.; Hill B.T.; Smith M.R.; Deol A.; Farooq U.; McSweeney P.; Munoz J.; Avivi I.; Castro J.E.; Westin J.R.; Chavez J.C.; Komanduri K.V.; Levy R.; Jacobsen E.D.; Witzig T.E.; Reagan P.; Bot A.; Rossi J.; Navale L.; Jiang Y.; Aycock J.; Elias M.; Chang D.; Wiezorek J.; Go W.Y.	2017	Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma	Outcomes
Ernst 2021	Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y.	2020	Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium	Outcomes
Ernst 2021	Locke FL, Ghobadi A, Lekakis LJ, Miklos DB, Jacobson CA, Jacobsen ED, Braunschweig I, Oluwole O, Siddiqi T, Lin Y, Reagan P.M, Farooq U, Deol A, Bot A, Rossi J.M, Jiang A, Xue A, Go W.Y, Neelapu S.S.	2018	Outcomes by prior lines of therapy (lot) in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B cell lymphoma.	Outcomes

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Swedish Orphan Biovitrum – none BMS - £11,000 in 2022 Incyte - £22,750 in 2022 Pfizer - £300 in 2022 Roche - £26,000 in 2022
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We reached out to our patient community for their experience of living with and receiving treatment for refractory or relapsed DLBCL, and high-grade B cell lymphomas, we received three responses. We also used information obtained from our prior experience of working with those affected by DLCBL, or their carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	DLBCL is a high grade (aggressive) form of lymphoma. Most people with DLBCL first notice enlarging painless lumps. These can be in the neck, groin or armpit and are enlarged lymph nodes. They tend to grow very rapidly, over a few weeks. In some cases, about 4 in 10, the cancer develops outside of the lymph nodes, this is extra nodal disease. Extra nodal DCLBL in the chest can cause a cough and shortness of breath. One of our patients described their initial symptoms – "*I had a cough for about 4 weeks that did not seem to be attributed to anything – no cold, virus or illness. It did not even feel like a proper cough and I could not understand why I even felt the need to cough. My chest felt a bit tight at times and a short walk would leave me feeling breathless. I then randomly felt a lump on my collar bone".* Due to its aggressive nature the symptoms from DLBCL and high grade B cell lymphomas often progress incredibly quickly, *"The disease appeared very quickly and progressed fast", "Symptoms came on quickly – stomach pain, night sweats, fatigue'.* Patients also described the *"psychological impact of diagnosis" as being "enormous." '* 1 in 3 people with DLCBL have B symptoms when they are diagnosed, examples of these are night sweats, weight loss and fatigue. From our patient responses fatigue is particularly debilitating and difficult to live with for DLBCL patients. When asked about what it is like to live with DLBCL, one patient said "I found it quite hard. The fatigue was the main one for me." DLBCL is treated with the aim of cure; however up to 45% are refractory to treatment, or relapse after the initial round of treatment. The prognosis for these people is poor, and the current treatment regimens available only confer a median survival of twelve months. Other high grade B cell lymphomas is a broad group with very different symptoms depending on which part of the body is affected. There is no standard treatment for these patients. They may be treated in the same way as DLBCL, however more intensive treatment regimens may be used because they can be more difficult to treat. Due to the aggressive nature of these lymphomas and their treatment patients often need to spend weeks in hospital isolated from their support network, and unable to work. This often leads to a financial strain on the family – "*Finances were a struggle, but my husband was able to support me financially".*

	Another patient described the psychological impact this can have – *"I had to spend weeks on end in hospital and leave my teenage children at home. Whilst in hospital I was very lonely and felt isolated from my family. I had fantastic care, but I was very anxious about relapse; this was more severe around the time my chemo finished and I was no longer being treated"*. The side effects from the disease and the treatment can last for months, or even years. This can be fatigue, peripheral neuropathy or depression/anxiety amongst others. One of our patients described the ongoing symptoms – *"I finished treatment a year ago and still struggle physically and mentally. Day to day life is as pre DLBCL but it is a constant reminder in my head and body".* Another patient described the long-term impact immobility during treatment can have on the body – "*When I was discharged, I was very weak, and it took me many months to get my physical strength back; the effects of being immobile during treatment should not be underestimated – this led to mobility issues, e.g. needing to use a wheelchair at times. I suffered from fatigue for several years after treatment."* These prolonged side effects are even worse in patients with refractory or relapsed disease because they may require more treatment as well as having the ongoing mental strain of not being in remission. This is how one patient who unfortunately relapsed described it – "*second time round my anxiety was high during the early weeks; I struggled to sleep and felt very low. Once treatment started I was able to focus on it, and I felt more in control of my treatment; the research I had done earlier was really helpful. Time in hospital for chemo and the stem cell transplant (SCT) meant I was away from work again, this time for about 10 months. Recovery from SCT was easier physically, because I had maintained my fitness up to SCT, but the fatigue remained for several years. Other symptoms included brain fog and memory problems, and ongoing bowel issues".* One other patient questioned described how that impact of relapse can lead to longer term psychological problems – "*I relapsed about 12 months after my first treatment ended. I spent the early days in a complete emotional state Each R-ICE round took a week as an inpatient – I was semi-conscious for much of it. Work was impossible at this time, despite my best intentions. Luckily my employers were very supportive. Time during recovery was bittersweet. The relief of coming home and getting back into some kind of normal life is marred by the anxiety of relapse and the worry that your body will somehow let you down. This fades with time, but it can be a roller-coaster of emotions."* Due to these symptoms and the impact of treatment, patients with DLBCL and high-grade B cell lymphomas require large amounts of support from their carers. It can be time consuming, for example taking the patient to

	various hospital appointments, emotionally draining and they often take on the financial burden for the family. *"My husband and daughter looked after me well, but both struggled with it emotionally."* DLBCL tends to be a disease of middle age which means that many of the patients may still have children to look after. This can put an additional strain on their partner, but in addition can impact on the child. One of our patients described the affect her diagnosis of DLBCL had on her son- *"My eldest was starting his A levels and for the first year of his studies he struggled. He didn't even tell his friends about my diagnosis. He used school to escape from it. Now, almost as soon as I got the all clear, his grades have picked back up again."* Having both a high grade B cell lymphoma and children is also very difficult for the patient – *'….. and had to tell my 17- and 14-year-old that I now had cancer. I had to be strong for them, so they could see that if I was not going to let this beat me, or get me down, then they would be able to stay positive too."* These thoughts and feelings were also reflected by another patient – "*The children were also affected by my diagnosis and treatment, which coincided with GCSE and A level exams. I wasn't able to be there for them to support them practically or emotionally. They had to see me at my lowest ebb, and it must have been a frightening time. It brought us all closer together as a family, but it left its mark, particularly with health-related anxiety."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The most common treatment for people with DLBCL and other high grade B cell lymphomas is a regimen of chemo-immunotherapy. Most people are diagnosed at stage 3 or 4 and therefore require a longer and more intensive regimen which causes more side effects. If patients do unfortunately relapse, or do not respond to treatment, they would require a further course of treatment. This is often salvage chemotherapy and followed by, if well enough, a stem cell transplant. Even if the current treatment available works, the physical side effects can be hard and prolonged. This is obviously worse with multiple and increasingly intense treatment regimens. One patient said *"RCHOP treatment worked well for me but the physical effect on your body is hard."* Another patient described in detail the physical impact of chemotherapy – *"Overall, I tolerated the RCHOP regime very well, but I did experience very bad mouth ulcers, tiredness and some nausea. I also had collapsed veins which meant I had a PICC line for the last 2 cycles, which I hated. I suffered from steroid crashes, when the dose of prednisolone was dramatically reduced between treatments. I also had to give myself injections which I got used to eventually. The anti-sickness meds gave me bad constipation as well, which was very uncomfortable."* The intensity and impact of current chemoimmunotherapy regimens was echoed by another patient *"R-CODOX - M/IVAC was a very hard treatment. I had significant nausea and sickness and struggled to eat anything whilst in hospital. I survived on build-up milkshakes for several weeks. I had severe headaches following each of seven intrathecal chemo treatments; there was no treatment for these headaches, apart from lying flat on my back. They headaches lasted a week or more. During my treatment, life was completely on hold. I spent progressively more time in hospital, as when I was allowed home, I usually developed neutropenic fevers and was admitted back into hospital for 3 days or more of IV antibiotics regularly."* As well as the treatment having a physical impact on the body, we have found that there is also a mental impact caused by current treatment. Patients have described anxiety during the treatment as well as 'chemo brain' which can make day to day life difficult, *"one of the effects of treatment was chemo brain, so I found it extremely difficult to get back into my job."* Some patients may also have radiotherapy if they have localised symptoms due to the lymphoma. This also causes a number of difficult side effects for patients – *"it was decided that I would benefit from 15 sessions of radiotherapy to 'finish it off'. I was warned I may get very tired and suffer from a sore throat. I did not suffer from the tiredness at all; however, the sore throat began after the first week and continued for about 10 days. I could only eat soup and rice pudding as it was so swollen. I was prescribed some chalky liquid which contained anaesthetic to soothe it. My PET scan after r/therapy confirmed it had worked – Complete Metabolic Response. I*

	still suffer from the feeling like something is stuck in my throat but have been advised this could stay for a while due to the damage the radiotherapy will have done internally."
8. Is there an unmet need for patients with this condition?	Patients feel that there are multiple treatment options currently available, but a more targeted therapy in refractory or relapsed DLBCL/High grade B cell lymphoma with potentially fewer side effects would be beneficial. Having more viable treatment options available is also desirable to patients, one patient said – *"R-CHOP doesn't work for everyone and DLBCL can recur so it's important to have a range of second and third-line treatment options that are effective, widely available and well tolerated."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients we spoke to felt that more targeted therapies, with less physical impact would be advantageous especially if these could lead to less time in hospital. This technology would only take 30 minutes every 3 weeks which is substantially quicker than current chemoimmunotherapy regimens. This was one patient's experience – *"RCHOP is basically a long day of treatment with several drugs (plus a lot of medication to take afterwards). I was often the first and last person in the Chemo suite as RCHOP takes such a long time to receive via IV."* Having less time in treatment would also be easier financially and would have less of an impact on carers. One patient succinctly explained what advantages this could have – *"This kind of antibody treatment has great advantages compared to chemotherapy; it will be less invasive, quicker to administer and may be better tolerated. The impacts on quality of life are likely to be significant for patients and their families or carers."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	N/A

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.	Due to the intensity and side effects of the current treatment regimens available one person felt that those who are less likely to tolerate this would benefit more from this new targeted therapy – "*Those who cannot tolerate chemotherapy or who have other health conditions; those who have caring responsibilities. All patients would potentially benefit from a treatment that extends and improves their quality of life.*"

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Refractory or relapsed DLBCL can be very difficult to treat with limited treatment options. • The current treatments available have a significant physical and mental burden on patients and their carers. Having alternative treatment options for those patients unable to tolerate this would be welcomed. • High grade B cell lymphomas are aggressive and due to the variety in types can be difficult to treat, and often require intensive regimens. Having a new targeted therapy could significantly change this.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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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 select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? A specialist in the clinical evidence base for this condition or technology? Other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (after 2 or more lines of systemic therapy). The therapy cannot be regarded as curative and is to prevent disease progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinical or radiological response to treatment, ie reduction in clinical symptoms or reduction in disease volume on imaging, aim would be for at least 50% reduction, though any reduction that resulted in improvement of symptoms/quality of life would be acceptable.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, third line DLBCL is difficult to treat. CAR-T cell therapy is routinely commissioned. However, patients have to have a good performance status and prior full-dose anthracycline treatment to be considered for CAR-T cell therapy. In addition, patients need successful T-cell collection and remain clinically stable during cell manufacturing to undergo CAR-T treatment. The rapidity of progression of disease for some patients means that CAR-T cell therapy is not a viable option, and they require more urgent treatment. For some patients, the intensity of CAR-T treatment and delivery being restricted to allograft centres will be a barrier for considering CAR-T.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	With Car-T cell therapy, 3rd line or bi-specific antibodies within clinical trials or with chemotherapy. The alternative option would be palliative care.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are clinical guidelines for the management of relapsed/refractory DLBCL - the BSH guidelines are currently being updated. There is NHSE guidance and approval for the use of CAR-T cell therapy in UK.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care beyond 2 lines of therapy is not well-defined. This is because it depends on a number of factors, eg timing of relapse related to previous therapies, previous therapies that have been delivered, ability to tolerate further treatment, localisation of disease, co-morbidites, performance status, patient preference. Therefore, there are a number of options for R/R DLBCL and the treatment course chosen depends on the factors above.
9c. What impact would the technology have on the current pathway of care?	It would be an additional treatment option which would be beneficial for those patients not regarded suitable for CAR-T cell therapy or who have relapsed beyond CAR-T cell therapy, or are ineligible for, or have relapsed after, a clinical trial. This is also an alternative to other chemotherapy which is known to have limited effectiveness.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be a treatment option for R/R DLBCL.
10a. How does healthcare resource use differ between the technology and current care?	This is an intravenous outpatient therapy so has less impact on hospital resource then some other treatments for R/R DLBCL, eg CAR-T cell therapy which requires inpatient stay for a minimum of 10days and significant impact on resources during admission (20-30% patients require intensive care support).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	R/R DLBCL pts are managed in secondary care and this treatment would be delivered through haematology departments in secondary care.
10c. What investment is needed to introduce the	Training of administration of drug and familiarity with side effects of treatment but no specific equipment or facilities beyond a haematology department required.

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	For some patients with R/R DLBCL, this will be the best option as they cannot tolerate other treatments and for those patients that have relapsed after more intensive treatment, this provides a new treatment option for them.
11a. Do you expect the technology to increase length of life more than current care?	More than palliative care which could be the alternative option for these patients and possibly could increase the length of life beyond other chemotherapy treatments.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Quality of life should be improved if the disease responds to treatment and no significant side effects develop.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Will be used in those patients who are not eligible for CAR-T so generally less well patients. Or for those patients post CAR-T or bi-specific antibodies, where they are very limited treatment options.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Training of administration of drug and familiarity with side effects of treatment but no specific equipment or facilities beyond a haematology department required. (as in 10c above). Not beyond current care and likely easier.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would be stopped if evidence of progression clinically or radiologically or if intolerant/toxicity of treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is an additional treatment option, the impact will be on a small number of patients for likely a limited period of time but should ensure improved quality of life and increased life expectancy.
16a. Is the technology a 'step-change' in the	An additional treatment option rather than step change.

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, as limited treated options at this stage of disease.
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?	Side effects include fatigue, oedema, effusions, gastrointestinal upset, haematological toxicity, and cutaneous reactions. These may impact on the patient's quality of life but equally the side effects may be less than the symptoms of lymphoma.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate and toxicity which was measured in trial as described below.184 patients were assessed for eligibility and 145 (79%) were enrolled and received at least one dose of loncastuximab tesirine, including patients with high-risk characteristics for poor prognosis, such as double-hit, triple-hit, transformed, or primary refractory DLBCL. 70 of 145 patients had complete or partial response (overall response rate 48·3% [95% CI 39·9-56·7]); 35 had complete response and 35 had partial response. The most common grade 3 or higher treatment-emergent adverse events were neutropenia (37 [26%] of 145 patients), thrombocytopenia (26 [18%]), and increased gamma-glutamyltransferase (24 [17%]). Serious adverse events were reported in 57 (39%) of 145 patients. Treatment-emergent adverse events with a

	fatal outcome occurred in eight (6%) of 145 patients; none were considered related to loncastuximab tesirine. Caimi PF et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial Lancet Oncol. 2021;22(6):790-800
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA306 (pixantrone), TA649 (polatuzuman vedotin), TA559 (axicabtagene	Yes, there is now data on Glofitamab and Epcoritamab, bi-specific CD20 x CD3 T-cell engager antibodies. Glofitamab: Presented at the American Society of Haematology conference, Dec 2022 and simultaneously published in the New England Journal of Medicine 'Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma' (6). Of the 155 patients who were enrolled, 154 received at least one dose of any study treatment (obinutuzumab or glofitamab). At a median follow-up of 12.6 months, 39% (95% confidence

ciloleucel) and TA567 tisagenlecleucel?	interval [CI], 32 to 48) of the patients had a complete response according to independent review. Results were consistent among the 52 patients who had previously received chimeric antigen receptor T-cell therapy (35% of whom had a complete response). The median time to a complete response was 42 days (95% CI, 42 to 44). The majority (78%) of complete responses were ongoing at 12 months. The 12-month progression-free survival was 37% (95% CI, 28 to 46). Discontinuation of glofitamab due to adverse events occurred in 9% of the patients. The most common adverse event was cytokine release syndrome (in 63% of the patients). Adverse events of grade 3 or higher occurred in 62% of the patients, with grade 3 or higher cytokine release syndrome in 4% and grade 3 or higher neurologic events in 3%. Dickinson M. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Published December 2022, at NEJM.org. DOI: 10.1056/NEJMoa2206913 Epcoritamab: Results from the phase I/II, single-arm, multicentre, open-label, dose-escalation/dose-expansion EPCORE NHL-1 trial in patients with relapsed/refractory mature B-cell lymphoma. Of 157 treated patients after a median of 3 prior therapies, 38.9% had prior CAR-T therapy. At a median follow-up of 10.7 months, the overall response rate was 63.1%, with a complete response rate of 38.9%. The median duration of response was 12.0 months (among complete responders: not reached). The median PFS was 4.4 months (95% CI, 3.0 - 7.9). 61.1% of patients had grade 3+ AEs, deemed treatment-related in26.8% of patients. The most common treatment-related AEs were CRS (49.7%). Thieblemont C. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. Published December 2022, JCO. DOI: 10.1200/JCO.22.01725 Both to be submitted to NICE later this year for 3rd line DLBCL.
21. How do data on real-world experience	Comparable with similar side effects as reported.

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.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Potential treatment option for R/R DLBCL • Provides a new option for these patients who are difficult to treat • Outpatient treatment • Well tolerated

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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ID3943: Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies.

External Assessment Group (EAG) Report

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None

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Rider on responsibility for report

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Contributions of authors

Mandy Maredza and Henry Nwankwo (Health Economists) critiqued the cost-effectiveness evidence and undertook EAG's modelling. Lena Al-Khudairy (Associate Professor) and Adel Elfeky (Research Fellow) critiqued clinical effectiveness evidence. Xavier Armoiry (Honorary Clinical Research Fellow) supported the critique of the clinical effectiveness evidence. Rachel Court (Senior Information Specialist) critiqued the company's searches and conducted additional EAG searches. Daniel Gallacher (Assistant Professor) critiqued survival analysis in the company submission. Mandy Maredza coordinated the project and commented on draft versions of the report. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [redacted] are 'academic in confidence' and 'commercial in confidence' (CIC) [redacted]. Depersonalised Data (DPD) is highlighted in pink.

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Summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) for loncastuximab tesirine within its marketing authorisation (MA) for treating adults with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

All issues identified in **Table 1** represent the EAG's view, not the opinion of NICE.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Choice of parametric extrapolation for loncastuximab tesirine OS and PFS (Section 4.2.6)
- Choice of parametric extrapolation for Pola+BR OS and PFS (Sections 4.2.6)
- Extrapolation of chemotherapy overall survival (Section 4.2.6.2.1)
- Choice of parametric extrapolation for chemotherapy PFS (Section 4.2.6.2.2)
- Proportions of patients on subsequent therapy in chemotherapy arm (Section 4.2.8.1)
- Appropriate QALY weighting to adjust for severity (Section 4.2.9)

Table 1: Summary of key issues

ID3934	Summary of key issue	Report sections
Issue 1	**Concerns over the suitability of the MAIC analyses performed and presented** • The MAIC analyses offer little improvement over a naïve comparison in terms of accounting for differences due to lack of information available on the target studies and small sample sizes. Any estimates of effect size are unlikely to be solely attributable to the treatment received. • For Pola+BR comparison to GO29365, most MAIC inputs come from a wider trial population, not the desired 3L+ population. This comparison is based on crude methodology using median survival times, as no other information is available.	3.3.2 3.3.3 3.3.4 4.2.6

	• The Company has not performed requested MAIC analysis for Pola+BR comparison. The EAG is concerned with the company's rationale for the inclusion of patients and variables in the MAIC analysis.	
Issue 2	**Unsupported degree of OS benefit of loncastuximab tesirine over Pola+BR** Company OS extrapolations are too optimistic There is a lack of evidence from MAIC analyses to support the difference in effect for OS between loncastuximab tesirine and Pola+BR	3.3.2 3.3.3 4.2.6
Issue 3	**Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine** For comparison to Pola+BR, the company base case predicts a PFS benefit which is not supported by the indirect comparison	4.2.6
Issue 4	**Lack of information for a meaningful extrapolation for PFS of chemotherapy.**	4.2.6
Issue 5	**For chemotherapy comparison: Inconsistent application of two-stage adjustment to remove benefit of CAR-T therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses** Whilst two-stage adjustment is applied in cost-effectiveness analysis, this is not done in clinical sections. The EAG believes that applying two-stage adjustment prior to calculating hazard ratios and MAIC weights would reduce the relative benefit of loncastuximab tesirine as measured by a hazard ratio	4.2.6.2.2
Issue 6	**Rate of subsequent autoSCT therapy in chemotherapy arm** The EAG considers the proportions of patients in the chemotherapy arm who receive autoSCT as 4th line (subsequent therapy) highly uncertain, potentially high and unlikely to be reflective of proportions seen in clinical practice.	4.2.8.1
Other issues		
Issue 7	**Appropriate QALY weighting to adjust for severity** The company base case analysis for Pola+BR indicates that a severity weighting does not apply for this appraisal whilst the chemotherapy comparison proposes that a 1.2x QALY weighting is justified. The EAG believes the appropriate QALY weighting should be based on the analysis from a comparator treatment considered the most relevant for this appraisal	4.2.9
Issue 8	**Appropriateness of comparator treatments**	Table 4 and section 2.3

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section **Error! Reference source not found.** provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.2 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

The company's submission (CS) of the comparative clinical effectiveness, safety, and cost effectiveness of loncastuximab tesirine was obtained exclusively from a specific cohort from a Phase 2, multicentre, open-label, single-arm, international clinical study (LOTIS-2, NCT03589469). The primary outcome for the study was the proportion of patients whose best overall response was a complete response (CR), or partial response (PR) based on a central review in all-treated patients.

Therefore, this EAG report focuses on the cohort of patients in LOTIS-2 (n=145, 31 from the UK) with R/R DLBCL and HGBL who had at least two prior lines of systemic therapy and who were treated with single-agent loncastuximab tesirine. This cohort is directly related to the marketing authorisation (MA) obtained.

- We refer to participants and data related specifically to this cohort as LOTIS-2 throughout this report

A matched adjusted indirect comparison (MAIC) was performed to indirectly compare loncastuximab tesirine to polatuzumab vedotin combined with bendamustine + rituximab **(**Pola+-BR) and to chemotherapy (see Section 3.3.2 and 3.4). For the comparators outlined in the NICE Final Scope:

- **Polatuzumab vedotin combined with bendamustine + rituximab (Pola+BR)** (critique provided in Sections 3.3 and 3.4) The company conducted two separate MAIC analyses: (i) using data from the extension

study of GO29365 [1] and, (ii) using real-world evidence (RWE) from COTA US database.[2]

- **Chemotherapy** (critique provided in Section 3.3.4 and 3.4) the company used data from the CORAL extension study for the MAIC analysis.[3]

1.1 *Overview of the EAG's key issues*

All issues identified in **Table 2** represent the EAG's view, not the opinion of NICE.

Table 2: Summary of key issues

ID3934	Summary of key issue	Report sections
Issue 1	**Concerns over the suitability of the MAIC analyses performed and presented** • The MAIC analyses offer little improvement over a naïve comparison in terms of accounting for differences due to lack of information available on the target studies and small sample sizes. Any estimates of effect size are unlikely to be solely attributable to the treatment received. • For comparison to Pola+BR using GO29365, most MAIC inputs come from a wider trial population, not the desired 3L+ population. This comparison is based on crude methodology using median survival times, as no other information is available. • The company has not performed requested MAIC analysis for Pola+BR comparison. The EAG is concerned with the company's rationale for the inclusion of patients and variables in the MAIC analysis.	3.3.2 3.3.3 3.3.4 4.2.6
Issue 2	**Unsupported degree of OS benefit of loncastuximab tesirine over Pola+BR** Company OS extrapolations are too optimistic There is a lack of evidence from MAIC analyses to support the difference in effect for OS between loncastuximab tesirine and Pola+BR	3.3.2 3.3.3 4.2.6
Issue 3	**Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine** For comparison to Pola+BR, the company base case predicts a PFS benefit which is not supported by the indirect comparison	4.2.6

Issue 4	**Lack of information for a meaningful extrapolation for PFS of chemotherapy.**	4.2.6
Issue 5	**For chemotherapy comparison: Inconsistent application of two-stage adjustment to remove benefit of CAR-T therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses** Whilst two-stage adjustment is applied in cost-effectiveness analysis, this is not done in clinical sections. The EAG believes that applying two-stage adjustment prior to calculating hazard ratios and MAIC weights would reduce the relative benefit of loncastuximab tesirine as measured by a hazard ratio	4.2.6.2.2
Issue 6	**Rate of subsequent autoSCT therapy in chemotherapy arm** EAG considers that the proportions of patients in the chemotherapy arm who receive chemotherapy as 4th line (subsequent therapy) is too high and unlikely to be reflective of proportions seen in clinical practice.	4.2.8.1
Other issues		
Issue 7	**Appropriate QALY weighting to adjust for severity** The company base case analysis for Pola+BR indicates that a severity weighting does not apply for this appraisal whilst the chemotherapy comparison proposes that a 1.2x QALY weighting is justified. The EAG believes the appropriate QALY weighting should be based on the analysis from a comparator treatment considered the most relevant for this appraisal	4.2.9
Issue 8	**Appropriateness of comparator treatments**	Table 4 and section 2.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions include adjusting the proportion of patients on 4th line subsequent chemotherapy therapy and the method and choices of survival extrapolation:

- Choice of parametric extrapolation for loncastuximab tesirine OS and PFS (Section 4.2.6)
- Method of extrapolation for Pola+BR OS and PFS (Sections 4.2.6)
- Extrapolation of chemotherapy overall survival (Section 4.2.6.2.1)
- Choice of parametric extrapolation for chemotherapy PFS (Section 4.2.6.2.2)
- Proportions of patients on subsequent therapy in chemotherapy arm (Section 4.2.8.1)

1.2 *The decision problem: summary of the EAG's key issues*

The population is in line with the final scope issued by NICE, however, the EAG consider the comparators only partially appropriate. Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) received a positive recommendation for untreated DLBCL (with IPI score 2 to 5 and within the marketing authorization). This is dependent on the front-line uptake of Pola+R-CHP as this may substantially decrease the use of Pola+BR (mainly in an older, less fit group of patients). The key deviations are described in Table 4 and Issue 8.

1.3 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival and overall survival

Overall, the technology is modelled to affect costs by:

- Costs of primary therapy.
- Rates of subsequent treatment (autoSCT) following disease progression

The modelling assumptions that have the greatest effect on the ICER are:

- Choice of parametric model fit to PFS and OS data
- Assumption of survival benefit
- Rates of autoSCT subsequent therapy following disease progression

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

- The company conducted a reasonable systematic literature review (SLR) to identify evidence on the efficacy and safety of loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies (Section 3.1).

- The direct clinical evidence presented in the CS on the efficacy of loncastuximab tesirine comes from a single arm, open label trial (LOTIS-2). Findings are suggestive of a positive response to treatment with loncastuximab tesirine in heavily pre-treated patients with DLBCL. However, with no comparator group it is unclear what magnitude of benefit loncastuximab tesirine offers over established clinical management.

- The LOTIS-2 study included in this assessment is 145 patients. Of those, only 31 patients are from the UK. This small number of UK patients raises some concerns relating to the generalisability of the findings from this cohort.

Issue 1: Concerns over the suitability of the MAIC analyses performed and presented

Report section	**3.3.2, 3.3.3, 3.3.4, 4.2.6**
Description of issue and why the EAG has identified it as important	**Unsuitable ITCs** The MAIC analyses offer little improvement over a naïve comparison in terms of accounting for differences due to lack of information available on the target studies and small sample sizes. Any estimates of effect size are unlikely to be solely attributable to the treatment received. For Pola+BR comparison to GO29365, most MAIC inputs come from a wider trial population, not the desired 3L+ population. This comparison is based on crude methodology using median survival times, as no other information is available. The Company has not performed requested MAIC analysis for Pola+BR comparison. The EAG is concerned with the company's rationale for the inclusion of patients and variables in the MAIC analysis.
What alternative approach has the EAG suggested?	The EAG advises caution when interpreting the results and does not carry all estimates forward into the cost-effectiveness analysis.
What is the expected effect on the cost-effectiveness?	The EAG assumptions reduce the benefit associated with loncastuximab tesirine compared to Pola+BR.
What additional evidence or analyses might help to resolve this key issue?	Additional sensitivity analyses relating to the inclusion of patients that were originally excluded from previous MAIC analyses could reduce the EAG's concerns with the MAIC analyses for Pola+BR comparison.

Issue 2: Unsupported degree of OS benefit of loncastuximab tesirine over Pola+BR

Report section	3.3.2, 3.3.3, 4.2.6
Description of issue and why the EAG has identified it as important	**Overly optimistic extrapolations** The company's OS extrapolations indicate an OS benefit for loncastuximab tesirine over Pola+BR but there is a lack of evidence from MAIC analyses to support the magnitude of difference in effect
What alternative approach has the EAG suggested?	The EAG prefers to set the Pola+BR OS to be equal to that of loncastuximab tesirine
What is the expected effect on the cost-effectiveness estimates?	Minimal
What additional evidence or analyses might help to resolve this key issue?	Additional analyses as described in Key issue 1 might resolve the issue

Issue 3: Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine

Report section	4.2.6
Description of issue and why the EAG has identified it as important	**Loncastuximab PFS benefit modelled by company** For the comparison to Pola+BR, the company base case predicts a strong progression-free benefit for loncastuximab tesirine which is not supported by the indirect comparison, or EAG's clinical advisor's opinion.
What alternative approach has the EAG suggested?	The EAG has modelled using different parametric extrapolations, and set of assumptions which assume equivalence in PFS between the technologies
What is the expected effect on the cost-effectiveness estimates?	Loncastuximab is cost-saving (but not dominant).
What additional evidence or analyses might help to resolve this key issue?	Additional analyses as described in Key issue 1 might resolve the issue

Issue 4: Lack of information for a meaningful extrapolation for PFS of chemotherapy

Report section	4.2.6
Description of issue and why the EAG has identified it as important	**Chemotherapy PFS benefit modelled by company** There was no PFS data in Coral extension studies to allow an estimate of relative effect of loncastuximab over chemotherapy.
What alternative approach has the EAG suggested?	The EAG has been unable to offer an alternative approach.
What is the expected effect on the cost-effectiveness estimates?	Uncertain
What additional evidence or analyses might help to resolve this key issue?	Head-to-head trials or other epidemiological studies that have collected data on PFS in R/R DLBCL patients at 3+ treatment line.

Issue 5: For chemotherapy comparison: Inconsistent application of two-stage adjustment to remove benefit of CAR-T therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses

Report section	4.2.6
Description of issue and why the EAG has identified it as important	**Inconsistent application of two-stage adjustment** The two-stage adjustment has not been consistently applied across the clinical and cost-effectiveness analyses. Applying the two-stage adjustment prior to calculating hazard ratios and MAIC weights could reduce the relative benefit of loncastuximab tesirine as measured by a hazard ratio
What alternative approach has the EAG suggested?	The EAG has been unable to implement alternative approaches to the company.
What is the expected effect on the cost-effectiveness estimates?	Small, the current adjustment does not seem to have a big effect.
What additional evidence or analyses might help to resolve this key issue?	Applying the adjustment prior to the calculation of MAIC weights and using the results in the economic model.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

- The company's review of cost-effectiveness evidence was reasonable, but with some limitations as detailed in Section 4.1.

- The company submitted a simple *de novo* cost-utility model using partitioned survival with a weekly cycle length and a 40-year time horizon. See Section 4.2.2 for our critique.

The EAG's concerns regarding the MAIC analysis and subsequent extrapolations generate uncertainty in the results of cost-effectiveness analysis (see Sections 4.2.6 and 5).

Issue 6: Rate of subsequent autoSCT therapy in chemotherapy arm

Report section	4.2.8.1
Description of issue and why the EAG has identified it as important	**Rate of subsequent autoSCT applied in model** There is lack of information to inform the rate of subsequent autoSCT in chemotherapy arm. Estimates from previous appraisals based on clinical expert opinion) vary greatly and this introduces uncertainty in cost-effectiveness estimates.
What alternative approach has the EAG suggested?	The EAG has performed additional sensitivity analyses varying rate of subsequent autoSCT from 0% to 25% and assumed the same rate as loncastuximab tesirine in the EAG's base case assumptions.
What is the expected effect on the cost-effectiveness estimates?	Large increase
What additional evidence or analyses might help to resolve this key issue?	Studies or datasets that allow prospective or retrospective analysis of subsequent therapy options in R/R DLBCL patients treated with chemotherapy at 3rd line plus.

1.6 *Other key issues: summary of the EAG's view*

In addition to the key issues outlined in Sections 1.4 and 1.5 the EAG note the following two 'other issues'. The EAG acknowledge that issue 8 relates to future change in clinical practice and cannot be dealt with in current appraisal.

Issue 7: Severity weighting

Report section	4.2.9, 7
Description of issue and why the EAG has identified it as important	**Choice of severity modifier** The QALY weightings that would apply for this appraisal (based on absolute and proportional QALY shortfall/ severity) approach differ by comparator treatment. The choice of QALY weighting will impact on cost-effectiveness estimates
What alternative approach has the EAG suggested?	None. The EAG proposes that recommendation be based on comparator treatment that is considered the most relevant for this appraisal.
What is the expected effect on the cost-effectiveness estimates?	Large depending on QALY weighting chosen
What additional evidence or analyses might help to resolve this key issue?	None

Issue 8: Appropriateness of Pola+BR comparator

Report section	2.3
Description of issue and why the EAG has identified it as important	**Appropriateness of comparator (Recent approval of Pola+R-CHP)** Pola+R-CHP recently received positive NICE recommendation for the treatment of for untreated DLBCL and this may affect the uptake of Pola+BR (less uptake).
What alternative approach has the EAG suggested?	No alternative approach for the time being. Observe change in clinical practice and whether a reduction in the uptake of Pola+BR takes place.
What is the expected effect on the cost-effectiveness estimates?	Uncertain

What additional evidence or analyses might help to resolve this key issue?	This issue relates to future change in clinical practice as a result of recent positive NICE guidance.

1.7 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG preferred assumptions for each comparison are as follows (see Section 6.3):

Loncastuximab tesirine vs Chemotherapy

EAG 01: OS Loncastuximab data source changed from unweighted two-stage to CORAL weights two-stage to reflect the MAIC analysis undertaken on Loncastuximab population.

EAG 02: OS Loncastuximab distribution changed from Gamma to Log-normal given the uncertainty around the long-term extrapolation of OS.

EAG 03: PFS Loncastuximab data source changed from unweighted IRC to CORAL extension study weights to reflect the MAIC analysis undertaken and better align both populations.

EAG 04: TTD data source changed from unweighted to CORAL extension study weights.

EAG 05: Proportion of progressed cohort who receive AutoSCT changed from 22% to 3%.

Loncastuximab vs Pola+BR

In all scenarios, TTD was set equal to the PFS in line with the company's base case assumptions.

EAG 01: Loncastuximab OS extrapolation changed from generalised gamma to log-normal

EAG 02: Loncastuximab OS extrapolation changed from generalised gamma to log-normal

EAG 03: Pola+BR OS set equal to Loncastuximab OS (with a log-normal extrapolation for Loncastuximab OS)

EAG 04: Pola+BR PFS set equal to Loncastuximab PFS (with a log-normal extrapolation for Loncastuximab PFS).

Table 3 shows the impact of individual assumptions on the ICER.

Table 3: Impact of individual EAG's preferred model assumptions on ICER

Preferred assumptions	Incremental costs	Incremental QALYs	ICER
Loncastuximab vs Chemotherapy			
Company base case			**£48,986**
EAG 01: OS data source changed from unweighted two-stage to CORAL weights two-stage	[redacted]	[redacted]	£48,005
EAG 02: OS distribution changed from Gen Gamma to Lognormal	[redacted]	[redacted]	£70,337
EAG O3: PFS data source changed from unweighted IRC to CORAL extension study weights	[redacted]	[redacted]	£49,052
EAG 04: TTD changed from unweighted to CORAL extension study weights.	[redacted]	[redacted]	£44,490
EAG 05: AutoSCT subsequent therapy changed from 22% to 3%	[redacted]	[redacted]	£55,606
Loncastuximab vs Pola+BR			
Company base case			Pola+BR Dominated
EAG O1: Loncastuximab OS changed to log-normal	[redacted]	[redacted]	£154,225 (SW quadrant; Lonca cost-saving)
EAG 02: Loncastuximab PFS changed to log-normal	[redacted]	[redacted]	£359,367 (SW: quadrant - Loncastuximab Cost-saving)
EAG 03: Pola+BR OS set equal to Loncastuximab	[redacted]	[redacted]	Pola+BR Dominated
EAG 04: Pola+BR PFS set equal to Loncastuximab	[redacted]	[redacted]	£317,96 (SW: quadrant - Loncastuximab Cost-saving)

Further details of the exploratory and sensitivity analyses done by the EAG are provided in Section 6

Abbreviations

AE	Adverse events
ASCT	Autologous stem cell transplantation
BMI	Body mass index
BOR	Best overall response
BR	Bendamustine plus rituximab
BSA	Body surface area
BSH	British Society for Haematology
CAR T-cell	Chimeric antigen receptor T cells
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CRR	Complete response rate
CS	Company Submission
CSR	Clinical study report
DECC	Dexamethasone, etoposide, chlorambucil, lomustine
DH	Double hit
DHAP	Cisplatin, cytarabine, dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
EAG	External Assessment Group
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol five dimension
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
GCB	Germinal centre B-cell
GDP	Cisplatin, gemcitabine, dexamethasone
HGBL	High-grade B-cell lymphoma
HSCT	Haematopoietic stem cell transplantation
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health State Utility value
HTA	Health Technology Assessments
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental Cost-Effectiveness Ratios
IPI	International Prognostic Index
IQR	Interquartile range
IRC	independent review committee
IVE	Ifosfamide, epirubicin and etoposide
ITC	Indirect treatment comparisons

KM	Kaplan-Meier
Lonca	Loncastuximab tesirine
MAIC	Matching- adjusted indirect comparison
LY	Life Year
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OR	Odds ratio
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PEPC	Prednisone, etoposide, cyclophosphamide and procarbazine
PF	Progression-free
PFS	Progression-free survival
PICOS	Population, intervention, comparators, outcomes, and study design
PMBCL	Primary mediastinal B-cell lymphoma
Pola+BR	Polatuzumab plus bendamustine plus rituximab
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
R	Rituximab
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CHP	Rituximab, cyclophosphamide, doxorubicin and prednisolone
RCTs	Randomised controlled trials
RDI	Relative dose intensity
RFS	Relapse-free survival
R-GemOx	Rituximab with gemcitabine and oxaliplatin
R/R	Relapsed or refractory
RWE	Real-world evidence
SCT	Stem cell transplantation
SD	Standard deviation
SLR	Systematic literature review
STA	Single technology appraisal
SWB	Social/family well-being
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TH	Triple hit
TSD	Technical Support Document
TTD	Time to treatment discontinuation

UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

Remit of the appraisal

To appraise the clinical and cost effectiveness of Loncastuximab tesirine within its marketing authorisation for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies.

Condition, symptoms, and economic burden

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignant neoplasms originating in the lymphocyte cells of the immune system.[4] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL and accounts for an estimated 32.5% of NHL.[5]

In the United Kingdom (UK), the Haematological Malignancy Research Network (HMRN) estimates that there will be approximately 5,510 new cases of DLBCL each year.[6] Age is an important prognostic indicator as DLBCL is more prevalent in the elderly population, with a median age at diagnosis of 70 years and a slightly higher incidence in men.[7]

Approximately 25% of DLBCL patients are diagnosed with localized or limited stage disease and typically have a more favourable prognosis; approximately 75% of DLBCL patients present with advanced stage disease, commonly defined as Ann Arbor Stage III and IV or Stage I and II with associated B-symptoms or bulky disease (≥10 cm).[8] Other difficult-to-treat disease includes double/triple hit disease and patients who have been heavily treated with two or more lines of prior systemic therapy. Symptom presentation in DLBCL is variable and dependent on the site of disease involvement. Patients with DLBCL typically present with a rapidly enlarging mass, most commonly nodal enlargement in the neck or abdomen, but may also present as a mass lesion anywhere in the body. The most common extranodal sites are gastrointestinal tract, head and neck, and skin and soft tissue.

DLBCL is the costliest lymphoma to treat in Europe compared with Hodgkin's lymphoma and follicular lymphoma. The main cost drivers are hospitalisation costs, cancer-related drugs, outpatient medication and productivity loss.[9] A cost modelling study in a representative population-based patient cohort in the UK, estimated that the total cost associated with treating new patients with DLBCL over a one-year period, was approximately £88 to £92 million.[10] However, there are currently limited cost studies completed for treatments used in later lines.

In general, these large B-cell lymphomas are curable with first-line chemoimmunotherapy in most patients.[11] However, approximately 40% of patients have refractory disease or relapse after initially responding to first-line chemoimmunotherapy, and the prognosis for patients with relapse/refractory R/R DLBCL remains poor.[12] Despite subsequent therapy, prognosis is particularly poor for patients with R/R DLBCL after two or more lines of systemic treatment, due to the progressive nature of the disease and the cumulative adverse effects of intensive therapy, with a median overall survival (OS) ranging from only four to ten months.[3, 13, 14]

2.2 *Background*

Loncastuximab tesirine is a medication for cancer used to treat adults with R/R DLBCL and high-grade B-cell lymphoma (HGBL) after 2 or more systemic therapies.

Mechanism of action

Loncastuximab tesirine is a highly selective CD-19-targeted antibody drug conjugate (ADC), it is made up of monoclonal antibody combined with a cytotoxin.[15]. Loncastuximab tesirine is a monotherapy which is more easily accessible with a less burdensome dosing regimen compared with traditional chemotherapies and recently approved treatments.[16]

Treatment overview

There have been a number of treatments for R/R DLBCL patients approved in recent years, however, it remains an unmet medical need. First-line treatment for DLBCL is chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).[17, 18] Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) has recently been recommended by NICE for

untreated DLBCL in adults if they have an International Prognostic Index (IPI) score of 2 to 5.[19]

Approximately 30% to 40% of patients with DLBCL who receive first-line chemoimmunotherapy do not have long-term disease control. Of these patients, 10% to 15% exhibit primary refractory disease, with no response to initial treatment or relapse within three months of initial treatment.[8] Another 20% to 25% of patients experience relapse following a response to initial treatment, the majority of which occurs within the first two to three years after first-line chemoimmunotherapy.[8, 11]

Patients who are not fit for intensive therapy may receive Polatuzumab plus bendamustine plus rituximab (Pola+BR) or chemotherapy. Patients who are fit for intensive therapy may receive intensive salvage chemotherapy followed by autologous stem cell transplant (ASCT). However, approximately half of the patients who are candidates for this intensive approach do not respond to second-line chemoimmunotherapy and therefore are unable to proceed to ASCT.[20]

Patients who are transplant ineligible may receive Pola+BR in the second-line setting, which has been recommended by NICE, the European Society for Medical Oncology (ESMO) and the British Society for Haematology (BSH).[21, 22]

In the third-line setting, Pola+BR would be the main treatment option for patients. Additional therapies recommended by NICE in the third-line setting include chimeric antigen receptor T cells (CAR T-cell) therapies and pixantrone monotherapy.[23] Pixantrone monotherapy is currently recommended by NICE in the third- and fourth-line settings.[24] The company stated that ‘‘It has been confirmed in an advisory board meeting with clinical experts in the UK that pixantrone is no longer used in clinical practice.’’ The EAG clinical advisor confirmed that Pixantrone is clinically ineffective. Two CAR T-cell therapies are currently available. Axicabtagene ciloleucel (TA559) has recently been recommended by NICE for patients with R/R DLBCL or primary mediastinal large B-cell lymphoma who have had ≥2 lines of prior systemic therapy.[23] Tisagenlecleucel is also recommended for use via the Cancer Drugs Fund (CDF) if patients are healthy enough to undergo the treatment and have previously received two or more systemic therapies.[25].

Position of the technology in the pathway

The CS states that “Loncastuximab tesirine is anticipated to be used as a third-line treatment for CAR-T ineligible patients with R/R DLBCL, and as a fourth-line treatment for patients relapsing after CAR-T therapy”. The EAG clinical advisor agree with this statement and believes that older patients with underlying co-morbidities may benefit from this treatment.

2.3 *Critique of company’s definition of decision problem*

The population is in line with the final scope issued by NICE, however, the EAG consider the comparators only partially appropriate. The recent (March 2023) decision by NICE [26] may change clinical practice. Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) received a positive recommendation for untreated DLBCL (with IPI score 2 to 5 and within the marketing authorization). This is dependent on the front-line uptake of Pola+R-CHP as this may substantially decrease the use of Pola+BR (mainly in an older, less fit group of patients). The key deviations are described in **Table 4**.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma who have had two or more systemic therapies	Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.	Aligned with marketing authorisation the submission addresses adults with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy.	The target population is similar to the NICE scope. However, the evidence submitted includes a very small number of UK patients therefore generalisability may not be applicable.
Intervention	Loncastuximab tesirine	Aligned with scope	Not applicable	Matches the NICE scope
Comparator**(s)**	Established clinical management which may include: Chemotherapy, such as: DHAP (cisplatin, cytarabine, dexamethasone) GDP (cisplatin, gemcitabine, dexamethasone) ICE (ifosfamide, carboplatin, etoposide) IVE (ifosfamide, epirubicin and etoposide) R-GemOx (rituximab, gemcitabine oxaliplatin) BR (bendamustine, rituximab) polatuzumab vedotin with rituximab and bendamustine (if haematopoietic stem cell transplantation is not possible) pixantrone axicabtagene ciloleucel (subject to NICE evaluation) tafasitamab with lenalidomide (if haematopoietic stem cell	Established clinical management which may include: Chemotherapy, such as: DHAP (cisplatin, cytarabine, dexamethasone) GDP (cisplatin, gemcitabine, dexamethasone) ICE (ifosfamide, carboplatin, etoposide) IVE (ifosfamide, epirubicin and etoposide) R-GemOx (rituximab + gemcitabine + oxaliplatin BR (bendamustine and rituximab) polatuzumab vedotin with rituximab and bendamustine (if haematopoietic stem cell transplantation is not possible)	Clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients who are not eligible for HSCT or CAR-T therapy. In the third-line setting, Pola+BR would be the main treatment option for patients. It is recognised that chemotherapy is also an option within this position in the treatment pathway, albeit less utilised due to its lower efficacy. The Company sought clinical opinion on which chemotherapy regimens were most widely used at third-line in R/R DLBCL. The clinicians stated that DHAP, ICE and IVE would not be used at this line as they are considered too toxic. The most commonly mentioned regimen was RGemOX, whereas (R)GDP, DECC, PEPC, gemcitabine monotherapy and R+lenalidomide were also considered as options at third-line-plus.	The EAG clinical advisor believes that Pola+BR is a suitable comparator. However, given the recent (March 2023) decision by NICE [26] may change clinical practice. Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) received a positive recommendation for untreated DLBCL (with IPI score 2 to 5 and within the marketing authorization). This is dependent on the front-line uptake of Pola+R-CHP as this may substantially decrease the use of Pola+BR (mainly in an older, less fit group of patients). The EAG clinical advisor agrees with toxicity associated with the use of DHAP, GDP, ICE and IVE. These treatments are substantially more toxic and require a fitter and younger group of patients.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	transplantation is not possible, subject to NICE evaluation)		While additional therapies are recommended by NICE in the third-line setting including a CAR T-cell therapy (axicabtagene ciloleucel) [27] and pixantrone monotherapy,[24] they have not been included as comparators in the model. Approximately 17.2% of DLBCL patients who receive ≥3 prior lines of treatment are treated with CAR T-cell therapy due to its severe treatment burden and most patients have a rapid clinical disease course rendering them unsuitable for the treatment.[28] Clinical input has indicated that the most likely position for loncastuximab tesirine in clinical practice would be in patients that are not eligible for transplant or CAR-T therapy (Sobi 2023 document 'Data on File: Clinical Interviews, Summary Report', provided with the CS). As such, CAR-T therapies are not considered as comparators in the submission. Pixantrone has not been included as a comparator. Previous appraisals of interventions for R/R DLBCL including TA559,[23] TA567,[25] TA649 [19] and GID-TA10645 [29] removed pixantrone as a comparator either at the scoping stage or through the committee process. The respective committees were informed by clinical experts that pixantrone is rarely used in the UK; therefore, they concluded in each case	With regards to tafasitamab, a guidance issued on May 2023 has concluded that this agent combined with lenalidomide is not recommended within its marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have an autologous stem cell transplant (TA883).[29]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			that it was not a relevant comparator. The clinicians interviewed to inform this submission further confirmed that pixantrone is not used in clinical practice (Sobi 2023 document 'Data on File: Clinical Interviews, Summary Report', provided with the CS), and also noted the exclusion of pixantrone as a treatment option for patients with R/R DLBCL in the BSH guidelines.[22] At the time of submission, tafasitamab with lenalidomide (if haematopoietic stem cell transplantation is not possible) is still subject to NICE evaluation with the final outcome pending).	
Outcomes	The outcome measures to be considered include: overall survival progression-free survival response rates adverse effects of treatment health-related quality of life.	The outcome measures to be considered in the submission include: overall survival progression-free survival response rates adverse effects of treatment health-related quality of life. Other outcomes collected in the trial included and these data are also presented in the submission (see CS Section B.2.3.6).	The listed outcome measures are as per final scope issued by NICE	The outcomes match the NICE scope and the trial evidence included additional secondary outcomes: duration of response, relapse-free survival and changes from baseline of safety laboratory variables, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for	As per the NICE reference case the cost-effectiveness of loncastuximab tesirine is expressed in terms of incremental costs per QALY, and costs have been considered	In line with final scope.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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.	from the perspective of the NHS and PSS.		
Subgroups to be considered	Not applicable. No subgroups specified in scope.	Subgroup data are provided in Section 0.	Not applicable; no subgroups specified in final scope	
Special considerations including issues related to equity or equality	Not applicable. No special considerations specified in scope.	No equality issues related to the use of loncastuximab tesirine in patients with R/R DLBCL have been identified.	Not applicable; no special considerations noted in final scope	

Source: NICE Final Scope [30]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DECC, dexamethasone, etoposide, chlorambucil, lomustine; DHAP, cisplatin, cytarabine, dexamethasone; DLBCL, diffuse large B-cell lymphoma; GDP, cisplatin, gemcitabine, dexamethasone; HGBL, high-grade B-cell lymphoma; HSCT, haematopoietic stem cell transplantation; ICE, ifosfamide, carboplatin, etoposide; IVE, ifosfamide, epirubicin and etoposide; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; Pola+BR, polatuzumab plus bendamustine plus rituximab ; PSS, personal social services; QALY, quality-adjusted life year; R, rituximab; RGemOX, rituximab with gemcitabine and oxaliplatin; TA, technology appraisal

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

The company conducted a systematic literature review (SLR) to identify all relevant clinical evidence on the efficacy and safety of loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies. Detailed descriptions of the methods and findings of the review can be found in Appendix D of the CS, although a pre-defined protocol was neither mentioned nor supplied. Randomised controlled trials (RCTs), non-randomised clinical studies and real-world observational studies were all eligible.

A total of 59 publications related to 45 unique studies were initially included in the review. As the inclusion criteria for the review were set much broader than the NICE scope for this appraisal, some of the identified studies evaluated treatments not listed in the scope, and/or included patients with mixed types of lymphoma and various lines of prior therapy.

Of the total included studies, a total of six publications reporting two studies (LOTIS-1 and LOTIS-2 pooled analysis and LOTIS-2) were identified that evaluated loncastuximab tesirine for the treatment of patients with DLBCL who have received two or more prior therapies. Of the 45 studies included in the SLR, only two studies (reported in six publications) were relevant for the indirect treatment comparisons (LOTIS-2 and GO29365 extension cohort). Due to the sparsity of relevant comparator data, consideration was given to how additional, relevant comparator data could be identified (see Appendix D (Section D2.2) for full description of the approach taken). This process led to the inclusion of an additional two studies reported in three publications.

The review processes were clearly described for screening, full-text assessment, data extraction and quality assessment. Screening and full text assessment of potentially eligible studies were carried out by two independent reviewers against the selection criteria. Data from the included studies were extracted by one reviewer into standardised, piloted data extraction tables and validated by conducting an independent internal data check. The EAG full assessment of risk of bias in the CS systematic review of clinical effectiveness using ROBIS tool [31] is in Appendix 1.

3.1.1 Search strategies

Searches in four appropriate bibliographic databases were undertaken on 25/10/2022 and full details of these searches are provided in the CS. The CS reports that database search strings were peer reviewed by an independent information specialist using a recognised checklist and suggested changes acted upon. A variety of terms, including those for population and stage of treatment / line of therapy, plus intervention / comparators and study types, were included, resulting in a sensitive search. In addition to database searches, the CS states that reference lists of relevant SLRs and HTA documents were screened, and reference details of these documents have been provided in response to our clarification questions. Additionally, searches of 7 relevant conference proceedings between 2019 and 2022, clinical trial registries, 12 HTA agencies and three other grey literature sources were reported as undertaken. Full details of these grey literature searches are not given in the CS, but details of the search keywords used to find those excluded are in the list of excluded studies from hand-searching provided in response to clarification questions.

3.1.2 Inclusion criteria and selection process

The eligibility criteria were defined according to population, intervention, comparators, outcomes, and study design (PICOS) framework (CS Appendix D, Table 5, page 24-26). The company provided a graphical display of the study selection process using a PRISMA flow diagram (CS Appendix D, page 16). Full-text articles were screened by two independent reviewers against the selection criteria and disagreements were resolved with a third, more senior reviewer.

- Non-English studies were excluded, and this may lead to an increased risk of bias or missing key evidence.

3.1.3 Critique of data extraction

Data from the included publications were extracted by one reviewer into standardised data extraction tables. Extracted data were checked and validated through an independent internal data check once all required data had been entered.

3.1.4 Quality assessment

Quality assessment of included studies was performed using the Cochrane RoB2 tool for RCTs [32] and the ROBINS-I tool for comparative cohort studies.[33] The company did not assess the risk of bias for the LOTIS-2 trial. The EAG used the Downs and Black checklist to rate the risk of bias in the LOTIS-2 study.[34] The EAG full assessment of risk of bias for the LOTIS-2 trial is in Appendix 2.

- Several domains of the quality assessment tool were not accessible. However, the EAG deemed the study to provide low level of evidence to support the efficacy.

3.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

Evidence on loncastuximab tesirine for the treatment of DLBCL included in the CS, was obtained exclusively from a specific cohort from a Phase 2, multicentre, open-label, single-arm, international clinical study (LOTIS-2, NCT03589469). A brief description of the overall study design for LOTIS-2 (which included a screening period [up to 28 days], a treatment period [cycles of three weeks] up to one year, and a follow-up period [visits approximately every 12 weeks for up to three years after treatment discontinuation] and patients with R/R DLBCL [including HGBL] who do not respond to or who have progressive disease after salvage therapies who have a poor prognosis) can be found in the CS Sections B.2.3.1.

The current assessment focuses on the cohort of patients with R/R DLBCL who had at least two prior lines of systemic therapy and who were treated with single-agent loncastuximab tesirine. We refer to participants and data related specifically to this cohort as LOTIS-2 in this report.

3.2.1 Critique of methods for LOTIS-2

Details of methods for LOTIS-2 can be found in CS Sections B.2.3 and B.2.4.

The key inclusion criteria for LOTIS-2 were:

• Adult patients with a pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification who had relapsed after or failed to respond to at least two prior lines of systemic therapy.

• Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

• Patients who received previous CD19-directed therapy were required to have a biopsy that showed CD19 protein expression after completion of the CD19-directed therapy

Differences in the inclusion criteria between LOTIS-2 and comparator studies with respect to the above items are key issues that need to be considered in the appraisal of indirect treatment comparisons (ITCs), which is detailed in Section 3.3 of this report. We highlight below some of issues related to study methods that may have implications for the interpretation of findings from LOTIS-2 and for the comparison with other studies.

Definition and assessment of treatment response

The primary outcome for the study was the proportion of patients whose best overall response was a complete response (CR) or partial response (PR) based on a central review in all-treated patients. Data on treatment response assessed by individual investigator were also presented in the CS. Treatment response was measured using the 2014 Lugano classification.[35] While this is well-accepted and widely used, different assessment criteria was used in some of the comparator studies (COTA US real-world evidence and CORAL extensions studies) used in the company's indirect treatment comparisons (ITCs).

- Different assessment criteria have implications for the comparability of outcomes related to treatment response rates and duration of response between studies and increases the uncertainty regarding the validity of relevant ITCs.

Sample size

The sample size was determined based on the assumption that loncastuximab tesirine would provide an ORR of at least 20% among patients with R/R DLBCL observed in a single-arm study.[16]

- Smaller sample sizes are usually observed in phase 2 studies for cancer therapies.

3.2.2 Characteristics of LOTIS-2 study participants

The LOTIS-2 study included 145 patients. Baseline characteristics of these patients are described in CS Table 9 (p.43-44). An issue worth highlighting is that most patients in LOTIS-2 were recruited from hospital sites in the USA (n=59 [41%]).

- Only 21% (n=31) of study population were enrolled at UK sites, and this may raise some concerns relating to the generalisability of the findings from this cohort.

3.2.3 Treatment outcomes of the LOTIS-2 cohort

The planned primary analysis for LOTIS-2 was based on a data-cut in April 2020. Findings from the study included in the CS were primarily based on a data-cut in April 2020. The company provided further findings based on two subsequent data cuts (1 March 2021 and 1 March 2022), but data were not available for all outcomes as outlined in **Table 5**. Limited data from the final data cut (15 September 2022) are available in **Table 5**. The CS stated that data from this data cut are currently available as a conference abstract [36] with the clinical study report (CSR) anticipated in Q3/Q4 2023. The company clarified during factual accuracy check (FAC) that the final CSR (LOTIS 2, Sept 2022 data cut), is now available. The EAG are yet to receive the data file.

Follow-up of patients for the study is planned to continue until [redacted].

Key effectiveness outcomes from LOTIS-2 are shown in **Table 6** below. Based on the April 2020 data-cut, the ORR was 48%; best overall response (BOR) was 24% with CR and 24% with PR as assessed by independent review committee (IRC). The BOR of stable disease (SD) was 15%. In both the 1 March 2021 and the 1 March 2022 data cut, in the all-treated population, the ORR was 48%. BORs were 25% with CR and 23% with PR. The BOR of stable disease was 15%.

The CS also presented treatment responses as assessed by investigators. The EAG notes that these figures are similar to the independent review committee IRC assessment.

- There is very little difference in effectiveness findings between the April 2020, March 2021 and March 2022 data-cuts.

Table 5: Outcome data available for each data cut

Data cut-off:	6 April 2020	1 March 2021	1 March 2022	September 2022†
ORR independent review	✓	✓	✓	✓†
ORR investigator assessed	✓	NA	NA	NA†
CRR	✓	✓	✓	✓†
DoR	✓	✓	✓	✓†
RFS	✓	Not reached	NA	NA†
PFS	✓	✓	✓¶	✓†
OS	✓	✓	✓¶	✓†
PRO/HRQoL	✓	NA	NA	NA†
Safety	✓	✓	NA	✓†
Subgroup analyses	✓	✓ǂ	NA	NA†

†Limited data available for submission (abstract level detail), CSR available Q3/Q4 2023; ǂSubgroup data for some outcomes refer to Appendix E; ¶Individual patient data only available for these outcomes.
Abbreviations: CRR, complete response rate; DoR, duration of response; HRQoL, health-related quality of life; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PRO, patient reported outcome; RFS, relapse free survival

Table 6: Key effectiveness outcomes from LOTIS-2 (n=145)

Outcome	Data-cut: 6 April 2020	Data-cut 1 March 2021	1 March 2022	September 2022
Duration of follow-up, months				
Treatment overall response rate as assessed by independent review committee (IRC)				
Complete response (CR)	24% (17% to 32%)	25% (CI not reported)	25 (18% to 33%)	25% (CI not reported)
Partial response (PR)	24%	23%	23%	23%
Stable disease (SD)	15%	15%	15%	NR
Not evaluable	16%	16%	16%	NR
Progressive disease (PD)	21%	21%	21%	NR
Overall response rate	48% (40% to 57%)	48% (40% to 57%)	48% (40% to 57%)	48%
Duration of response (DOR), median, months	10.25 months (95% CI: 6.87 to NE)	13.37 months (95% CI: 6.87 to NE).	13.37 months (95% CI: 6.87 to NE)	13.4 months (95% CI: 6.9 to NE)
Treatment overall response rate as per investigator assessment				
Complete response	25% (18.0% to 33%)	NR	NR	NR
Partial response	25%	NR	NR	NR

Outcome	Data-cut: 6 April 2020	Data-cut 1 March 2021	1 March 2022	September 2022
Stable disease	14%	NR	NR	NR
Not evaluable	3%	NR	NR	NR
Progressive disease	34%	NR	NR	NR
Overall response rate	50% (41% to 58%)	NR	NR	NR
Survival				
Relapse-free survival (RFS), median, months	13.37 months (95% CI: 10.25, to NE)	The median RFS was not reached.	No data for RFS were available	No data for RFS were available
Progression-free survival (PFS), median, months	4.93 months (95% CI: 2.89, 8.31)	4.93 months (95% CI: 2.89, 8.31)	No data were available	4.93 months (95% CI: 2.89, 8.31).
Overall survival (OS), median, months	9.92 months (95% CI: 6.74, 11.47)	9.53 months (95% CI: 6.93, 11.47)	No OS data were available	9.5 months (95% CI: 6.7 to 11.5) [36]

Data source: CS Section B.2.6; the percentages have been rounded up to whole numbers as EAG considers the decimal place unnecessary given the relatively small sample size (n=145). Numbers shown in brackets are 95% confidence intervals unless otherwise stated.

IRC: independent review committee; CI, confidence interval; CR, complete response; NR, not reported; ORR, overall response rate; PR, partial response. NE: not estimable; OS: overall survival; RFS: relapse free survival; PFS: progression free survival

The EAG notes that the clinical effectiveness outcomes from LOTIS-2 were reported over a reasonable time frame and are suggestive of positive response to treatment with loncastuximab tesirine in heavily pre-treated patients with DLBCL. Findings were similar between the April 2020, March 2021 and March 2022 data-cuts. However, with no comparator group it is unclear what magnitude of benefit loncastuximab tesirine offers over established clinical management. This is discussed in more detail in Section 3.3 (indirect treatment comparison).

HRQoL

The patient-reported outcomes (PRO)/ health-related quality of life assessments (HRQoL) were assessed using the EQ-5D-5L and FACT-Lym questionnaires in the PRO population (n=130).

Around 97% of patients in the all-treated population completed the baseline EQ-5D-5L assessment. The mean (SD) EQ-5D-5L visual analogue scale (VAS) score was 71.4 (19.1) at baseline. When averaging the change from baseline scores for each patient across visits during the course of treatment, more patients showed improvement by at least seven points (27.9%) than deterioration by at least seven points (20.7%) and approximately half of the patients (51.4%) remained stable (1 March 2021). No data were available from 1 March 2022 data cut or final data cut (15 September 2022) for the EQ-5D-5L outcome.

Mean changes in all FACT-Lym subscale and composite scores were generally stable over time. FACT-Lym subscales that showed an improvement from baseline over time were emotional well-being (except Cycle 15 Day 1) and lymphoma subscale (except Cycle 15 Day 1). The subscales of psychological well-being and functional well-being (except Cycle 15 Day 1) were relatively stable from baseline over time and the subscale of social/family well-being showed a deterioration from baseline over time (1 March 2021 data cut). No data were available from 1 March 2022 data cut or final data cut (15 September 2022) for the FACT-Lym outcome.

Treatment-emergent adverse events (TEAEs) reported in LOTIS-2

Treatment-emergent adverse events (TEAEs) reported in LOTIS-2 are presented in Table 4. Of the 145 patients in the all-treated population, 143 patients (98.6%) had at least one TEAE; 117 patients (80.7%) had at least one TEAE related to loncastuximab tesirine; and 105 patients (72.4%) had at least one TEAE of Grade ≥3. Fifty-seven patients (39.3%) had at least one serious TEAE; eight patients (5.5%) had a TEAE leading to a fatal outcome; and 34 patients (23.4%) had a TEAE leading to withdrawal of treatment. Seven patients (4.8%) had an infusion-related reaction (6 April 2020 data cut).

Data from the 1 March 2021 data cut were consistent with earlier data from the 6 April 2020 data cut (**Table 7**).

As of the final data cut off (15 September 2022), all-grade TEAEs occurring in ≥30% of all patients were increased gamma-glutamyl transferase (42%), neutropenia (40%), and thrombocytopenia (33%).

Table 7: Overall summary of TEAEs (all-treated population)

Data cut	6 April 2020	1 March 2021
Population	**All-treated population (N=145)**	**All-treated population (N=145)**
Number of TEAEs	1761	N/A
Death during study	53.1%	N/A
Any TEAE	98.6%	98.6%
Grade 3 or higher TEAE	72.4%	73.8%
TEAE related to lonca	80.7%	81.4%
TEAE leading to lonca dose delay or reduction	51.7%	51.7%
TEAE leading to lonca withdrawal	23.4%	24.8%
Any serious TEAE	39.3%	39.3%
Any TEAE with fatal outcome	5.5%	5.5%
Patients with infusion-related reaction	4.8%	N/A

Subgroup analysis

Outcomes on ORR, DOR and survival between the overall cohort and subgroups with high-risk disease characteristics were consistent.[16] In patients who relapsed after CAR T-cell therapy, representing a difficult to treat patient population, subgroup analyses indicated a similar response (ORR of 46.2%) to loncastuximab tesirine compared to the overall cohort.[37] Outcomes among patients who received three or >3 prior lines of therapy were also consistent with those from the overall cohort; ORR in these subgroups were 48.6% and 48.9%, respectively (data cut 6 April 2020).[16]

A subgroup analysis was performed on frail patients from LOTIS-2 with age ≥75 years or with ECOG performance status (PS)=2 who did not receive CAR-T prior to nor after treatment with loncastuximab tesirine. The efficacy was [redacted] with a median DOR [redacted]. The median PFS was [redacted] and the median OS was [redacted] (data cut 6 April 2020, supplied in three documents with the CS - Sobi 'ADCT-402-201 Statistical Analysis Plan Final v2 (02 Mar 2020)', 'ADCT-402-201 Clinical Study Report 7 Aug 2020', and 'DataOnFile-Sobi-Zynlonta 2022_Appendix_TLFs').

Data from subgroup analyses of primary and key secondary outcomes (data cuts 6 April 2020 and 1 March 2021) are reported in Appendix E. No subgroup data were available for data cuts 1 March 2022 or the final data cut (15 September 2022).

3.3 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

3.3.1 Indirect comparison introduction

As no head-to-head evidence was available, the company was reliant on indirect treatment comparisons to assess the relative benefit of loncastuximab tesirine. As the company only had patient data from the single arm LOTIS-2 trial, the CS implemented matching adjusted indirect comparisons (MAIC) to generate weighted populations from LOTIS-2 that matched the available summary characteristics of the populations from the comparator studies. Baseline characteristics for studies included in the MAIC analyses are presented in **Table 8**. The MAIC analyses allowed comparison of PFS, OS and ORR outcomes.

An overview of the variables included is shown in

Table 9. Prior to conducting the MAIC, the company established a set of preferred variables following dialogue with their clinical experts which would capture the main prognostic and treatment-effect modifying variables. These variables were not all available for the targeted studies, and if the International Prognostic Index (IPI) stage variable was available, the company originally preferred not to include the variables age, Ann Arbor or ECOG as these are included in the calculation of IPI.

The EAG is not supportive of this rationale to exclude these variables if IPI stage is available, as the aim of the MAIC is to match the populations as closely as possible. Hence the EAG requested additional analyses including these variables for the relevant comparisons. This led the company to alter their preferred MAIC analysis.

Across the company's originally preferred analyses, only three to four variables are matched meaning it is unlikely that the resulting populations can be considered comparable with so few variables included and so many key variables unable to be matched, even if those that are used in the matching are well balanced. It's possible that these comparisons offer little benefit over completely naïve comparisons that do not adjust for any covariates. The evidence produced from these comparisons is unlikely to represent the true relative efficacy of loncastuximab tesirine.

Table 8: **Comparison of baseline characteristics (LOTIS-2 vs comparator studies)**

Characteristic	**Description**	**LOTIS-2 (N=145) Loncastuximab tesirine**	**GO29365 extension study (N=152)† Pola+BR**	**Hamadani 2022 (N=43) Pola+BR**	**CORAL extension studies (N=278) Chemotherapy**
Age	-	Median (IQR) [range]: 66 (56, 71) [23, 94]	69 [Range: 24, 94]	65 (IQR 56, 74)	Mean / median: NR [Range: 19.0, 67.7]
Gender, n (%)	Male	85 (59)	84 (55)	26 (60)	175 (63.0)
Histology, n (%)	DLBCL, not o/w specified HGBL PMBCL Unknown	127 (88) 11 (8) 7 (5) 0 (0)	142 (95) 5 (3) 0 (0) 3 (2)	NR 5 (12) NR NR	NR
GCB or ABC DLBCL, n (%)	GCB ABC Unknown	48 (33) 23 (16) 74 (51)	58 (39) 73 (49) 0 (0)	NR	64 (23.0) Non-GCB: 82 (29.5)

Characteristic	Description	LOTIS-2 (N=145) Loncastuximab tesirine	GO29365 extension study (N=152)† Pola+BR	Hamadani 2022 (N=43) Pola+BR	CORAL extension studies (N=278) Chemotherapy
					132 (47.5)
Double-hit or triple-hit DLBCL, n (%)	-	15 (10)	NR	NR	3 (1.1)
Double-expressor or triple-expressor DLBCL, n (%)	-	20 (14)	NR	NR	2 (0.7)
Bulky disease, n (%)	Yes No	8 (6) 137 (94)	39 (26)‡ NR	NR	NR
Transformed DLBCL, n (%)	-	29 (20)	NR	NR	NR
Disease stage, n (%)	I-II III-IV	33 (23) 112 (77)	NR 122 (80)	NR	NR
ECOG PS, n (%)	0 1 2 NR	58 (40) 78 (54) 9 (6) 0 (0)	44 (29) 87 (57) 20 (13) 1 (1)	NR	NR
IPI score, n (%)	≤2 >2	[redacted]	NR 94 (62)	NR	170 (61) 108 (39)
Previous systemic therapy	Median (IQR) lines, n (%) lines, n (%) 3+ lines, n (%)	3.0 (2.0, 4.0) 63 (43) 35 (24) 47 (32)	2.0 (1.0, 7.0) 50 (33) 42 (28) 60 (39) (≥3) NR	NR 0 (0) 32 (74) 5 (12) 6 (14)	NR
Response to 1st line, n (%)	Relapse Refractory Other	99 (68) 29 (20)¶ 17 (12)	NR 97 (64)§ NR	NR	NR
Response to most recent line of systemic therapy, n (%)	Relapse Refractory Other	43 (30) 84 (58)¶ 18 (12)	NR 116 (76)§ NR	NR	NR
Refractory to all previous therapies, n (%)	Yes No Other	25 (17) 115 (79) 5 (3)	NR	NR	NR
Relapse within 3 months of first-line therapy, n (%)	Yes No	35 (24) 110 (76)	NR	NR	NR

Characteristic	Description	LOTIS-2 (N=145) Loncastuximab tesirine	GO29365 extension study (N=152)† Pola+BR	Hamadani 2022 (N=43) Pola+BR	CORAL extension studies (N=278) Chemotherapy
Relapse within 6 months of first-line therapy, n (%)	Yes No	57 (39) 88 (61)	NR	NR	NR
Previous HSCT, n (%)	Allogeneic Autologous Both	(1) 21 (14) 1 (1)	27 (18) 125 (82)	NR	NR 75 (26.9) NR
Previous CAR T-cell therapy, n (%)	Yes No	13 (9) 132 (91)	1 (1) 151 (99)	NR	NR

†Baseline characteristics only reported for second- or later-line patients, not the third- or later-line subgroup
‡ Unclear if bulky disease definition matches that in LOTIS-2
¶Defined as no response
§Defined as no response or progression or relapse within 6 months of first antilymphoma therapy end date. Definitions for LOTIS-2 and GO29365 differ
Abbreviations: ABC, activated B-cell; CAR T, Chimeric antigen receptor T; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell; HGBL, high grade B-cell lymphoma; HSCT, haematopoietic stem-cell transplantation; IPI, International Prognostic Index; IQR, interquartile range; NR, not reported; o/w, otherwise; PMBCL, primary mediastinal large B-cell lymphoma.

Table 9: Overview of variables included in company MAICs

Comparator	Polatuzumab BR Trial (original)	Polatuzumab BR Trial (post clarification)	Polatuzumab BR RWE	Chemotherapy RWE
Source	GO29365 extension study	GO29365 extension study	COTA US	CORAL extension study
	Priority Variables Included in MAIC			
Refractory to 1st line	Yes	Yes		
Prior Lines of therapy	Yes	Yes	Yes	
Refractory to prev' therapy	No*	No*		
IPI	Yes	No		Yes
Age	No	Yes	Yes	
Ann Arbor stage	No	Yes		
ECOG	No	Yes		
HGBL	Yes	Yes	Yes	
Double/triple hit				
Transformed				
Cell of origin				
	Additional Variables included in MAIC			
Sex	No	Yes	Yes	Yes
Prior ASCT				Yes

* indicates definition differed between studies, blank cell indicates variable was not reported by target study

3.3.2 Indirect comparison – Pola+BR 1

The company's first MAIC analysis for the comparison to Pola+BR was using data from the extension study of GO29365. The Pola+BR study did not include patients with transformed lymphoma disease (when a slow-growing [low-grade] lymphoma changes into a faster-growing [high-grade] lymphoma) and so 29 patients with this in the LOTIS-2 trial were excluded from the MAIC analysis. A further 14 patients were excluded as they were missing data for variables necessary for matching, leaving 102 patients in the loncastuximab population prior to matching. GO29365 originally had 152 patients in, however 50 received Pola+BR as second-line treatment, and so the target population also had 102 patients.

The GO29365 study reported some outcome data (reported later) specifically for the 3+ line patients, however the baseline characteristics were only available for the whole population. Ideally the MAIC would match to data available for the desired

population, but in lieu of this, the only option is to impute the values for the desired subgroup based on the broader population. However, the EAG noted that the main source of information for the GO29365 extension study [1] reports that 50 patients are second line. This means we can discount these 50 patients from the target proportion who were on 3rd line or later, allowing calculation of a value relevant for the desired population. The EAG requested that the company repeat their base case analysis amending this change. The EAG also requested that the company implement a MAIC analysis that included all available variables to maximise the comparability of the two populations. In response, the company did not provide the desired analysis and excluded variables for refractory to previous therapy and IPI. The variables matched by the company, and their target values are shown in **Table 10**.

Additional differences between the populations included that in GO29365, 9/152 (5.9%) of patients received subsequent CAR-T therapy, compared to 16/145 (11.0%) in LOTIS-2. Subsequent SCT was received by four (2.7%) patients in GO29365 and 12 (8.3%) in LOTIS-2.

Table 10: Comparison of baseline characteristics LOTIS-2 vs GO29365 extension study including "other" patients in LOTIS-2 dataset, with individual component adjustment replacing IPI

Treatment (study)	N/ ESS	HGBL (%)	Age <65 (%)	Male (%)	ECOG PS 0-1 (%)	Prior lines ≥3 (%)	Primary refractory or progression / relapse <6 months (%)	Disease stage ≥3 (%)
Lonca unadjusted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lonca weighted (LOTIS-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola+BR (GO29365 extension)	102.0	3.0	32.0	55.0	87.0	58.8	64.0	80.0

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; N, sample size; Pola+BR, polatuzumab plus bendamustine plus rituximab.

Overview of MAIC outcomes

The company investigated the relative treatment effect of loncastuximab tesirine across the following outcomes: progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and discontinuation due to AEs.

Usually, comparisons for time to event outcomes (OS and PFS) would use actual or recreated patient level data for the comparator treatment, alongside the MAIC-weighted data from the company's own study. In this comparison, no Kaplan-Meier data for the desired subgroup of the GO29365 study were obtainable, and the only relevant information was the median PFS and OS times with their associated 95% confidence intervals. The company used the approach described by Tierney et al. to compare median survival times.[38] Whilst this was the only information for a comparison, it is a much inferior analysis to one based on patient level data, as it does not account for the number of people at risk throughout the analysis which is incredibly important in survival analysis, nor does it consider any differences in survival before or after the points of median survival.

The median OS from LOTIS-2 was [redacted] before adjustment, and was [redacted] after the MAIC weights were applied. The reported median OS from the subgroup of GO29365 was 9.5 months (7.6, 14.2).

The median PFS from LOTIS-2 was [redacted] prior to adjustment and after was [redacted]. Whilst the relevant median PFS from GO29365 was 6.1 months (4.5, 8.0).

The resulting hazard ratios were calculated based on an analysis of these median survival estimates. For ORR, the analysis was based on standard data available for the relevant subgroup from GO29365, whilst for discontinuation due to AEs, only information from the whole population from the GO29365 extension was available.

An overview of the results from the MAIC analyses using data from GO29365 is shown in **Table 11**. It is apparent from this limited analysis that loncastuximab has similar or slightly inferior efficacy compared to Pola+BR. The EAG's preferred MAIC analysis as requested in the clarification questions was not provided by the company.

Table 11: Outcomes from MAIC analysis to Pola+BR using GO29365

Outcome	Naïve comparison	Company updated preferred MAIC analysis	EAG preferred MAIC analysis
Overall Survival*	[redacted]	[redacted]	N/A
Progression Free Survival*	[redacted]	[redacted]	N/A
ORR**	[redacted]	[redacted]	N/A
Discontinuation to AEs**	[redacted]	[redacted]	N/A

** treatment effect measured as hazard ratio, using new company preferred MAIC analysis ;*
*** treatment effect measured as odds ratio, using original company preferred MAIC analysis*

Additionally, the EAG requested that the company re-perform their original meta-analysis, adjusting only the proportion of patients who had three or more prior lines of therapy (clarification A1). The EAG shows the comparison of the different MAIC analyses presented by the company, where the analysis for Pola+BR is unchanged (Table 12). The correction of this proportion has no effect on the median PFS, however it increases the effective sample size and decreases the median OS for loncastuximab resulting in a worse hazard ratio and fewer QALYs.

For the company's new preferred analysis in response to A3 with additional covariates, the company also included 14 additional patients from LOTIS-2 that were originally excluded from previous MAIC analyses, including the analysis conducted in response to clarification A1. The EAG had not requested their inclusion. These patients had missing data for response to primary therapy which was the justification for their previous exclusion, and were categorised as "Other" for this variable. To include these 14 patients, the company assume that their response to primary treatment is non-refractory. The company claim that this is a conservative assumption, however it is possible that they experienced partial remission. This "Other" group had 17 patients according to the company submission, but the company clarified three of these had transformed disease. The EAG is unable to conclude whether the late inclusion of these patients is appropriate.

The company said they were unable to adjust for refractory to previous therapy due to a mismatch of definitions used across the two studies, and a lack of available data to emulate the GO29365 version for the LOTIS-2 patients. The company also did not include the IPI variable as requested by the EAG.

From Table 12 it is apparent that this final analysis has the most optimistic estimation of benefit for OS. It's possible these changes are as a result of the possibly inappropriate inclusion of these additional patients rather than any improvements in the MAIC analysis. Additional sensitivity analyses relating to the inclusion of the patients and variables could reduce the EAG's concerns with the MAIC analyses, however they will remain limited by the potential matching variables.

Table 12: Comparison of MAIC analysis vs Pola+BR GO29365

Analysis	ESS for Ionca (Starting sample size)	Median PFS (months) PFS HR	Median OS (months) OS HR	Incremental QALYs from company preferred assumptions
Original Company base case (incorrect proportion for 3+ prior therapies)	[redacted]	[redacted]	[redacted]	[redacted]
Amended original company base case (amended prior therapies, clarification A1)	[redacted]	[redacted]	[redacted]	[redacted]
New company base case (amended prior therapies plus additional patients and covariates, clarification A3)	[redacted]	[redacted]	[redacted]	[redacted]

3.3.3 Indirect Comparison Pola+BR 2

The company's second MAIC analysis against Pola+BR used RWE for Pola+BR

coming from the COTA US database.[2] No patients from LOTIS-2 were excluded, meaning all 145 LOTIS-2 patients were featured in the MAIC against the 43 patients in the COTA dataset. The COTA study information was only reported in a conference abstract and so minimal information was available. The source provided by the company appeared to report slightly different values to those reported by the company, and the EAG requested clarification for this deviation.

The MAIC analyses was based on just four variables, only three of which were in the company's preferred list. The values used by the company are shown in **Table 13**. The EAG notes discrepancies between the values reported by the published abstract for the COTA study and those used by the company. There were also differences in the outcomes used in the statistical comparison. The company clarified that their information came from an alternative source, which was provided in the company clarification response, and was a conference poster based on an updated data-cut. 23% of patients in COTA receive subsequent CAR-T therapy, compared with 11% in the whole LOTIS-2 population. For subsequent SCT, the percentage was not reported for COTA, and 8% in LOTIS-2.

Table 13: Variables and values matched in MAIC to COTA

Treatment (study)	N/ ESS	Age <65 (%)	Male (%)	Prior lines ≥3 (%)	HGBL (%)
Lonca unadjusted (LOTIS-2)	145.0	44.8	58.6	56.6	7.6
Pola+BR (Company values)	43.0	50.0	60.0	26.0	12.0
Pola+BR (Hamadani 2022)	43	**<50% (median 67)**	**63%**	?	12%

Overview of MAIC outcomes

For this comparison of LOTIS-2 trial data to RWE from the COTA study, the company were able to compare PFS, OS and ORR outcomes. In this instance, the hazard ratios were calculated from the available patient level data, where the data for COTA were digitally recreated. Median data were also available.

The hazard and odds ratios are shown in Table 14. For overall survival, the MAIC weights changed the median OS from 9.53 months (6.74, 11.47) to [redacted] for LOTIS 2, compared to 7.00 months (4.95, 10.05) for COTA. For progression-free survival, the MAIC analysis shifted the original median PFS from 4.93 months (2.89, 8.31) to [redacted], compared to 3.70 months (2.59, 4.89) for Pola+BR in COTA.

The original source provided by the company for the COTA study reported a median OS of 7.3 months (5.6, 15.0) and a median PFS of 4.6 months (3.0, 7.5), both slightly higher than the values used by the company in their analyses. [2]

Overall, the results from this MAIC analysis are contradictory- (further critique is provided in section 0), with loncastuximab tesirine appearing superior for PFS and OS, but inferior for ORR though this may be partially explained by uncertainty around the response definition used in COTA.

Table 14: Outcomes from MAIC analysis to Pola+BR using COTA US database

Outcome	Naïve comparison	Company preferred MAIC analysis
Overall Survival*	[redacted]	[redacted]
Progression Free Survival*		
ORR**	0.67 (0.33,1.33)	[redacted]

** treatment effect measured as hazard ratio ; ** treatment effect measured as odds ratio*

3.3.4 Indirect Comparison Chemotherapy

The company's third MAIC analysis compared against chemotherapy and used data from the CORAL extension study.[3] The company's analysis resembled one published by Hamadani et al.[39] however they used a different data-cut from LOTIS-2. The EAG queried why the starting sample size reported by the company differed from the published study. The company clarified that this discrepancy is due to a difference in the data cuts included in the two analyses. Data cut-off for the Hamadani analyses was 26 October 2020; in comparison, the Company submitted analyses included a data cut-off of 01 March 2022.

This MAIC analysis was based on just three variables with only one from the company's preferred list. The EAG has been able to obtain the inputs used by the

company based on the published information from CORAL. A summary is shown in **Table 15**.

Table 15: Variables and values matched in MAIC to CORAL

Treatment (study)	N/ ESS	Male (%)	Prior ASCT (%)	IPI ≥3 (%)
Lonca unadjusted (LOTIS-2)	80.0	66.2	21.2	38.8
Chemotherapy (CORAL extension)	266.0	63.0	27.0	39.0
Chemotherapy (CORAL extension) [39]	**278 or 231**	63.0	27.0	39.0

Overview of MAIC outcomes

For the comparison to chemotherapy, only OS and ORR outcomes were available, as PFS and safety information was not available for the CORAL extension. Median OS for loncastuximab tesirine was 10.12 months (6.14, 12.09) before adjustment, and 10.12 months (6.34, 13.63) after the MAIC weights were applied. For chemotherapy, median OS was 5.85 months (4.80, 7.14). The hazard ratio is shown in Table 16.

Repeating the company's approach to estimating a hazard ratio from median survival times on those reported in this analysis versus chemotherapy produces a hazard ratio of 0.58, compared to the hazard ratio of 0.67 from a model fitted to the data, suggesting this approach does not always yield accurate estimates of the hazard ratio.

Again, the MAIC weightings have minimal impact on the effect size estimates for the two outcomes. The weak evidence from this analysis suggests that loncastuximab tesirine is associated with a lower OS hazard rate and higher response rate than chemotherapy.

Table 16: Outcomes from MAIC analysis to Chemotherapy using CORAL extension study

Outcome	Naïve comparison	Company MAIC analysis
Overall Survival*	0.69 (0.51, 0.94)	0.67 (0.51, 0.86)
ORR**	1.51 (0.91, 2.50)	1.53 (0.91, 2.54)

** treatment effect measured as hazard ratio ; ** treatment effect measured as odds ratio*

3.3.5 Additional EAG analysis

The EAG was concerned that the estimated hazard ratios of difference between the populations of LOTIS-2 and COTA US study might not be attributable to the treatments received, but at least in part the nature of the different study designs with COTA coming from real world use of Pola+BR.

The EAG performed a naïve comparison of the PFS and OS outcomes from the GO29365 and COTA studies, using the same methodology implemented by the company which calculated hazard ratios and standard errors from median survival times and total numbers of events, shown in Table 17. Compared to the naïve comparison of COTA and LOTIS-2, the level of effect is similar, supporting the hypothesis that the effect sizes estimated in the company's COTA comparison may not be representative of any potential benefit of loncastuximab tesirine.

Table 17: Outcomes of comparisons for COTA against LOTIS 2 and GO29365 data

	GO29365 (EAG analysis)	LOTIS 2 (unweighted)	LOTIS 2 (weighted)	COTA
Median OS	9.5 months (7.6, 14.2)	9.53 months (6.74, 11.47)	[redacted]	7.00 months (4.95, 10.05)
Naïve Hazard Ratio OS (vs COTA)	0.74 (0.48, 1.13)	[redacted]	[redacted]	-
Median PFS	6.1 months (4.5, 8.0)	4.93 months (2.89, 8.31)	[redacted]	3.70 months (2.59, 4.89)
Naïve Hazard Ratio PFS (vs COTA)	0.61 (0.41, 0.90)	[redacted]	[redacted]	-

3.4 *Critique of the indirect comparison and/or multiple treatment comparison*

Plausibility of the MAIC estimates

The company has undertaken MAIC in order to indirectly compare loncastuximab tesirine to Pola+BR and to chemotherapy, both listed as relevant comparators in the NICE scope. For the Pola+BR comparison, two sources of clinical data were used, namely the COTA US and the GO29365 studies.

To review the plausibility of MAIC results, the EAG have examined whether there was consistency between outcomes. One would expect a correlation between ORR, PFS, and OS. For example, one would expect a gain in ORR to result in a gain in PFS and subsequently in a gain in OS, though with a possible reduced magnitude.

Table 18 below summarises the results from the MAIC analyses.

Table 18: MAIC analyses outcomes (unweighted to weighted analyses)

Comparison	**Source of data used in the MAIC for Pola+BR**	**Range of ORR OR (95% CI)**	**Range of PFS HR (95% CI)**	**Range of OS HR (95% CI)**
Lonca vs Pola+BR	COTA US database	[redacted]	[redacted]	[redacted]
	GO29365 extension study	[redacted]	[redacted]	[redacted]
Lonca vs chemo	CORAL extension	[redacted]	None provided due to lack of PFS data	[redacted]

The results for the loncastuximab tesirine vs Pola+BR comparison, based on the GO29365 study, suggest a reasonable degree of consistency since all measures of treatment effect indicate an absence of difference between the two therapies.

Similarly, the results for the loncastuximab tesirine vs chemotherapy comparison show a good degree of consistency, with the limitation due to the absence of reported analyses on PFS: an ORR OR of [redacted], suggestive of better outcome with loncastuximab tesirine, is associated with improved OS outcomes as illustrated by an OS HR around [redacted].

Conversely, the results for the loncastuximab tesirine vs Pola+BR comparison, based on the COTA US Database, indicate a limited degree of consistency: indeed, while the PFS and OS comparisons are suggestive of a potential benefit for loncastuximab tesirine relative to Pola+BR, given the HR around [redacted], the ORR OR was found at [redacted], which could denote a worse outcome for loncastuximab tesirine vs Pola+BR (though not statistically significant due to the 95%CI overlap with 1); one would have expected the central estimate of ORR OR to be >1.

3.5 *Additional work on clinical effectiveness undertaken by the EAG*

The EAG conducted no further additional work beyond what has been presented in Section 3.3.5

3.6 *Conclusions of the clinical effectiveness section*

- The company conducted a reasonable systematic literature review (SLR) to identify evidence on the efficacy and safety of loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies (Section 3.1).

- The direct clinical evidence presented in the CS on the efficacy of loncastuximab tesirine comes from a single arm, open label trial (LOTIS-2). Findings are suggestive of a positive response to treatment with loncastuximab tesirine in heavily pre-treated patients with DLBCL. However,

with no comparator group it is unclear what magnitude of benefit loncastuximab tesirine offers over established clinical management.

- The LOTIS-2 study included in this assessment is 145 patients. Of those, only 31 patients are from the UK. This small number of UK patients raises some concerns relating to the generalisability of the findings from this cohort.
- Only median OS and PFS were reported for the 3L+ population of Pola+BR patients in the GO29365 extension study. The lack of KM curves for the 3L+ population of the GO29365 extension study significantly limits the inferences for the Pola+BR comparison.
- The COTA US electronic data base is based exclusively on patients in the United States. Furthermore, the database contains only a small number of relevant 3L+ Pola+BR patients (n=43).
- No PFS data were available for the CORAL extension study. The hazard ratio derived from the OS curves was applied to the loncastuximab-weighted PFS curve in the economic model. This significantly limits the inferences that can be made for the chemotherapy comparison.

4 COST EFFECTIVENESS

4.1 *EAG comment on company's review of cost-effectiveness evidence*

The CS (Appendices G, H and I) provides detailed reports of 3 systematic reviews (SRs), aimed at identifying; a) cost-effectiveness studies; b) HRQoL data; c) cost and resource use data.

4.1.1 Search Strategies

4.1.1.1 Published cost-effectiveness studies SR (CS Doc Section B.3.1 and Appendix G)

Searches combining suitable terms for the population, intervention or comparators, and a broad cost-effectiveness search filter [40] were conducted in a number of relevant databases on 24/10/2022.

The sensitivity of the main database searches is slightly restricted by the inclusion of specific named intervention / comparator terms, which may have resulted in some broader, relevant evaluations (e.g., of several treatments in DLBCL or HGBL) not being retrieved. Hand-searching of a range of sources was used to supplement all three SRs and provided opportunities to find these types of study. Brief details are provided in the CS of these supplementary searches. The keywords used to find those excluded and a list of excluded studies were provided in response to clarification questions. Reference lists of relevant SLRs and HTA documents were also screened, and reference details of these documents have been provided in response to our clarification questions.

4.1.1.2 HRQoL studies SR (CS Doc B, section B.3.4.3 and Appendix H)

The main database searches, which were undertaken on 24/10/2022, combined a variety of terms for the population and stage of treatment / line of therapy with an HRQoL search filter. Appropriately, intervention / comparator terms were not included, but the inclusion of stage of treatment / line of therapy in the search may

have meant that some records of relevant, broader studies on all stages or where stage was not mentioned were not retrieved. Reassuringly, the EAG re-ran the MEDLINE search without the 'stage of treatment' concept and checked the unique studies this retrieved, finding none that were relevant. Searches were limited to English language. Hand-searching of a range of sources was used to supplement all three SRs, as mentioned in section 5.1.1.1.

4.1.1.3 Cost and resource use SR (CS Doc B, section B.3.5 introductory sentence and Appendix I).

Searches were undertaken in a range of databases on 24/10/2023. These searches combined a suitable variety of terms for the population, stage of treatment / line of therapy, and cost / resource use. Appropriately, intervention / comparator terms were not included in the searches, which were limited to English language and to articles published on or after 2012. Hand-searching of a range of sources was used to supplement all three SRs, as mentioned in section 5.1.1.1.

4.1.1 Inclusion/exclusion criteria used in the study selection

The inclusion and exclusion criteria for the review of cost-effectiveness evidence, health state utility values, and costs and resource use are presented in Table 25 of Appendix G, Table 33 of Appendix H, and Table 41 of Appendix I. The list of included and excluded studies are reported in Appendices, G, H and I with some updates provided during clarification (see Appendix B, Company Clarification Responses).

- The EAG agrees that the eligibility criteria are broadly suitable to fulfil the company's objective to identify cost effectiveness studies**,** with some limitations highlighted bel.

4.1.2 Included/ excluded studies in the cost-effectiveness review

A total of 60 publications (7 UK and 53 non-UK studies) were included in the SLR review. However, the CS stated that the focus of the SLR was on UK studies to maximise relevance to the decision problem, thus only the 7 UK-based publications informed the cost-effectiveness evidence for this appraisal. Of the 7 studies, one

was a conference abstract whilst the rest were HTA appraisals conducted by the SMC and NICE. Details of these studies are provided in Appendix G.

- The seven included studies are relevant to the decision problem. However, it is worth re-iterating that the sensitivity of the main database searches may have been slightly restricted by the inclusion of specific named intervention / comparator terms.

Details on HRQoL studies included in the cost-effectiveness review are provided in section 4.2.7.1

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The eligibility criteria were suitable for the SLR performed. The SLR search strategies were comprehensive enough despite some limitations highlighted above

The information obtained from the SLR for health state utility values and costs and resource use were used in some ways to inform the de novo analysis (Sections 4.2.7 and 4.2.8).

The partitioned-survival modelling approach taken for the company's base case followed that of previous appraisals and was appropriate for the decision problem. However, there were issues surrounding treatment extrapolation approaches and data used to inform analyses (Sections 4.2.3 and 4.2.6).

There is great uncertainty surrounding the company's cost-effectiveness analysis which is largely due to issues with the company's presented MAIC analyses (Section 4.2.6)

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference case checklist is presented in Table 19

Table 19: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company used a *de-novo* cost-utility partitioned survival model with a weekly cycle length and time horizon of 40 years. The model has three health states: progression free survival (PFS), progressed disease (PD) and death (absorbing state). All patients begin in the PFS state and remain there until disease progression or death. Patients in the PD health state remain there until death as shown in Figure 1 below.

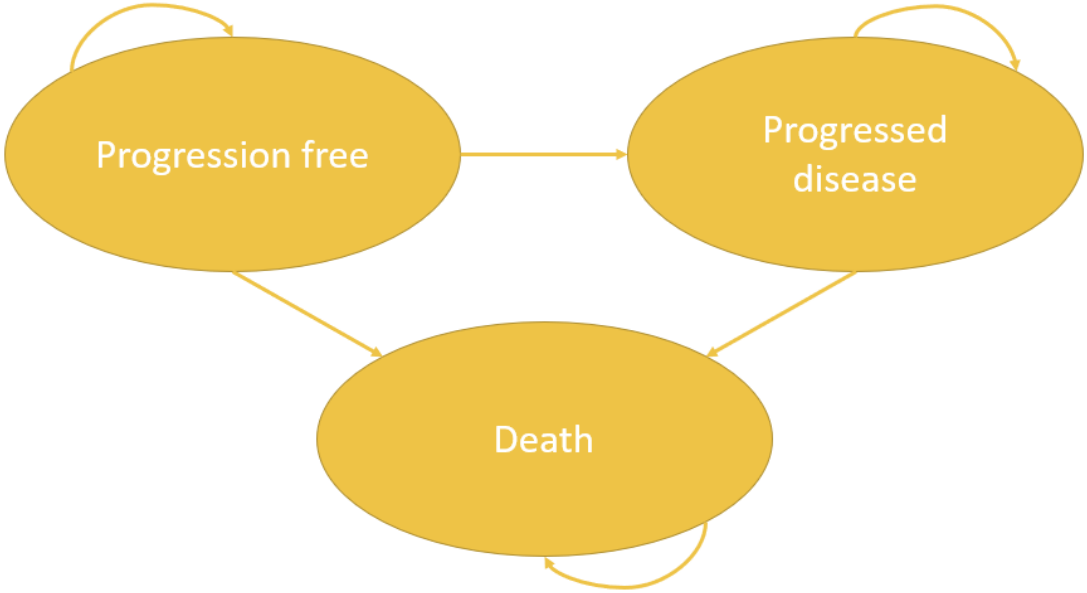

Figure 1 Model Structure

Source: Figure 23 – Company Submission

The partitioned survival method model uses “area under the curve” approach, where the number of patients in each state at a given time point is taken directly from survival curves fitted to the clinical data. The PFS curves show at a given time point, the proportion of patients who have not progressed or died, whilst the OS curves show the proportion of patients who are alive at a given time point. The proportion of the patients in the PD state was calculated as the difference between the proportion of living patients (OS health state) and the proportion of patients who are both living and pre-progression (PFS health state). The OS and PFS curves were determined by fitting parametric curves to the LOTIS-2 data. For the comparators, the OS and PFS distributions were determined by fitting parametric models to the reconstructed KM curves from comparator data.

Time to treatment discontinuation (TTD) in the PFS state for the loncastuximab arm was determined by fitting survival curves to the clinical data on treatment duration and capped at 1 year. For the Pola+BR comparison, TTD was set equal to the PFS and capped at 1 year. For the chemotherapy comparison, a fixed treatment duration was used and patients were assumed to receive all cycles of treatment until progression

EAG comments:

- The health states capture the two important clinical endpoints of PFS and OS, that are relevant to the disease area and used in previous technology appraisals.
- The weekly cycle length was short enough to capture changes over the relevant time interval.
- The 40-year time horizon was long enough to capture important differences in costs and clinical outcomes.
- Given the company has IPD on time on and off treatment, TTD should be modelled using actual KM data, not fitted survival curves. At 12 months, between 2.1% to 2.8% of patients in the loncastuximab arm remained on treatment. Given the 12-month treatment duration cap in the model this proportion of patients (although small) go on to receive the benefits of treatment without incurring any of the costs.

4.2.3 Population

Loncastuximab tesirine (Lonca) does not currently have a marketing authorisation in the UK. The patient population considered in the model is in line with the proposed license: adults with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DBCL) who have had two or more systemic therapies. Patients with high-grade B-cell lymphoma (8%) (HGBL) and primary mediastinal large B cell lymphoma (5%) (PMBCL) were included in the analysis population, and this aligns with the final scope issued by NICE.

As reported in section 2.2, the company submission relies on a single arm study, the LOTIS-2 trial, a multi-centre, phase II, open label study. The LOTIS-2 study provided

data on clinical efficacy, safety and time on treatment of loncastuximab tesirine for treatment of adult patients with DLBCL. Baseline characteristics of the population were derived from baseline characteristics of the LOTIS-2 population (i.e., mean age: 62.7 years; baseline body weight: 77.1kg; baseline BSA: 1.86m^2; and baseline males in cohort: 41%) (Table 67 CS).

Two studies informed comparisons with the Pola+BR: GO29365 extension study and the COTA US database. Efficacy estimates were drawn from both studies for the Pola+BR comparison. Efficacy estimates for the chemotherapy comparison were based on the CORAL extension study.

EAG comments:

- Only median OS and PFS were reported for the 3L+ population. The lack of KM curves for the 3L+ population of the GO29365 extension study significantly limits the inferences for the Pola+BR comparison.
- The COTA US electronic data base is based exclusively on patients in the United States. Furthermore, the database contains only a small number of included patients (n=44).
- No PFS data were available for the CORAL extension study. The hazard ratio derived from the OS curves was applied to the Loncastuximab-weighted PFS curve. This significantly limits the inferences that can be made for the chemotherapy comparison.

4.2.4 Interventions and comparators

The final scope issued by NICE as seen in Table 1 of the company submission includes the following regimen in addition to the comparators considered in this appraisal: pixantrone; axicabtagene ciloleucel (CAR-T); and tafasitamab with lenalidomide. The company excluded pixantrone monotherapy because it is rarely used in the UK. As indicated in section 2.3, tafasitamab with lenalidomide was rightfully excluded since it has been not recommended by NICE in TA883.[29] The company argues that loncastuximab tesirine is most likely suitable for patients not eligible for CAR-T therapy hence CAR T-cell therapy (axicabtagene ciloleucel) was

excluded. The EAG considers the comparators partially appropriate as discussed in section 2.3 .

4.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE reference case, with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. In the base case, costs and benefits were discounted at an annual rate of 3.5% in line with NICE reference case. The 40-year time horizon is sufficient to capture the extrapolated OS curves given the model cohort age.

4.2.6 Treatment effectiveness and extrapolation

The company's economic model was a partitioned survival model, meaning it used multiple time-to-event inputs from the various analyses. The key inputs were progression-free survival, overall survival, and time to treatment discontinuation. These will be summarised and critiqued for each comparison below. The company used standard parametric models to extrapolate data available, and reported considering spline models if the parametric models fitted poorly to the data.

The time-to-event data used in the economic model uses the March 2022 datacut. The economic model also uses inputs from the company's MAIC analyses, which the EAG proceeds to critique and use despite aforementioned concerns over their suitability.

4.2.6.1 Comparison to Pola+BR

For the comparison to Pola+BR the company used data from the LOTIS-2 and GO29365 studies. The MAIC weights were applied to the LOTIS-2 data for some of the modelling. When responding to clarification responses, the company changed their preferred MAIC analysis which affected their base case economic analysis for this comparison. The company did not provide updated information on the survival extrapolation, and so the EAG proceeds to critique the original information provided by the company on the assumption it is still relevant.

Previous testing by the company using the COTA and LOTIS-2 data found that the proportional hazards assumption did not hold for the comparison of Pola+BR and loncastuximab tesirine for either PFS or OS.

4.2.6.1.1 Overall survival

Loncastuximab tesirine OS

The company fitted a routine set of parametric models to the LOTIS-2 data using MAIC weights from the relevant indirect comparison.

After consideration of information criteria (AIC and BIC), and plausibility of extrapolations, the company selected the generalised gamma extrapolation. The EAG notes that the log-normal and log-logistic models fit very similarly to the generalised gamma, both visually and according to AIC and BIC, and should also be considered. All three models are consistent with the observed hazard rate. The main difference between these models is the long term predictions (Figure 2). The 10-year overall survival predicted by the generalised gamma model is [redacted], compared to [redacted] for the log-normal and log-logistic models. The clinical expert consulted by the EAG suggested that a figure closer to 5% would be more plausible for this targeted population who are typically frail and ineligible for CAR-T therapy. Hence, the EAG prefers to use a log-normal model in their base case.

Figure 2: Long term extrapolations for loncastuximab tesirine overall survival weighted against the GO29365 population, taken from Figure 27 of CS.

Pola+BR OS

Due to the lack of proportional hazards, the company did not apply the hazard ratio estimated from the MAIC analysis. Instead they performed an extrapolation of the OS data for the wider GO29365 population, including those who received Pola+BR as second line therapy, using a regular set of candidate parametric models. To obtain an extrapolation for the desired third line plus subgroup, the company estimated something similar to a hazard ratio for the effect of being third line or greater relative to the whole population and applied this to the survival model fitted to the full GO29365 data.

For the extrapolation of the whole population, the company use a generalised gamma parametric model reportedly based on it "showing the best fit to the observed data". The EAG is unable to verify the visual fit as this was not provided by the company however the generalised gamma did have the lowest AIC and BIC indicating the most parsimonious fit.

The company then applied their hazard ratio to this generalised gamma extrapolation. The EAG has some concerns with this approach.

Firstly, the calculation of this hazard ratio assumes that the starting ratio of second line to third line plus patients is sustained throughout the observed period, which is not plausible given the different hazard rates of the two subgroups.

Furthermore, the application of the hazard ratio assumes that the hazard rate is proportional for the duration of the extrapolation. To investigate this further, the EAG requested that the company perform an analysis on the LOTIS-2 data investigating whether the proportionality assumption held between the subgroups based on the number of previous lines of therapy (clarification A9). The company's analysis demonstrated that there is an increasing hazard ratio over time for overall survival (Figure 3), though a global test for proportional hazards did not reject the assumption at the 0.05 threshold (p=0.44). Testing for proportional hazards is not recommended and is heavily informed by the sample size and power. [41]

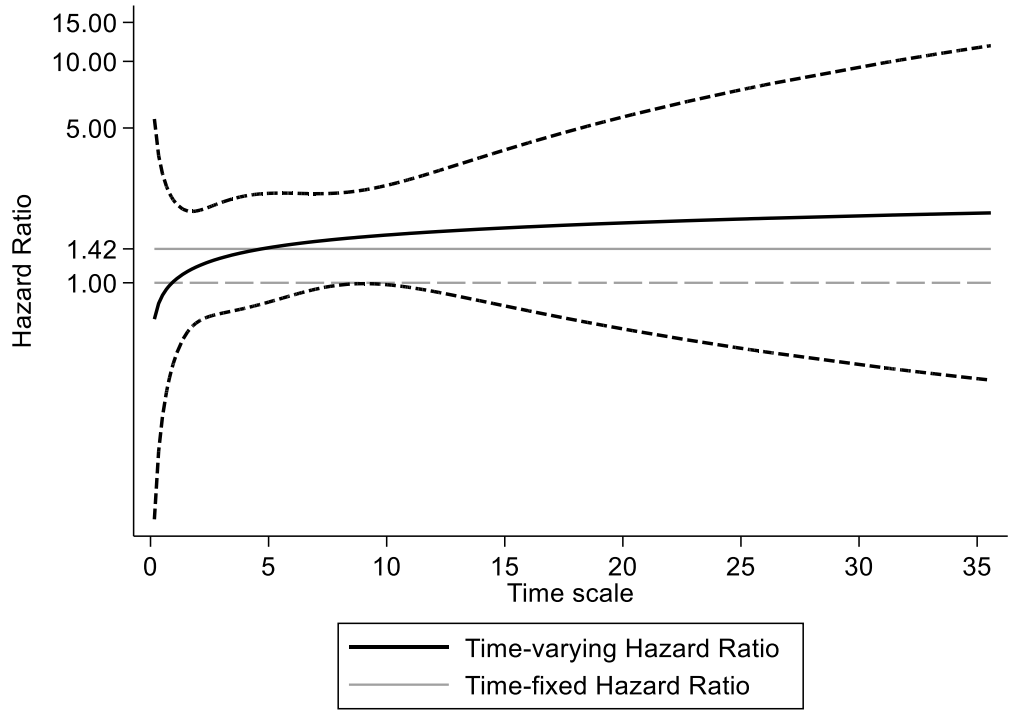

Figure 3: Time varying hazard ratio for LOTIS-2 US overall survival comparing number of previous therapy subgroups, taken from Figure 14 of company clarification response.

The company also conducted a similar analysis using reported information from the US COTA study. This analysis had a smaller sample size, and so it is expected that a global test for proportional hazards did not reject the assumption (p=0.91). The

company fitted time-varying hazard ratio and provided the output (Figure 4). The EAG disagrees with the company's interpretation that "the time-varying HR remains relatively close to the time-fixed HR". Rather, a decreasing trend is clear which nearly crosses one, deviating considerably from the constant hazard ratio.

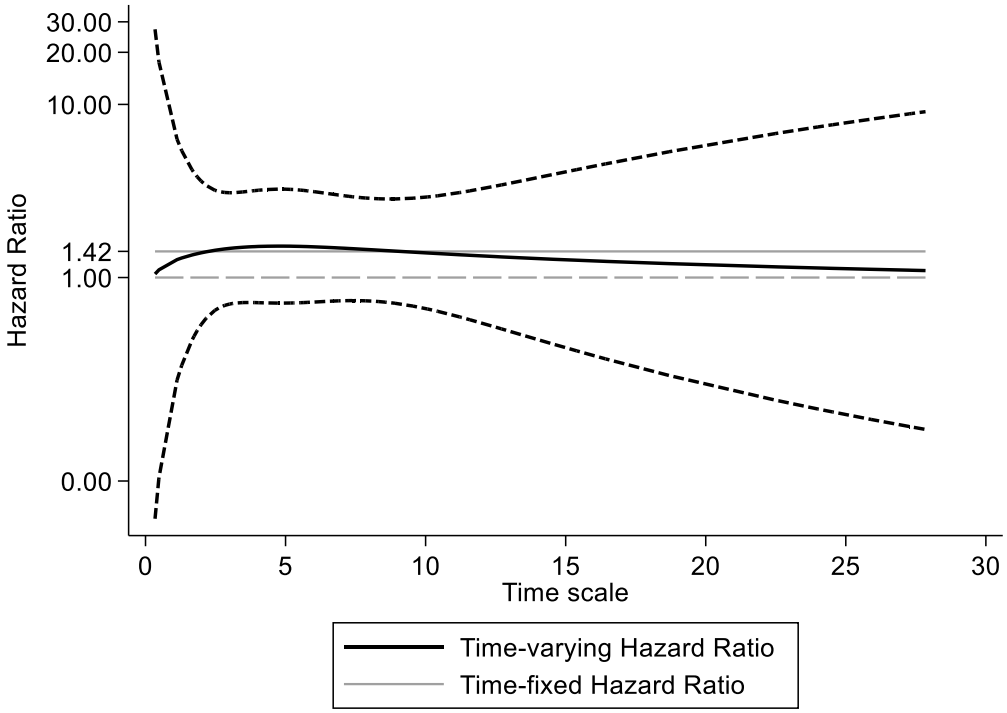

Figure 4: Time varying hazard ratio for COTA US overall survival comparing number of previous therapy subgroups, taken from Figure 22 of company clarification response.

For these reasons, the EAG is not satisfied with the company's approach for the OS modelling for Pola+BR. Given the lack of evidence of a difference in effect for OS from the MAIC analyses, the EAG prefers to set the Pola+BR OS to be equal to that of loncastuximab tesirine. In relative terms, this is similar to the company's modelling as minimal difference was predicted between these therapies, consistent with findings from MAIC analyses as described in section 2.4.1.

Both the EAG's and company's preferred methods of obtaining an OS extrapolation for Pola+BR produce estimates of median OS that fall within the confidence interval for median OS reported for the relevant subgroup of GO29365 (Table 20).

Table 20: Comparison of median OS estimates for Pola+BR

Source	Median OS
GO29365 (observed)	9.5 months (95% CI: 7.6, 14.2)
Company preferred extrapolation (gen gamma and hazard ratio)	10.3 months
EAG preferred modelling (using lonca log-normal)	11.0 months

4.2.6.1.2 Progression-free survival

Loncastuximab tesirine PFS

Similarly to OS, the company fitted parametric models to the MAIC weighted data from LOTIS-2. The set of extrapolations is shown in Figure 5. The Gompertz model is disregarded for being implausibly optimistic. The company's preference is the generalised gamma model which is associated with the lowest AIC and BIC of the candidate models. The generalised gamma model has a more optimistic extrapolation compared to all remaining parametric models. While this appears visually consistent with the apparent plateau of the LOTIS-2 data, there are very few patients remaining at risk. From 12 months, there are just [redacted] at risk, which decreases to [redacted] at 24 months. This is far too few patients to provide evidence of a plateau as suggested by the company in their response to clarification question B3. [42]

Figure 5: Extrapolations of PFS for loncastuximab tesirine weighted for Pola+BR comparison, taken from Figure 34 of CS

The EAG compares the PFS data from LOTIS-2 and GO29365 in Figure 6. The number of patients at risk decreases much more suddenly in LOTIS-2 than in GO29365. Where the Kaplan-Meier estimators cross at 10 months, there remains too few patients to provide a reliable comparison of relative trajectories. It is only the first months of follow-up where there are sufficient numbers at risk that allow a meaningful comparison, and here loncastuximab tesirine shows no benefit to either the whole GO29365 population of the third-line-plus subgroup. There is insufficient evidence to support the company's choice of a generalised gamma model which predicts a substantially improved PFS for loncastuximab tesirine over Pola+BR in the future. Hence the EAG disregards the generalised gamma model as implausible and prefers a log-normal extrapolation, which has the lowest AIC and BIC of the remaining plausible models.

Figure 6: An overlayed comparison of the PFS for weighted LOTIS-2 data and the whole population of GO29365 with risk table, with median for desired subgroup from GO29365 indicated by the square

Pola+BR PFS

The company again reject the assumption of proportional hazards between Pola+BR and loncastuximab tesirine based on an analysis using the COTA data. However, had the company applied the hazard ratio estimated from the MAIC analysis onto the loncastuximab tesirine extrapolation, Pola+BR would have had a superior progression-free survival extrapolation relative to loncastuximab tesirine.

As with OS, the company extrapolates data for the whole GO29365 population, and applies its estimated PFS hazard ratio to obtain an extrapolation for the desired third line plus population. Figure 7 shows the extrapolations for the set of candidate parametric models. There is strong agreement between the models, and all are much lower than the extrapolation preferred by the company for loncastuximab tesirine.

Figure 7: PFS extrapolations for Pola+BR, taken from Figure 35 of CS

The EAG again has concerns with this approach taken by the company regarding the assumption of proportionality of hazards between the subgroups of patients based on their number of prior lines of therapy. A time-varying hazard ratio model fitted to LOTIS-2 data is shown in Figure 8 showing an increasing trend over time. An equivalent model fitted to COTA data did demonstrate a more constant hazard ratio (Figure 9), however there was virtually no difference in PFS between patients who received 2 vs 3+ lines of previous therapy (Figure 10), which suggests a hazard ratio does not need to be applied to the extrapolation of the PFS for the whole GO29365 population.

Given the dearth of evidence of a benefit of loncastuximab tesirine over Pola+BR, the EAG assumes that the PFS extrapolation for Pola+BR is identical to that of loncastuximab tesirine in their base case.

A comparison of the median survival times from the company's and EAG's preferred approaches is shown in Table 21, where all estimates are within the 95% confidence interval reported by the study.

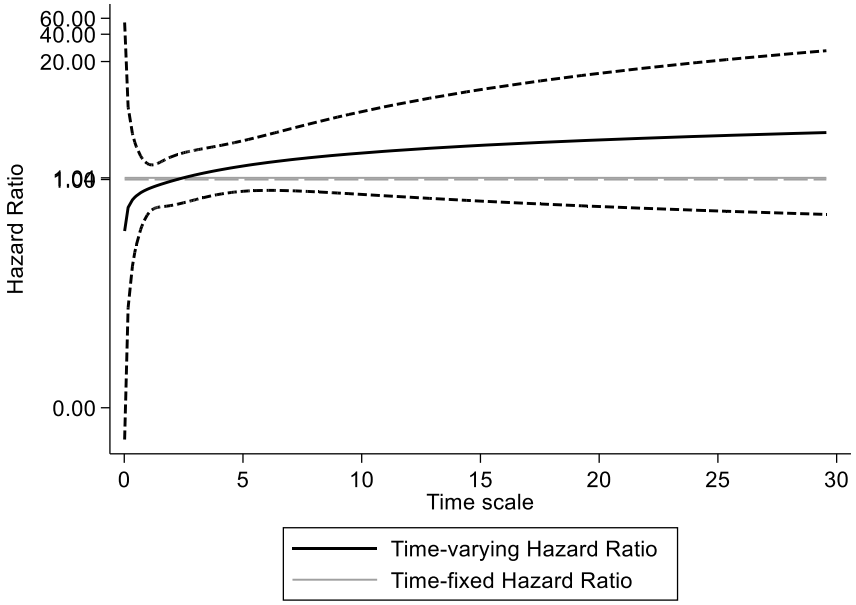

Figure 8: Time varying hazard ratio for a model fitted to LOTIS-2 PFS data, taken from Figure 10 of company clarification response.

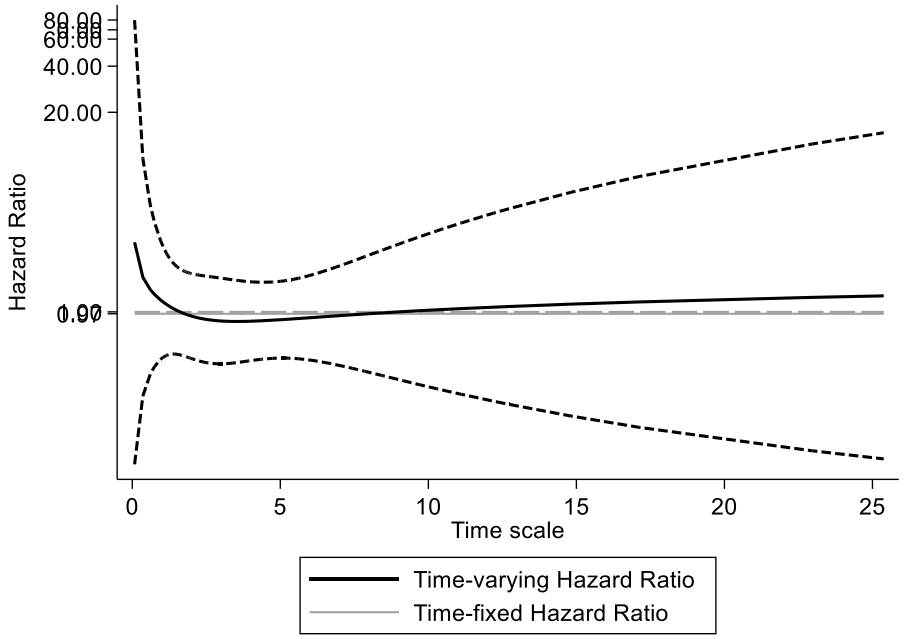

Figure 9: Time varying hazard ratio for a model fitted to COTA PFS data, taken from Figure 18 of company clarification response.

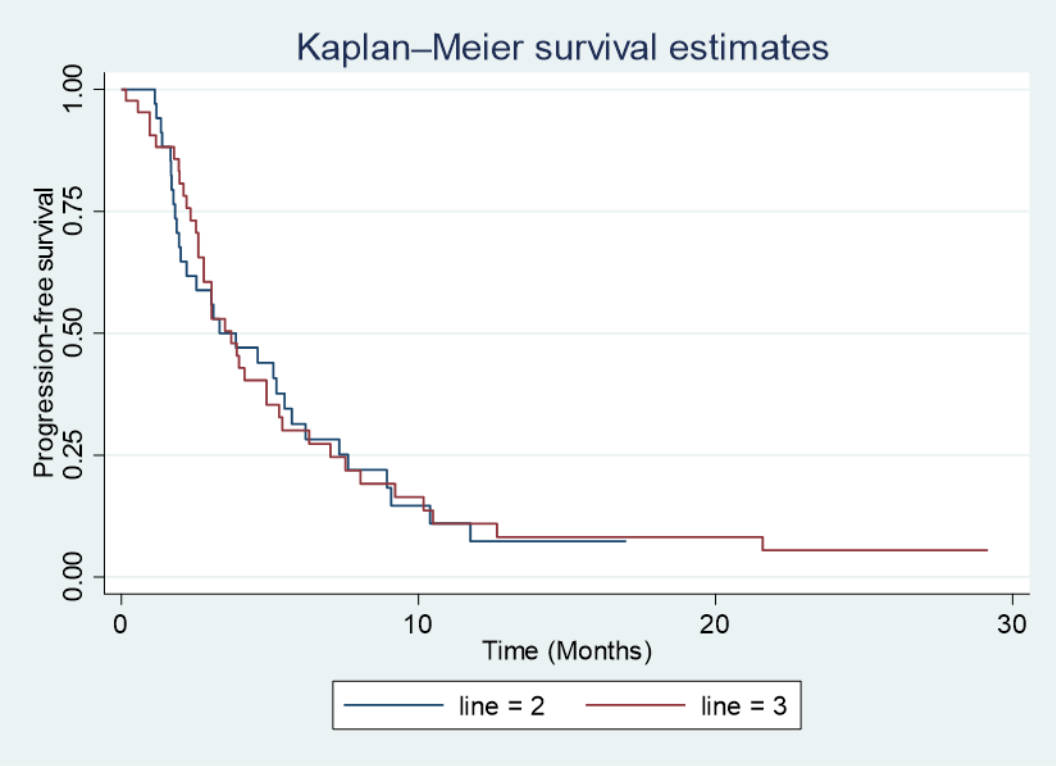

Figure 10: PFS from COTA based on number of lines of prior therapy, taken from Figure 15 of company clarification responses

Table 21: Comparison of median PFS estimates for Pola+BR

Source	Median PFS
GO29365 3L+ subgroup (observed)	6.1 months (95% CI: 4.5, 8.0)
Company preferred extrapolation (gen gamma and hazard ratio)	5.5 months
EAG preferred modelling (using lonca log-normal)	5.3 months

4.2.6.1.3 Overview of time-to-event modelling for loncastuximab tesirine and Pola+BR

The combination of the company's modelling choices for OS and PFS is shown in the Markov trace plot shown in Figure 11 for loncastuximab tesirine, and in Figure 12 for Pola+BR. It is apparent that the modelling for OS is very similar across the two populations. However, the graphs demonstrate the impact of the PFS curves and the difference of the post-progression survival health states in this comparison. Note, for loncastuximab tesirine, the company's modelling predicts a vanishing post-progression health state, which disappears from 15 years. There is insufficient

evidence to support such a strong progression-free benefit for loncastuximab tesirine relative to Pola+BR, and the EAG's clinical advisor stated that it was "most unlikely that any or very few isolated patients will be cured of their disease", and "almost all patients will relapse". This has been further critiqued by the EAG in section 4.1 examining the plausibility of cost-effectiveness estimates. The effect of background mortality is also evident, having effect around years 18 and 16 for loncastuximab tesirine and Pola+BR respectively.

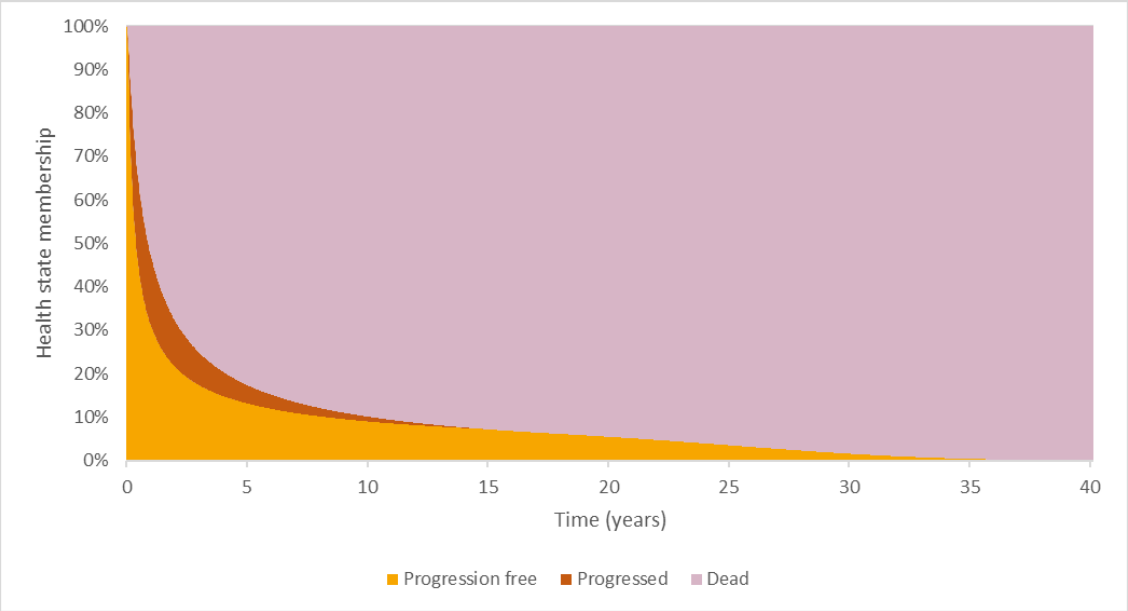

Figure 11: Markov trace of loncastuximab tesirine for company base case

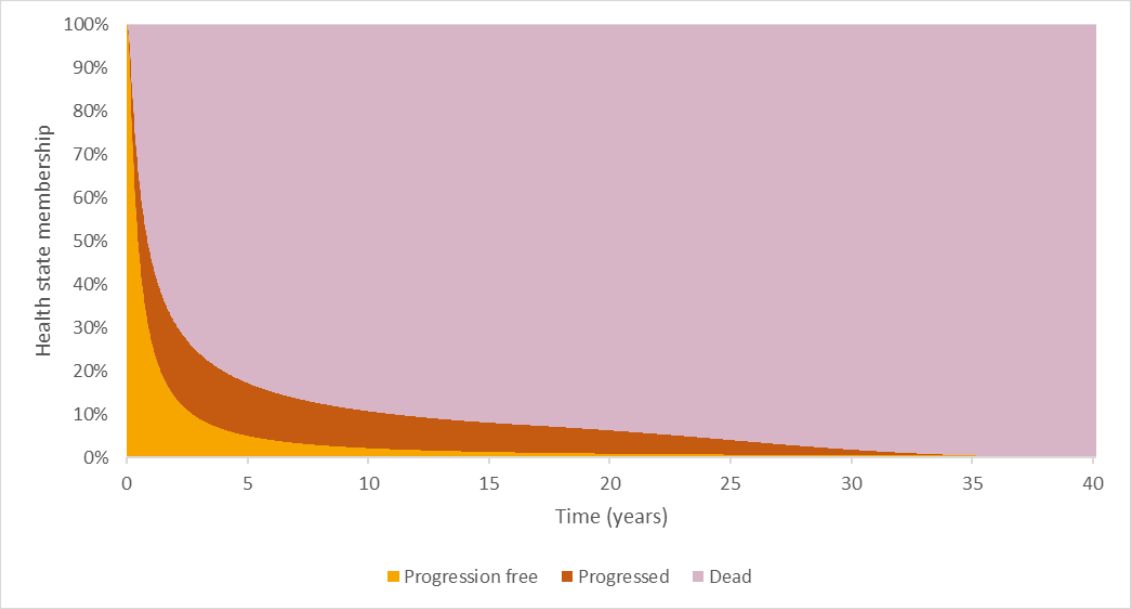

Figure 12: Markov trace of Pola+BR for company base case

For comparison, the combination of the EAG's preferred assumptions is shown in Figure 13. This is applicable for both Pola+BR and loncastuximab tesirine as the EAG assumes equivalence between the technologies for PFS and OS. This is consistent with the view that most patients will experience disease progression, and reflects the view of the EAG's clinical expert.

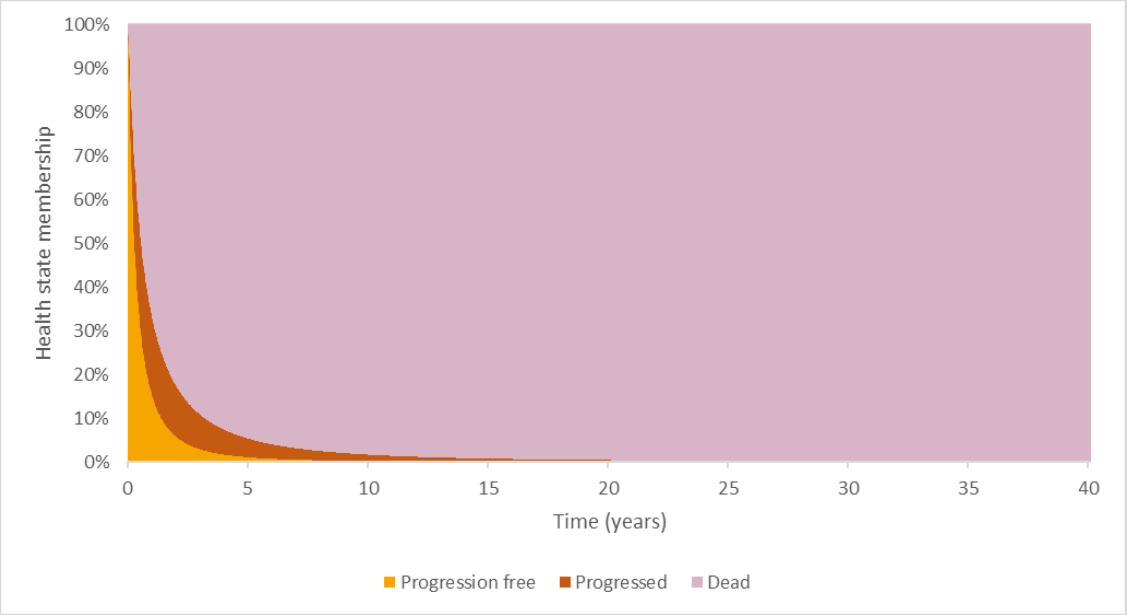

Figure 13: Markov trace of Pola+BR and loncastuximab tesirine for the EAG base case

4.2.6.1.4 Time to treatment discontinuation

Loncastuximab TTD

The company selected a generalised gamma model fitted to the TTD data for the LOTIS-2 trial, with MAIC weights applied from the comparison to GO29365. The maximum duration was capped at a year, however most patients had stopped prior to this. This data were mature, and multiple models could have been used with little variability in their estimates. Hence the EAG is content with the company's choice of model.

Pola+BR TTD

The company assume that patients receive six cycles of treatment, unless disease progression occurred prior to completion. The EAG is satisfied with this approach.

4.2.6.2 Comparison to Chemotherapy

The primary source of information for this comparison came from the company's MAIC analysis comparing data from LOTIS-2 to the CORAL extension study.

4.2.6.2.1 Overall survival

Loncastuximab tesirine OS

For loncastuximab tesirine, the company uses the original OS data from LOTIS-2 for extrapolation, without applying the MAIC weightings calculated in the clinical section. This also means the data for extrapolation includes patients from LOTIS-2 who were excluded from the MAIC analysis for being older than 67.7 at baseline. The company does however apply a two-stage adjustment to remove the benefit gained by some patients in LOTIS-2 who received CAR-T therapies. The EAG requested additional information on this adjustment, as little was initially provided by the company. This adjustment was not applied in the clinical section. If this was applied, it would reduce the relative benefit of loncastuximab tesirine.

The EAG is unclear why these two unusual inconsistencies between the clinical and cost-effectiveness analyses are present for the company's comparison of loncastuximab tesirine and chemotherapy.

The EAG preference is to apply the two-stage adjustment prior to calculation of hazard ratios and MAIC weights, and to use this MAIC weighted data for fitting models to be used in the economic analysis.

In clarification response B1 the company explained that instead they estimated and applied the two-stage adjustment after applying the MAIC weights. The EAG disagrees with this rationale as it is decreasing the power in the calculation of the two-stage adjustment.

The company proceeded to fit a standard set of parametric models to their preferred data (Figure 14). The EAG notes that all models deviate from the Kaplan-Meier estimator around 12 months. Spline models were presented in the company appendix submission which were a better fit to the data however extrapolated to predict a very low future hazard rate which was deemed implausible.

The company's preferred model is the generalised gamma as it had the lowest AIC and second lowest BIC, with a lower value indicating a better fit to the data. The EAG will also consider the log-normal model as this had only slightly higher AIC and BIC than the generalised gamma, whilst also having a plausible extrapolation. The generalised gamma extrapolation preferred by the company could be consider implausibly optimistic as the extrapolation is affected by the background mortality restriction, where the modelled hazard rate is constrained to not fall beneath the hazard rate for the age and sex matched general population. The long term estimates of the log-normal model are also consistent with the EAG's clinical expert. Hence the EAG prefer to use the log-normal extrapolation fitted to MAIC weighted data.

Figure 14: Parametric models fitted to company preferred data for loncastuximab in comparison to chemotherapy (taken from Figure 43 of company submission)

Chemotherapy OS

The company visually checked if the proportional hazards assumption held, and performed a statistical test, and were content that the assumption was not clearly

violated. The EAG accepts that the assumption appears to hold for the observed period, however it is unknown whether this assumption is appropriate for future follow-up. Hence, the EAG prefers to extrapolate the CORAL data directly, to capture any trends that might be present in the data and lost in the estimation of a single hazard ratio.

The company proceeded to apply the hazard ratio for OS estimated from the earlier MAIC to their preferred OS extrapolation for loncastuximab tesirine. The limitation with the company's approach is that this hazard ratio came from the restricted and weighted population of LOTIS-2, which differs from the population of LOTIS-2.

A consequence of the company's approach is that chemotherapy patients are modelled to have a much larger post-progression survival time than those receiving loncastuximab tesirine. The EAG explored the models fitted directly to the CORAL data and found that a generalised gamma extrapolation combined with the other EAG assumptions predicted a post-progression survival time that was very similar to loncastuximab tesirine.

4.2.6.2.2 Progression-free survival

Loncastuximab tesirine PFS

The company implement an identical approach for the PFS extrapolations. The data from the complete and unweighted population of LOTIS-2 were used for model fitting in the company base case.

The generalised gamma clearly had the lowest AIC and BIC and also was a good visual fit to the data. However, under the company's assumptions, the PFS model converges onto the OS extrapolation at around 5 years, meaning there are no patients present in the post-progression health state beyond this point. The EAG find this to be unsupported by the evidence, and so prefer to use a log-normal model which is fitted to the MAIC weighted PFS data.

As a scenario, the EAG also explore extrapolating unweighted investigator assessed PFS.

Chemotherapy PFS

No information was available to assess PFS for chemotherapy, or estimate a relative effect. The company proceed to assume that the proportional hazards assumption holds and that the hazard ratio of effect is identical to that for overall survival, as estimated in the MAIC. Given a lack of alternative options, the EAG is unable to suggest a robust alternative approach and so maintain this assumption in the EAG base-case.

The company could have explored the possibility of estimating a hazard ratio between OS and PFS for loncastuximab tesirine and applying this to chemotherapy OS extrapolation, however it is possible this would have obtained a similar result.

4.2.6.2.3 Overview of time-to-event modelling for loncastuximab tesirine and chemotherapy

The results of the company's base case assumptions for their modelling of loncastuximab tesirine and chemotherapy are shown in the Markov traces in Figure 15 and Figure 16 respectively. The Markov traces for the EAGs preferred assumptions are shown in Figure 17 and Figure 18. The EAG's set of assumptions maintain a post-progression health state for both treatments, and ensure a balanced post-progression survival time.

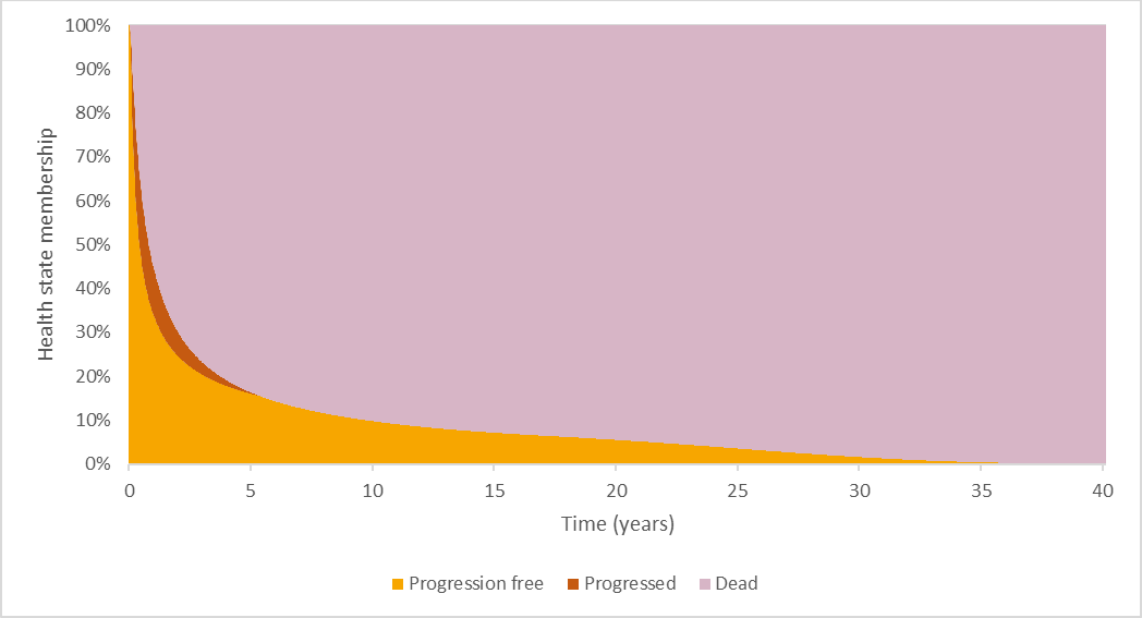

Figure 15: Markov trace for loncastuximab tesirine using company's base case assumptions

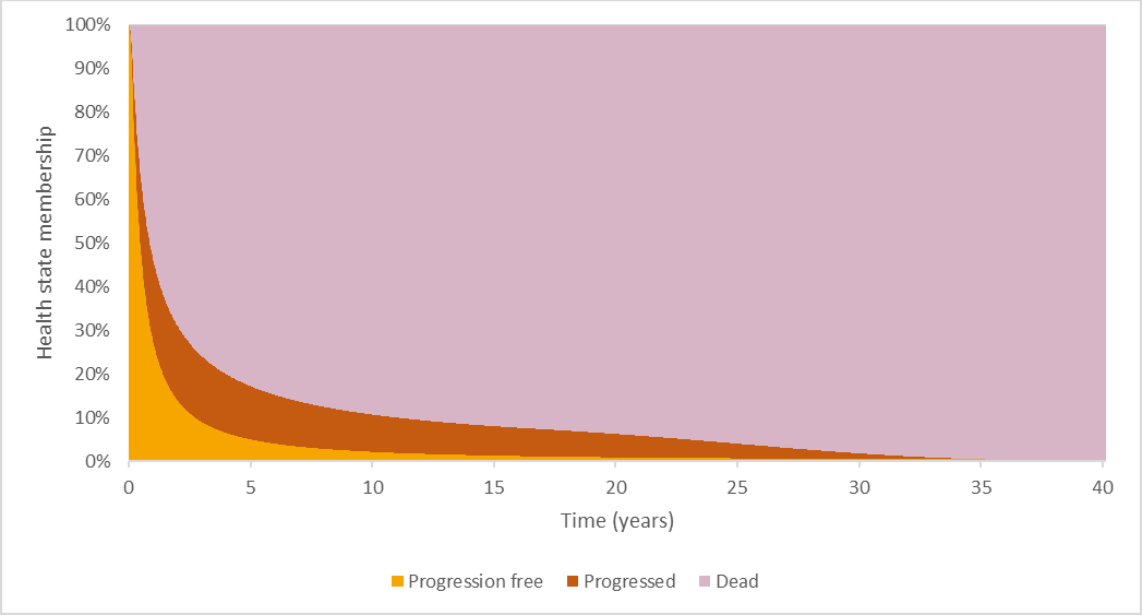

Figure 16: Markov trace for chemotherapy using company's base case assumptions

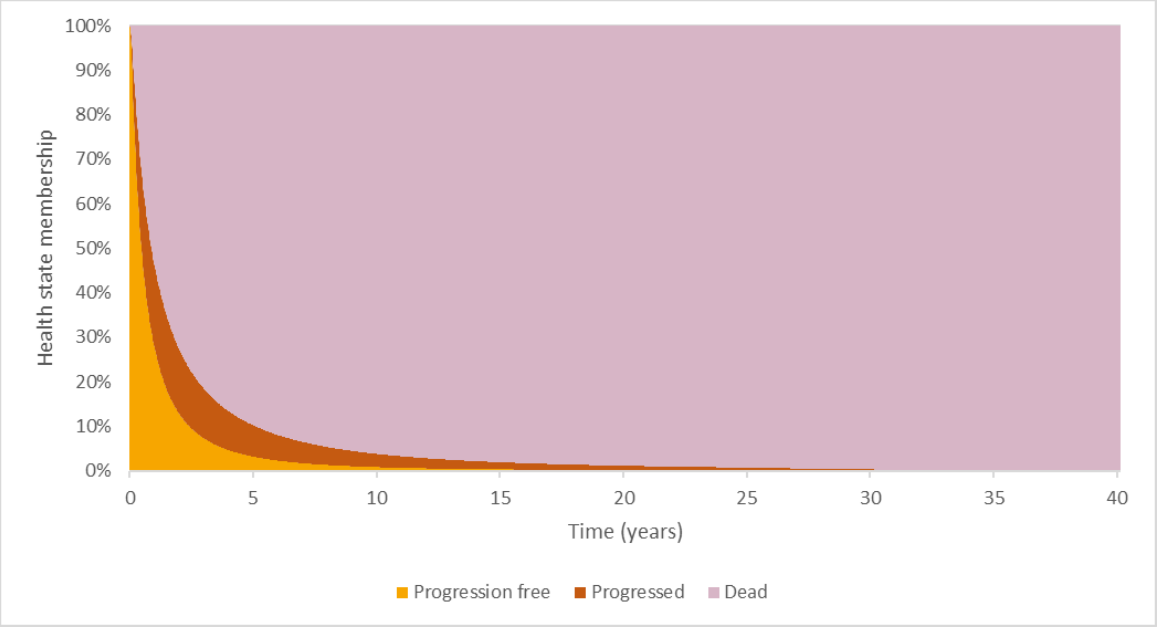

Figure 17: Markov trace for loncastuximab tesirine using EAG's base case assumptions

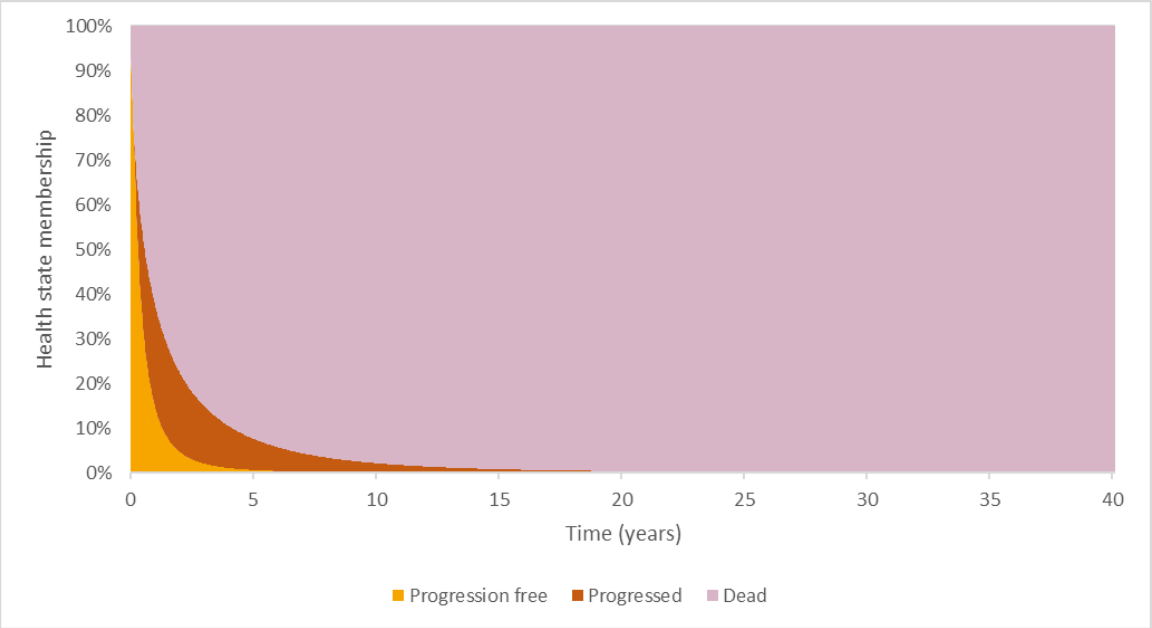

Figure 18: Markov trace for chemotherapy using EAG's base case assumptions

4.2.6.2.4 Time to treatment discontinuation

Loncastuximab TTD

The company selected a generalised gamma model fitted to the TTD data for the whole LOTIS-2 population. The maximum duration was capped at a year, however most patients had stopped prior to this. These data were mature, and multiple models could have been used with little variability in their estimates. Hence the EAG is content with the company's choice of model.

However, as with the other outcomes, the EAG prefer to extrapolate MAIC weighted data, and does so using a generalised gamma in the EAG base case.

Chemotherapy TTD

The company assume that patients receive the full 3 month fixed duration of chemotherapy unless they experienced disease progression prior to completion. The EAG accepts this rationale.

4.2.7 Health related quality of life

The utility values were calculated based on EQ-5D-5L data (mapped onto EQ-5D-3L valuation set) collected in LOTIS-2. Linear mixed regression models were used to estimate utilities for the different heath states (PFS and PPS). Two models were estimated, one adjusting for progression status and ongoing Grade ≥3 AEs, and the other adjusting for progression status only. Both models adjusted for baseline utility centred on the mean. The company chose Health State Utility Values (HSUVs) from the first model which adjusts for grade 3 AEs and progression status in the base case analysis.

Age-related disutility was applied to the estimates using general population utility values for the UK taken from Hernández Alava et al, 2023.[43]

4.2.7.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified a total of 13 studies which reported health state utility values (HSUVs) associated with patients with R/R DLBCL in the 3L+ treatment setting. Out of these, the company considered the utility values of TA649, TA559, TA567 and the studies of Wang et al., as most relevant.[19, 23, 25, 44]

4.2.7.2 Health state utility values

The utility values resulting from the mixed effects model were used to inform the health states in the model for loncastuximab and both comparators and absolute utility values from the ZUMA-1 trial (reported in NICE TA559) and the Juliet trial (reported in NICE TA567) were tested in scenario analyses (**Table 22**). Additional

scenarios applying the progression decrement from each trial to the baseline value from LOTIS-2 were tested and these modelled health state utility values from previous appraisals are presented in Table 23. The CS does not provide justification for why utility values from Wang et al. were not explored in scenario analysis even though they were deemed relevant.

- The EAG believes the values from Wang et al. were not adaptable to the loncastuximab model structure

Table 22: Base case utility values and scenario utility values

Scenario	State	Utility values	Standard Error	Source
Base case	PFS	0.685	0.01	Utility values estimated using mixed regression methods and based on LOTIS-2 pivotal trial
	Disutility for progressed disease	-0.056	0.021	
	AE disutility	-0.045	0.16	
Scenario (ZUMA-1 trial) used in TA649 and TA559	PFS	0.72	0.03	Neelapu 2017, et al.[45]
	PPS	0.65	0.06	
Scenario (Juliet trial) used in TA567	PFS	0.83	-	Schuster 2019, et al.[46]
	PPS	0.71	-	
Source: Table 74 CS; Table 34 (Company Submission Appendices)				

Table 23: Health state utility values

Health state	Utility value (disutility associated with progression)	Source
Progression-free	0.72	ZUMA-1 [45]
	0.83	JULIET [46]
Progressed disease	0.65 (0.07)	ZUMA-1 [45]
	0.71 (0.12)	JULIET [46]

4.2.7.3 Adverse event disutilities

The impact of adverse events (AEs) on HRQoL was modelled as a once-off QALY loss at the beginning of the first cycle based on AE rates for each comparator [19, 25], mean durations of AEs (LOTIS-2 data used for all comparators) and the AE disutility

(Table 24). Only Grade ≥ 3 AEs with an incidence rate > 5%, were included in the model and this is consistent with recommended approach taken in previous health technology appraisals.[47] For the base case analysis, a mean disutility value of 0.045 was assumed to apply to all AEs in the model for all treatments. This was calculated from mixed effects regression model used to analyse EQ-5D-3L utilities for loncastuximab tesirine based on LOTIS-2 data. The mixed effects regression model adjusted for progression status (i.e., whether the patient had progressed disease at time of completing EQ-5D-5L questionnaire) and ongoing AE (i.e., patient was experiencing AE at the time of completing questionnaire). A scenario is presented that explores the impact, on ICER, of using AE disutilities from previous NICE appraisals in R/R DLBCL [19, 25]

Table 24: AE disutilities and durations

Adverse event	Disutility (LOTIS-2)	Duration (days)	Disutility (scenario)
Neutropenia	0.045	8.95	0.090
Thrombocytopenia		13.45	0.110
Gamma-glutamyltransferase increase		0†	0.000
Anaemia		5.67	0.250
Leukopenia		9.05	0.090
Hypophosphatemia		6.08	0.250
Lymphopenia		16.64	0.090
Hypokalaemia		7.14	0.090
Febrile neutropenia		5.5	0.150
Lower respiratory tract infection		6.75	0.200
Diarrhoea		6.75	0.100
Fatigue		2	0.012
Nausea		6.75‡	0.050
Vomiting		6.75‡	0.050

†Assumed to have no impact of quality of life
‡Assumed equal to diarrhoea
Abbreviations: AE, adverse event.
Source: Table 70 (CS)

EAG Comments

- The company used an acceptable approach to selecting AEs to include in the model

- Applying impact of AEs as a one-off QALY loss is consistent with approach taken in previous appraisals. Clinical advice suggests that AEs occur most frequently within the first weeks of treatment
- Whereas previous NICE appraisals have applied one-time AE-related utility decrement at the beginning of the first cycle based on treatment-specific AE risks, mean durations of AEs, and the additive disutility associated with AEs, the company applied the same disutility value of 0.045 across all AEs. The chosen value is lower than literature-cited disutility values (except for fatigue) and using this approach will bias in favour of treatment with higher incidence of AEs. The company has presented scenario analysis to indicate the impact of alternative assumptions.

4.2.8 Resources and costs

4.2.8.1 Intervention and comparator costs

The costs of loncastuximab tesirine for each cycle were made up of drug acquisition (**Table 25**) and administration costs (**Table 26**; **Table 27**). Dosing schedule followed that in LOTIS-2 trial: 150 µg/kg for 2 cycles, 75 µg/kg thereafter. Relative dose intensity (RDI) data was taken from LOTIS-2 for loncastuximab tesirine. Dexamethasone (4mg) was given twice daily for 3 days. Vial wastage was included in the costs of the drug, and where multiple vial sizes were available, the smallest possible vial wastage was assumed.

A patient access scheme (PAS), incorporating discounted drug price (£[redacted] per vial and £[redacted] for average course of treatment) was applied to the loncastuximab tesirine drug acquisition costs. The base case analysis of the economic evaluation was based on loncastuximab tesirine drug costs (with PAS applied).

The drugs costs for comparators included acquisition and administration costs. The CS does not state the source of the dosing schedule for comparators; this was assumed to be TA649 for Pola+BR. RDI for Pola+BR was based on TA649 whilst Table 25 and Table 27 show the drug acquisition and administration costs for comparators and the targeted doses. Vial wastage was included in calculating costs for drugs that are dosed by weight or body surface area (BSA) using the method of

moments and assuming a normal distribution around the mean weight or BSA. All comparator drug costs were based on list prices

Table 25: Drug acquisition costs

Regimen	Drug	Strength	Units / pack	Cost/ pack	Target dose	RDI	Cost/ cycle
Loncastuximab	Loncastuximab tesirine	10 mg	1	List price: £15,200.00 PAS price: [redacted]	150 µg/kg for 2 cycles, 75 µg/kg thereafter	98.09 %	Cycles 1 & 2: [redacted] Cycle 3+: [redacted]
	Dexamethasone	4 mg	50	£19.62	4 mg orally, twice daily for 3 days	98.09 %	£2.35
Pola+BR	Polatuzumab vedotin	30 mg	1	£2,370.00	1.8 mg/kg	99.5%	£11,687.32
		140 mg	1	£11,060.00			
	Bendamustine	25 mg	5	£34.08	90 mg/m^2	95.4%	£65.91
		100 mg	5	£82.89			
	Rituximab	100 mg	1	£157.17	375 mg/m^2	99.4%	£1,169.94
		500 mg	1	£785.84			
RGemOx	Rituximab	100 mg	1	£157.17	375 mg/m^2	100%	£1,177.00
		500 mg	1	£785.84			
	Gemcitabine	200 mg	1	£8.59	1000 mg/m^2	100%	£39.40
		1000 mg	1	£3.30			
	Oxaliplatin	50 mg	1	£46.78	100 mg/m^2	100%	£66.61
		100 mg	1	£60.29			
		200 mg	1	£20.45			

Abbreviations: Pola+BR, polatuzumab plus bendamustine rituximab; RDI, relative dose intensity; R-GemOx, rituximab, gemcitabine and oxaliplatin; TBC, to be confirmed.

Source: Table 75 (CS)

Table 26: Drug administration costs by currency code

Currency code	Description	Setting	Cost
SB13Z	Deliver more Complex Parenteral Chemotherapy at First Attendance	Outpatient	£258.56
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	Outpatient	£342.66
SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle	Outpatient	£438.38

Source: Table 76 (CS)

Table 27: Drug administration costs by regimen

Regimen	Per cycle administration cost
Loncastuximab tesirine	£258.56
Pola+BR	£696.94
RGemOx	£342.66

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

Source: Table 77 (CS)

* Administration costs for Pola+BR are consistent with what was reported in TA649

4.2.8.1 Cost of subsequent treatments

Subsequent treatments were included in the model as an average one-off cost to patients entering the PPS heath state, taking into account the mean duration of treatment, the proportion assumed to use each treatment option (i.e. treatments available at fourth and subsequent lines of R/R DLBCL treatment) and the costs.

The CS stated that data on subsequent therapy use were based on clinical input, but the advice on what proportion of patients are expected to receive subsequent treatment and the type of therapy received, varied. Table 28 and Table 29 show the mean duration and percentage share of each therapy class included in the post-discontinuation treatment for loncastuximab tesirine, Pola+BR and chemotherapy and the total post-discontinuation costs which were highest for the Pola+BR arm and loncastuximab tesirine arm in the comparison between loncastuximab tesirine and Pola+BR (Table 28)..

*Company submission states subsequent therapies were applied as a one-off cost at the time of a PFS event rather than a PPS event. The EAG considers this a textual error as model applies costs at occurrence of PPS event.

Table 28: Subsequent therapy use and costs, loncastuximab tesirine vs. Pola+BR

Treatment	Chemotherapy	AutoSCT	AlloSCT	CAR-T	Average cost
Loncastuximab	54%	3%	8%	11%	£48,004.37
Pola+BR	54%	3%	8%	11%	£48,004.37

Table 29: Subsequent therapy use and costs, loncastuximab tesirine vs. chemotherapy

Treatment	Chemotherapy	AutoSCT	AlloSCT	CAR-T	Average cost
Loncastuximab	54%	3%	8%	0%	£12,180.53
Chemotherapy	54%	22%	8%	0%	£18,258.25

EAG Comments

- The EAG's clinical advisor confirmed that the rates of subsequent therapy use for loncastuximab tesirine and Pola+BR appear reasonable. However, for the chemotherapy arm, it is unlikely that 54% of patients who were on chemotherapy at 3rd line will go on to receive chemotherapy as 4th line treatment. The rate of subsequent autoSCT for the chemotherapy arm is a key source of uncertainty raised in previous appraisals [25]. In TA567, the company assumed that no patients in salvage chemotherapy arm would receive subsequent SCT (based on clinical advisor input which predicted less than 5% of patients would go on to SCT) whilst the EAG's clinical advisor predicted that 20-25% of patients may go on to receive SCT [25]. The EAG explores the impact, on ICER, of differing SCT rates from 0% to 25% in scenario analysis. For the EAG's base case analysis, the EAG assumes the same rate of subsequent autoSCT (3%) in chemotherapy arm as applied by the company for loncastuximab tesirine.

4.2.9 Severity

Severity is one the of the decision-making modifiers (i.e., a value judgement previously applied to treatments at end of life) that the committee will consider when evaluating treatments for patients with severe disease. For the reference case, the committee considers all QALYs as being of equal weight. However, when the treatment being appraised is for a severe disease, a QALY weighting may be formally applied to give extra weights to the QALY gains (benefits) of the appraised technology . NICE's new severity modifier considers two different – but related – measures of disease severity: absolute QALY shortfall (AS) and proportional QALY

shortfall (PS). Absolute shortfall represents the number of future QALYs that are lost by people living with the disease and *on current standard of care* whilst proportional shortfall represents the proportion of future QALYs that are lost by people living with the disease and *on current standard of care*. If both scores indicate that a QALY weight should be applied, and the weights differ, the higher weight is applied. The current approach reflects a spectrum of severity using 3 categories or cut-offs. This means that a QALY weight of 1 does not imply that the disease is not severe but that the proportional and/or absolute QALY shortfalls under current standard of care do not justify applying a severity weighting (i.e., the AS <12 and PS <0.85).

Table 30 below shows the cut-off levels for AS and PS used to guide the QALY weights for adjusting the QALYs in the reference case.

Table 30: **QALY weightings for severity**

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

In its submission, the company could not provide evidence that a QALY weighting was justified when Pola+BR is the comparator treatment (i.e., established current treatment) for people with this condition and at 3rd line of treatment within the NHS. However, the company analysis indicated that, a 1.2x severity modifier adjustment was justified if chemotherapy was the established current treatment.

The company's QALY shortfall analysis followed the NICE's health technology evaluations manual. Absolute QALY shortfall was estimated as the future health lost by adult patients living with the condition, including quality and length of life compared with the expected future health that adults without the condition would accrue over their remaining lifetimes. Proportional QALY shortfall was estimated as the proportion of future health that is lost by people living with the condition, including quality and length of life. The number of QALYs that the general population living without the condition would be expected to accrue for the rest of their lifetime was

estimated to be 11.66 and was based on the characteristics of the LOTIS-2 trial population i.e., age =62.72 years and proportion females = 41%. The remaining QALYs accrued by people living with the condition and on current standard of care were estimated using the company's base case cost-effectiveness model. These were [redacted] for Pola+BR and [redacted] for chemotherapy. The resulting QALY shortfalls (absolute and proportional) are shown in Table 31 below and correspond to QALY weights of 1.0x and 1.2x for Pola+BR and chemotherapy, respectively in accordance with NICE guidance (Table 31).

Table 31: Summary of QALY shortfall analysis based on mean QALYs derived from company's deterministic cost-effectiveness analysis

Factor	Mean QALY in expectation	Absolute shortfall	Proportional shortfall	Corresponding QALY weight
No disease	11.66	N/A	N/A	
Pola+BR	[redacted]	[redacted]	[redacted]	1.0
Chemotherapy	[redacted]	[redacted]	[redacted]	1.2

EAG comments

- The company appropriately estimated the absolute and proportional QALY shortfalls, separately by comparator arm, using preferred value sets (i.e., Hernández Alava et al. (2023)[43] to crosswalk from EQ-5D-5L to EQ-5D-3L).
- The EAG was able to replicate the QALY shortfall values in the company submission.
- The EAG recalculated the QALY shortfalls based on EAG's base case assumptions and arrived at the same conclusions as the company i.e., a severity weighting does not apply for Pola+Br comparison but a x1.2 weighting applies for chemotherapy comparison. The proportional QALY shortfall based on EAG's base case assumptions for chemotherapy comparison was 0.939.
- It is worth noting the company considers Pola+BR the most appropriate comparator for this appraisal, suggesting that a severity QALY weighting is unlikely to apply for this appraisal.

5 COST EFFECTIVENESS RESULTS

5.1 *Company's cost effectiveness results*

The company base case assumed the following distribution for PFS and OS for the Loncastuximab population (Table 32).

Table 32: Summary of survival outcomes assumptions applied in the economic model

Parameter	Model base case
Lonca PFS	Generalised gamma
Lonca OS	Generalised gamma
Lonca TTD	Generalised gamma
Pola+BR PFS	Generalised gamma
Pola+BR OS	Generalised gamma
Chemotherapy OS	Proportional hazard assumed and hazard ratio applied.
Chemotherapy PFS	Proportional hazard assumed and hazard ratio applied.

The discounted and undiscounted costs and QALYs between Loncastuximab and its comparators are shown below in Table 33

Table 33: Base case total costs and total QALYs for loncastuximab, Pola+BR and chemotherapy

	Lonca, G029365 weighted	Lonca, CORAL ext. weighted	Pola+BR	Chemotherapy
Total costs (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]

The results for the company's base case cost-effectiveness analysis, provided at clarification, are presented below (**Table 34**; **Table 35**). The ICERs are presented at 3 severity weightings.

EAG comment:

- The CS indicates that a QALY weighting does not apply for Pola+BR; a x1.2 severity weighting weighting would apply for chemotherapy comparison based on proportional QALY shortfalls

Table 34: New base-case deterministic cost-effectiveness results, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine)

Severity modifier	Comparator	Total costs	Total QALYs	ICER (£/QALY)
No severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated
1.2 severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated
1.7 severity modifier	Loncastuximab	[redacted]	[redacted]	-
	Pola+BR	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; loncastuximab, loncastuximab tesirine; PAS, patient access scheme; Pola+BR, polatuzumab plus bendamustine plus rituximab; QALYs, quality-adjusted life years; vs, versus.

Source: Table 20 Company clarification responses

Table 35: Submitted base-case deterministic cost-effectiveness results, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

Severity modifier	Comparator	Total costs	Total QALYs	ICER (£/QALY)
No severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£48,986
1.2 severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£40,821
1.7 severity modifier	Chemotherapy	[redacted]	[redacted]	-
	Loncastuximab	[redacted]	[redacted]	£28,815

Source: Table 21 Company clarification responses

EAG Comments:

Plausibility of the cost-effectiveness estimates

In the company's base case, the table of disaggregated outcomes (**Table 36**) suggests a much improved mean PFS for loncastuximab compared to Pola+BR (almost +18 months) despite a reduced median PFS (-1.15 months). This lacks clinical plausibility.

Table 36: Disaggregated outcomes – cost-effectiveness analysis

	Loncastuximab	Chemotherapy	Pola+BR	Incremental vs. Pola+BR
Median PFS (months)	[redacted]	[redacted]	[redacted]	[redacted]
Mean PFS (months)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (months)	[redacted]	[redacted]	[redacted]	[redacted]
Mean post-progression survival (months)*	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS (months)	[redacted]	[redacted]	[redacted]	[redacted]
PFS QALY	[redacted]	[redacted]	[redacted]	[redacted]
PD QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
PFS, progression-free survival; OS, Overall survival; QALYs, quality-adjusted-life years				

At clarification stage, the company was asked to explain the discrepancy and replied that the mean PFS was higher for loncastuximab tesirine compared with Pola+BR due to a longer tail in the PFS curve for loncastuximab tesirine. They added that "*clinical experts highlighted that patients that are progression free after 2 years are often discharged from care and there is evidence of a plateau in survival for patients treated with loncastuximab, without the need for further therapies, indicating that a proportion of patients achieve long-term remission on loncastuximab*".

In the EAG's view, this latter statement is not supported by robust evidence, which explains why eventually the company choose not to assume an assumption of cure in the base-model case.

With regards to the longer tail in the PFS curve for loncastuximab tesirine compared to Pola+BR, the EAG considers that there is also little evidence to support this. Indeed, the number of patients still at risk in the PFS KM curve is very limited (10 at 12 months and 8 at 18 months for loncastuximab tesirine weighted population versus 17 at 12 months and 4 at 18 months for the GO29365 extension study) which means interpretation of PFS curves beyond 12 months should be made very cautiously.

One would expect a similar distribution between pre-progression and post-progression LY and QALY between loncastuximab tesirine and Pola+BR.

However, based on the values reported above:

- This distribution in terms of LYs is respectively 78%/22% for loncastuximab tesirine and 37%/67% for Pola+BR
- this distribution in terms of QALYs is respectively 79%/21% for loncastuximab tesirine and 40%/60% for Pola+BR.

These distributions suggest a strong imbalance that is not explained by clinical evidence or a specific mechanism of action that one drug may have relative to the other. The implications are notable since an increase of the life expectancy within the pre-progression health state, as seen for loncastuximab tesirine, is associated with an increase of quality of life and therefore contributes to increasing the gain of QALYs compared to Pola+BR.

5.2 *Company's sensitivity analyses*

Loncastuximab vs Pola+BR

The company conducted a range of deterministic and probabilistic sensitivity analyses (PSA) on the base case. PSA included 5000 Monte Carlo simulations. Compared to Pola+BR, loncastuximab tesirine was dominant in [redacted]% of simulations, more effective in [redacted] of simulations and cost saving in [redacted] of simulations (see Figure 19; Figure 20

Figure 19 probabilistic cost-effectiveness results, loncastuximab tesirine vs Pola+BR: simulations (with PAS price for loncastuximab tesirine)

Figure 20 Base case cost-effectiveness acceptability curve, loncastuximab tesirine vs Pola+BR (with PAS price for loncastuximab tesirine

The results of the revised univariate sensitivity analysis are presented in the form of a tornado diagram below (Figure 21). The most influential parameters for the comparison to Pola+BR are parameters related to survival models for PFS. In the

comparison to Pola+BR, loncastuximab tesirine is either cost-effective in the south-west quadrant or dominant in all scenarios.

Figure 21 Base case deterministic sensitivity analyses, loncastuximab tesirine vs Pola+BR: tornado diagram (with PAS price for loncastuximab tesirine)

Denotes a south-west quadrant ICER, i.e. loncastuximab tesirine is less costly and less effective.
Abbreviations: 3L+, third-line plus; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPI, International Prognostic Index; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; Pola+BR, polatuzumab plus bendamustine plus rituximab; TTD, time to discontinuation; vs, versus

Loncastuximab vs Chemotherapy

Loncastuximab tesirine was cost-effective in [redacted] of scenarios at a WTP threshold of £50,000. The probabilistic cost-effectiveness results and the CEAC at different WTP thresholds are shown in Figure 22 and Figure 23.

Figure 22 Probabilistic cost-effectiveness results, loncastuximab vs chemotherapy: simulations (with PAS price for loncastuximab tesirine)

Figure 23 Cost-effectiveness acceptability curve, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)

For the comparison to chemotherapy ICERs range from [redacted], with parameters linked to OS being the most influential (Figure 24).

Figure 24 Deterministic sensitivity analyses, loncastuximab tesirine vs chemotherapy: tornado diagram (with PAS price for loncastuximab tesirine)

5.3 *Model validation and face validity check*

The EAG conducted an extensive review of the model submitted by the company.

- The model appears to reflect the assumptions made by the company. However, the EAG were unable to produce CEAC for its preferred scenarios using the company's model as running the PSA reverted to company's default assumptions.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 *Exploratory and sensitivity analyses undertaken by the EAG*

The EAG's main exploratory analyses informed the base case and are described below (section 6.3). In addition, the EAG conducted a sensitivity analysis varying the proportion of patients on autoSCT in chemotherapy arm and the results are presented in **Table 37** below.

Table 37: Deterministic cost-effectiveness results exploring impact of differing autoSCT rates in chemotherapy arm

Technology	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
0% subsequent autoSCT					
Chemotherapy	[redacted]	[redacted]			
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£56,641
5% subsequent autoSCT					
Chemotherapy	[redacted]	[redacted]			

Technology	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£54,915
10% subsequent autoSCT					
Chemotherapy	[redacted]	[redacted]			
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£53,190
15% subsequent autoSCT					
Chemotherapy	[redacted]	[redacted]			
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£51,464
20% subsequent autoSCT					
Chemotherapy	[redacted]	[redacted]			
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£49,738
25% subsequent autoSCT					
Chemotherapy	[redacted]	[redacted]			
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£48,013

6.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Table 38 summarises the main issues highlighted by the EAG throughout this report that could impact loncastuximab tesirine's cost-effectiveness.

It shows the expected direction of bias introduced by these issues and whether these are examined in any exploratory analyses or incorporated in the EAG base-case

Table 38: Main EAG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER	EAG analyses	Addressed in company analyses
Population, intervention and comparators, perspective, and time horizon (Section 4.2.3 to 4.2.5)			
The base case analysis includes Pola+Br which the EAG has some reservations	NA	None	No
Treatment effectiveness and extrapolation (Section 4.2.6)			
Overly optimistic OS and PFS extrapolations for loncastuximab	+	Base case	No
Choice of parametric extrapolations for loncastuximab PFS and OS	+/-	Base-case Scenarios	Scenarios
Lack of data to model relative effect (PFS benefit) of loncastuximab versus chemotherapy	Unknown	None	No
Inconsistent application of two-stage adjustment to remove effect	+/- (small impact)	No	No

Issue	Likely direction of bias introduced in ICER	EAG analyses	Addressed in company analyses
of CAR-T in some loncastuximab patients for chemotherapy comparison			
Resource use and cost (Section 4.2.8)			
Rate of subsequent autoSCT in chemotherapy uncertain	+	Base case Scenarios	No
Cost-effectiveness analyses (Section 5.1 to 6.4)			
Different base case assumptions and scenarios were explored	+ and -	Base case Scenarios	Scenarios
Severity 4.2.9			
Choice of severity weighting to apply in appraisal	+	Base case	Scenarios
Footnotes: Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; '+/-' indicates that the bias introduced by the issue is unclear to the EAG; while '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator and '+and -' indicates the EAG believes the potential bias can be positive or negative depending on the assumptions used.			

6.3 *EAG's preferred assumptions* (EAG revised base case)

The adjustments made to the company's model are summarised below for each pairwise comparison.

Loncastuximab tesirine vs Chemotherapy

EAG 01: OS loncastuximab data source changed from unweighted two-stage to CORAL weights two-stage to reflect the MAIC analysis undertaken on loncastuximab population.

EAG 02: OS loncastuximab distribution changed from Gamma to Log-normal given the uncertainty around the long-term extrapolation of OS.

EAG 03: PFS loncastuximab data source changed from unweighted IRC to CORAL extension study weights to reflect the MAIC analysis undertaken and better align both populations.

EAG 04: TTD data source changed from unweighted to CORAL extension study weights.

EAG 05: Proportion of progressed cohort who receive AutoSCT changed from 22% to 3%.

Loncastuximab vs Pola+BR

In all scenarios, TTD was set equal to the PFS in line with the company's base case assumptions.

EAG 01: Loncastuximab OS extrapolation changed from generalised gamma to log-normal

EAG O2: Loncastuximab OS extrapolation changed from generalised gamma to log-normal

EAG 03: Pola+BR OS set equal to loncastuximab OS (with a log-normal extrapolation for Loncastuximab OS)

EAG 04: Pola+BR PFS set equal to loncastuximab PFS (with a log-normal extrapolation for Loncastuximab PFS).

Table 39 shows the impact of individual assumptions on the ICER.

Table 39: Impact of individual EAG's preferred model assumptions on ICER

Preferred assumptions	**EAG report sections**	**ICER**
Loncastuximab vs Chemotherapy		
Company base case		**£48,986**
EAG 01: OS data source changed from unweighted two-stage to CORAL weights two-stage	4.2.6	£48,005
EAG 02: OS distribution changed from Gen Gamma to Lognormal	4.2.6	£70,337
EAG O3: PFS data source changed from unweighted IRC to CORAL extension study weights	4.2.6	£49,052
EAG 04: TTD changed from unweighted to CORAL extension study weights.	4.2.6	£44,490
EAG 05: AutoSCT subsequent therapy changed from 22% to 3%	4.2.8.1	£55,606
Loncastuximab vs Pola+BR		
Company base case		Pola+BR Dominated
EAG O1: Loncastuximab OS changed to log-normal	4.2.6	£154,225
EAG 02: Loncastuximab PFS changed to log-normal	4.2.6	£359,367 (SW quadrant: Loncastuximab Cost-saving)
EAG 03: Pola+BR OS set equal to Loncastuximab	4.2.6	Pola+BR Dominated

Preferred assumptions	EAG report sections	ICER
EAG 04: Pola+BR PFS set equal to Loncastuximab	4.2.6	£317,96 (SW quadrant: Loncastuximab Cost-saving)

EAG deterministic base case results

The cumulative results of all EAG changes on the deterministic cost-effectiveness results for each pairwise comparison is shown in Table 40 below

For the chemotherapy comparison, the incremental costs were £43,616 and incremental QALYs were 0.55 which resulted in an ICER of £79,832. The main driver of the increased ICER was the choice of the OS curves. For the Pola+BR comparison, the incremental costs were -£10,174 and the QALYs were equivalent. The main driver of the ICER was the cost of Pola+BR, choice of parametric curve used to extrapolate loncastuximab tesirine and proportion of individuals partitioned to each health state.

Table 40: EAG Deterministic base case cost-effectiveness analysis including PAS discount for loncastuximab tesirine

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Loncastuximab vs Chemotherapy					
Loncastuximab	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£79,832
Loncastuximab vs Pola+BR					
Loncastuximab	[redacted]	[redacted]			
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	Loncastuximab (Cost-saving)

EAG Probabilistic base case cost-effectiveness results

The EAG base case was subject to a probabilistic sensitivity analysis using 1000 iterations drawn from EAG parametric assumptions. For the Pola+BR comparison, the incremental costs were -£5,435 and the QALYs were equivalent. For the

chemotherapy comparison, the incremental costs were £55,392 and incremental QALYs were 0.68 generating an ICER of £78,857.

EAG scenario analysis

Loncastuximab vs Chemotherapy

Given the sensitivity of the health state distribution about parametric extrapolation, the EAG explores the following scenarios. In all scenarios, the EAG maintains its base case assumption unless otherwise specified in the chosen scenario.

Scenario 1: Gen gamma used for OS Loncastuximab distribution.

Scenario 2: unweighted PFS-INV data source used to extrapolate PFS Loncastuximab distribution.

Scenario 3: unweighted PFS-INV data source used to extrapolate PFS Loncastuximab distribution using company base case.

The impact of each scenario on deterministic ICER is presented in Table 41

Table 41: Impact of alternative assumptions explored in scenario analyses on ICER

	Incremental costs	Incremental QALYs	Incremental £/QALYs
Scenario 1	[redacted]	[redacted]	£48,005
Scenario 2	[redacted]	[redacted]	£85,888
Scenario 3	[redacted]	[redacted]	£66,656

6.4 *Conclusions of the cost effectiveness section*

In summary, the model constructed by the company appears to be logical.

The EAG has the following concerns regarding the cost-effectiveness analysis (as detailed in Section 1.1):

- Uncertainty in the estimates of relative effectiveness of loncastuximab tesirine compared with comparator interventions obtained from the ITCs. The EAG was particularly concerned that the OS and PFS benefits modelled by the company were unsupported by the MAIC analysis. The EAG has explored

alternative assumptions regarding OS and PFS benefits, including choosing alternative parametric distributions and this has varying impact on the ICER.

- Uncertainty in the rate of subsequent autoSCT for the chemotherapy arm.
    - The company's choice of rate of subsequent autoSCT for patients in chemotherapy arm appears too high. This has a significant impact on costs of subsequent treatment and consequently on the ICER. The EAG has explored, via scenario analysis, the impact on cost-effectiveness of differing autoSCT rates in chemotherapy arm. This considers the clinical expert opinions from previous appraisals.

Other important factors that had an impact on the cost-effectiveness results included:

- The choice of severity modifier to apply: the company provides cost-effectiveness results across the 3 severity cut-off levels but does not appear to indicate which modifier should apply for the appraisal.

The EAG have presented scenarios with a preferred base-case analysis for each pairwise comparison. The ICER has increased compared with the CS.

7 SEVERITY MODIFIERS

NICE's approach to using severity as a decision modifier is based on proportional and absolute QALY shortfall (section 4.2.9)

- NICE proposes shortfall be calculated based on the difference in the quality-adjusted life expectancy (QALE) of a person with and a person without a particular disease (at a given age)
    - Absolute shortfall = expected total QALY loss
    - Proportional shortfall = percentage of the QALYs that are lost

Table 42 shows the information required to calculate QALY shortfall and the EAG's assessment of the company's QALY shortfall analysis are summarised based on that.

Table 42: QALY shortfall calculation checklist

Element of QALY shortfall assessed	Current guidance *	EAG comment on company's submission
QALE for general population		
Mean age and sex	Mean age and sex in general population should reflect patient population with the condition, at the point in the pathway where technology is being assessed. i.e., using the same values as that for the economic modelling	Yes. Mean age and sex estimates based on LOTIS-2 data
Life tables (probability of death by age and sex)	Life tables used should be consistent with what was used in submitted cost-effectiveness model	Yes
Quality of life by age and sex	No source specified but for consistency default source should be the same for CEA as for QALE for general population	Yes
Discount rate	Reference case discount rate (3.5%) to be used	Yes
QALYs accrued by patients with the condition	Expectation is values taken directly from comparator arm of submitted cost-effectiveness model	Yes. QALYs based on submitted CEA model
CEA, cost-effectiveness analysis; QALYs, quality-adjusted life years; QALE, quality-adjusted life expectancy		

***** There are situations when adjustments to QALY shortfall analysis may be needed, and in such cases the approach used may deviate from current guidance in table

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9 APPENDICES

Appendix 1: EAG assessment of risks of bias of the CS systematic review

ROBIS domain, and signalling questions	EAG's assessment of whether criteria met, with comments
1: Study eligibility criteria	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably yes.** Eligibility criteria are outlined in table 5, appendix D. Inclusion and exclusion criteria were applied to the search strategy.
1.2 Were the eligibility criteria appropriate for the review question?	1 **Yes**. The objective of the submission was to evaluate the efficacy and safety of loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies. All areas were covered within the criteria reported.
1.3 Were eligibility criteria unambiguous?	**Yes.** All eligibility criteria clear in table 5, appendix D.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Yes.** Restrictions were applied to the population, interventions, comparators, study design and publication type. The EAG deemed All restrictions appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes.** Information regarding restrictions in eligibility criteria is provided in table 5, appendix D. Studies were excluded for not reporting on intervention, comparator and outcomes of interest. Non-English language studies were excluded. Phase I trials, pharmacokinetic studies, reviews/editorials/commentaries/letters, *In vitro*/animal studies/pre-clinical studies and case reports were excluded.
Domain 1 risk of bias	**Low**
2: Identification and selection of studies	
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**. Searches were conducted in an appropriate set of bibliographic databases (MEDLINE, MEDLINE In-Process, EMBASE, CDSR, Cochrane Library).
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**. Supplementary searches of conferences (published between 2019 and 2022) and clinical trial registries were conducted as well as hand searching referencing lists of systematic literature reviews and other grey literature sources.

2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably yes**. Detailed search strategy provided (CS Appendix D, Tables 2 – 4). Suitable terms for the condition, treatment and study types were included and combined appropriately.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Yes**. No restrictions based on date. Language was restricted to English. The restrictions applied to publication format were appropriate.
2.5 Were efforts made to minimise errors in selection of studies?	**Probably yes.** Appropriate study selection by two independent reviewers, with discrepancies resolved by a third reviewer. The PRISMA flow diagram and reasons for exclusion at full-text review are clearly presented (Figure 1 and Table 7, appendix D).
Domain 2 risk of bias	**Low**
3: Data collection and study appraisal	
3.1 Were efforts made to minimise error in data collection?	**Yes**. Data from the included publications were extracted by one reviewer into standardised, piloted data extraction tables (DETs) in Microsoft® Excel. To ensure that the final Excel database was of the highest quality, the information was checked and validated by conducting an independent internal data check once all required data had been entered.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Probably yes**. Extensive information about the LOTIS-2 trial is presented in the CS (Pages 34-68 and appendix D). Additional information is provided regarding the studies included in the SLR and indirect comparisons (appendix D).
3.3 Were all relevant study results collected for use in the synthesis?	**Probably yes**. Extensive information about the LOTIS-2 trial is presented in the CS (Pages 34-68 and appendix D). Additional information is provided regarding the studies identified from the SLR and included in the indirect comparisons (appendix D).
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Partially**. Quality assessment of included studies was performed using the Cochrane RoB2 tool for RCTs and the ROBINS-I tool for comparative cohort studies. Single arm trials (including LOTIS-2), case series and studies published as conference abstracts were not quality assessed.

3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes.** The quality assessment was completed by two independent reviewers.
Domain 3 risk of bias	**Some risk of bias**
4: Synthesis and findings	
4.1 Did the synthesis include all studies that it should?	**Yes.** The search queries are suggestive of a very sensitive search which would mean a very low probability that potentially relevant studies were missed.
4.2 Were all predefined analyses followed or departures explained?	**Yes.** Section B.2.8 Document B
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Yes.** The SLR reported in Section **Error! Reference source not found.** and Appendix D identified studies for loncastuximab tesirine and relevant comparators for the treatment of patients with DLBCL who have received two or more prior therapies. However, as LOTIS-2 is a single group study, there was no connected network to enable a network meta-analysis (NMA). To assess the relative effectiveness of loncastuximab tesirine vs comparators and inform the cost-effectiveness model, indirect comparisons for efficacy outcomes (PFS and OS outcomes) were made using an unanchored MAIC approach.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Yes.** Variation between studies was discussed in the considerations of statistical synthesis such as MAIC.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable due to narrative synthesis.
Domain 4 risk of bias	**Low**
Overall risk of bias in the review	

Appendix 2: EAG assessment of risk of bias in LOTIS-2 (Downs and Black checklist)

Checklist item	EAG judgement and rationale
Is the hypothesis/aim/objective of the study clearly described?	**Yes** Clinical study report states "to evaluate the clinical and cost-effectiveness of loncastuximab tesirine for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy"
Are the main outcomes to be measured clearly described in the introduction or methods section?	**Yes** Primary and secondary endpoints are listed (CS, section B.2.3.6)
Are the characteristics of the patients included in the study clearly described?	**Yes** CS, Table 9
Are the interventions of interest clearly described?	**Yes**
Are the distributions of principal confounders in each group of patients to be compared clearly described?	N/A Only 1 group
Are the main findings of the study clearly described?	Yes See CS, section B.2.6
Does the study provide estimates of the random variability in the data for the main outcomes?	**Yes** Mostly. Confidence intervals are reported
Have all important adverse events that may be a consequence of the intervention been reported?	**Yes** Adverse events reported in CS, section B.2.10
Have the characteristics of patients lost to follow-up been described?	No Only reported information is that there were 5 deaths, and 6 withdrawals
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N/A Results are medians, %. No comparisons were made
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Unable to determine Extensive inclusion/exclusion criteria, not stated in clinical study report if sample was consecutive or random

Were those patients who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine No information presented on whether included participants were representative of people with relapsed or refractory large B-cell lymphomas overall.
Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	**Yes**
Was an attempt made to blind study patients to the intervention they received?	**No** Single-arm, open-label study design
Was an attempt made to blind those measuring the main outcomes of the intervention?	**No** Single-arm, open-label study design
If any of the results of the study were based on 'data dredging', was this made clear?	**No** No apparent data-dredging
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	**Yes** Descriptive statistics. All outcomes reported at data cut-off points.
Were the statistical tests used to assess the main outcomes appropriate?	**Yes** Descriptive statistics
Was compliance with the intervention(s) reliable?	**Yes**
Were the main outcome measures used accurate (valid and reliable)?	**Yes** Lugano criteria
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A Only 1 group
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A Only 1 group
Were study patients randomised to intervention groups?	N/A Only 1 group
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A Only 1 group

Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N/A Only 1 group
Were losses of patients to follow-up taken into account?	**Yes** All treated population used in the primary analyses of efficacy and safety
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	**Probably yes** Power calculation for the study was based on a comparison with an ORR of 20% among patients with R/R DLBCL.

Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 16 June 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' and 'academic in confidence' in [redacted] [redacted], and all information submitted as '[redacted]' in pink.

Issue 1 Points of clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 2.2, page 25	Please change from: "…to treat adults with relapsed or R/R DLBCL and high-grade B-cell lymphoma…" to "…to treat adults with R/R DLBCL and high-grade B-cell lymphoma (HGBL)…"	Clarity and abbreviation	Amended as requested
EAG report, Section 3.2.3, Table 7, page 40	In the "Death during study" row, please add "N/A" in the "1 March 2021" column	Clarity	Amended as requested
EAG report, Section 3.2.3, page 40, **&** **Section 3.2.3, Table 5, page 41**	Please note that the final CSR is now available, LOTIS 2 (Sept 2022 data cut). Therefore, the phrase "CSR available Q3/Q4 2023" should be altered.	Clarity	No change made. The sentence is referencing what was stated in the CS. We have included an additional sentence highlighting further clarity was provided

<table>
<tr><td></td><td></td><td></td><td>during FAC (Section 3.2.3, page 36)</td></tr>
<tr><td>EAG report, Section 3.3.2, Table 11, page 47</td><td>Please add a footnote to clarify that the ORR calculation and discontinuations due to AEs is unchanged as these are from the original calculation and not the updated preferred MAIC analyses. Only PFS and OS analyses were re-run to enable the CEM to be updated.

Table 1: Outcomes from MAIC analysis to Pola+BR using GO29365
<table>
<tr><td>Outcome</td><td>Naïve comparison</td><td>Company updated preferred MAIC analysis</td><td>EAG preferred MAIC analysis</td></tr>
<tr><td>Overall Survival*</td><td></td><td></td><td>N/A</td></tr>
<tr><td>Progression Free Survival*</td><td></td><td></td><td>N/A</td></tr>
<tr><td>ORR**</td><td></td><td></td><td>N/A</td></tr>
<tr><td>Discontinuation to AEs**</td><td></td><td></td><td>N/A</td></tr>
</table>
* treatment effect measured as hazard ratio ; ** treatment effect measured as odds ratio
†Results from original company submission, the analysis for discontinuations due to AEs was not impacted by the update</td><td>Clarity</td><td>Text has been added to improve clarity</td></tr>
</table>

EAG report, Section 3.3.2, page 47	Please remove this sentence as it leads to confusion "This "Other" group had 17 patients according to the company submission, so it is not clear why 3 patients remain omitted" We would not automatically expect there to be 17 "other" patients in the analysis set. This is due to the fact that it's 17/145 patients (all LOTIS-2) versus 14/116 patients with non-transformed lymphoma included in the analyses.	Clarity	Text has been added to improve clarity
EAG report, Section 3.3.3, page 49	For clarity about the source of the data the company used, please add that this "alternative source" was the poster accompanying the conference abstract. Please change "The company clarified that their information came from an alternative source, which was provided in the company clarification response …" to "The company clarified that their information came from the accompanying poster for the conference abstract, which was provided in the company clarification …"	Clarity	Text has been added to improve clarity
EAG report, Section 3.3.4, page 51	Please change "Repeating the company's analysis for estimating a hazard ratio from median survival times on those reported in this analysis produces a hazard ratio of 0.58" to "Repeating the company's analysis for estimating a hazard ratio from median survival times in the comparison with Pola+BR to ~~on~~ those reported in this chemotherapy analysis, …"	Clarity, reader may believe company calculated comparison with chemotherapy using median survival times	Text has been added to improve clarity
EAG report, Section 3.3.4, page 51	Please add the same discussion that you have for chemotherapy in the COTA data results section.	Clarity, in order to present the full picture	Not a factual error. No change made.

	"Repeating the company's analysis for estimating a hazard ratio from median survival times on those reported in this analysis produces a hazard ratio of 0.58, compared to the hazard ratio of 0.67 from a model fitted to the data, suggesting this approach does not always yield accurate estimates of the hazard ratio." Estimating the HR for OS from median survival for COTA is HR = 7/9.53 = 0.73, which is similar to the 0.75 estimated from the unadjusted model		
EAG report, Section 3.3.4, Table 18, page 53	**Please update caption for Table 18** Please change "Table 18: MAIC analyses outcomes" to "Table 18: Unadjusted and weighted MAIC analyses outcomes"	Clarity, Table 18 shows unadjusted as well as MAIC analyses outcomes	Text has been added to improve clarity
EAG report, Section 3.6, page 54	Please change "Only median OS and PFS were reported for the 3L+ population …" to "Only median OS and PFS were reported for the 3L+ population of Pola+BR patients in the GO29365 extension study…"	Clarity, may initially be interpreted as relating to LOTIS-2 data	Amended as requested
EAG, Section 3.6, page 54	Please change "The hazard ratio derived from the OS curves was applied to the loncastuximab-weighted PFS curve" to "The hazard ratio derived from the OS curves was applied to the loncastuximab-weighted PFS curve in the economic model"	Clarity	Amended as requested
EAG report, Section 4.2.2, page 59	Please change from: "…between 2.1% to 2.8% of patients in the loncastuximab remained on treatment." to "…between 2.1% to 2.8% of patients in the loncastuximab arm remained on treatment.	Clarity	Added "arm" in sentence as requested

EAG report, Section 4.2.7.3, page 84	Please change from: “Applying impact of TRAEs as a one-off QALY…” to “Applying impact of AEs as a one-off QALY loss…”	Clarity	Amended as requested

Issue 2 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 2.2, page 25	Please change from: “…combined with a cytotoxine.[15]….” to “…combined with a cytotoxin.[15]…”	Spelling	Amended as requested
EAG report, Section 2.2, page 25	Please change from: “First line treatment for DLBCL is…” to “First-line treatment for DLBCL is…”	Spelling	Amended as requested
EAG report, Section 1.2, page 13, Section 2.3, page 27, Table 4, page 28	Please change from: “R CHP” to “R-CHP”	Abbreviation	Amended as requested
EAG report, Section 1.2, page 13, Section 1.6, page 18,	Please change from: “Pola-R CHP” to	Abbreviation	Amended as requested

Section 2.3, page 27, Table 4, page 28	"Pola+R-CHP"		
EAG report, Section 3.2, page 34	Please change from: "LOTIS-2 ((which included a screening period (up to 28 days), a treatment period (cycles of three weeks) up to one year, and a follow-up period (visits approximately every 12 weeks for up to three years after treatment discontinuation) and patients with R/R DLBCL (including HGBL) who do not respond to or who have progressive disease after salvage therapies who have a poor prognosis) can be found…" to "LOTIS-2 (which included a screening period [up to 28 days], a treatment period [cycles of three weeks] up to one year, and a follow-up period [visits approximately every 12 weeks for up to three years after treatment discontinuation] and patients with R/R DLBCL [including HGBL] who do not respond to or who have progressive disease after salvage therapies who have a poor prognosis) can be found…"	Use of brackets	Amended as requested
EAG report, Section 3.2.2, page 36	Please change from: "…USA (n=59 (41%))" to "…USA (n=59 [41%])"	Use of brackets	Amended as requested
EAG report, Section 3.2.3, page 39	Please change from: "Treatment-emergent adverse events (TEAE)…" to "Treatment-emergent adverse events (TEAEs)…"	Abbreviation in plural	Amended as requested

<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>EAG report, Section 3.3.2, page 44</td><td>Please change from: “…(when a slow-growing (low-grade) lymphoma changes into a faster-growing (high-grade) lymphoma)…”
to
“…(when a slow-growing [low-grade] lymphoma changes into a faster-growing [high-grade] lymphoma)…”</td><td>Use of brackets</td><td>Amended as requested</td></tr>
<tr><td>EAG report, Section 3.3.2, page 44</td><td>Please change from: “Pola+BR as second line treatment…”
to
“Pola+BR as second-line treatment…”</td><td>Spelling</td><td>Amended as requested</td></tr>
<tr><td>EAG report, Section 3.3.4, Table 15, page 51</td><td>Please remove unused columns that were not included in the MAIC and change font colour from green to black

Table 15: Variables and values matched in MAIC to CORAL
<table>
<tr><th>Treatment (study)</th><th>N/ ESS</th><th>Male (%)</th><th>Prior AS CT (%)</th><th>IPI ≥3 (%)</th><th>Age ≥65 (%)</th><th>Ann Arbor 3-4 (%)</th><th>ECOG 2 (%)</th></tr>
<tr><td>Lonca unadjusted (LOTIS-2)</td><td>80.0</td><td>66.2</td><td>21.2</td><td>38.8</td><td></td><td></td><td></td></tr>
<tr><td>Chemotherapy (CORAL</td><td>266.0</td><td>63.0</td><td>27.0</td><td>39.0</td><td></td><td></td><td></td></tr>
</table></td><td>Consistent font colour and removal of unused columns</td><td>These columns have been removed and text colour changed</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>extension)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Chemotherapy (CORAL extension) [39]</td><td>278 or 231</td><td>63.0</td><td>27.0</td><td>39.0</td><td></td><td></td><td></td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>EAG report, Section 3.3.4, Table 18, page 53</td><td>Please change “… due lack …” to “… due to lack …”
<table>
<tr><td>Lonca vs chemo</td><td>CORAL extension</td><td>[redacted]</td><td>None provided due to lack of PFS data</td><td>[redacted]</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>EAG report, Section 5.1, page 91
EAG comment</td><td>Please change “…a QALY weighting does not apply for Pola+Br” to “a QALY weighting does not apply for Pola+BR”</td><td>Abbreviation</td><td>Amended as requested</td></tr>
</table>

Issue 3 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 3.2.3, page 36	Please change from “… currently available as a conference abstract (provided as academic in confidence)…” to “… currently available as a conference abstract…”	These data have been presented at the European Hematology Association (EHA) 2023 Congress on the 8th of June 2023 and no longer marked as AiC	Not a factual accuracy. This was correct at time of EAG report submission. However, we have made the change as reflected on page 36 (section 3.2.3)

EAG report, Section 3.2.3, Table 6, page 37 Progressive disease (PD) – September 2022 data-cut	Please change from: "21%" to "NR"	To accurately reflect what is stated in the Company submission (Section B.2.6.1.1, Table 13)	Amended as requested
EAG report, Section 3.2.3, Table 6, page 37 Overall response rate – September 2022 data-cut	Please change from: "NR" to "48%"	To accurately reflect what is stated in the Company submission (Section B.2.6.1.1, Table 13)	Amended as requested
EAG report, Section 3.2.3, Table 6, page 38 Overall survival (OS), median,	Please change from: "95% CI: 6.9 to 11.5" to "95% CI: 6.7 to 11.5"	Correction of 95% CI value	The EAG has updated this value. The EAG had previously used the value reported in CS.

<table>
<tr><td>months – September 2022 data-cut</td><td></td><td></td><td></td></tr>
<tr><td>EAG report, Section 3.3.2, page 45

Indirect comparison – Pola+BR 1</td><td>Please change from: “…the target proportion who were on 4th line or later…” to “…the target proportion who were on 3rd line or later…”</td><td>Correction of target population line</td><td>The change has been made</td></tr>
<tr><td>EAG report, Section 3.3.2, Table 12, page 48</td><td>Please correct the HR values in Table 12 for OS from “1.07 (0.76, 1.50)” to 1.07 (0.75, 1.51)” and for PFS from “1.24 (0.88, 1.73)” to “1.24 (0.88, 1.74)”.
Please correct the incremental QALY value for the original Company base case in Table 12 from “-0.05” to “+0.05”.

<table><tr><td>Original Company base case (incorrect proportion for 3+ prior therapies)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Correction of upper 95% CI value</td><td>These changes have been made</td></tr>
</table>

<table>
<tr><td></td><td>New company base case (amended prior therapies plus additional patients and covariates, clarification A3)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>EAG report, Section 3.3.3, Table 13, page 49</td><td>Please insert missing row in Table 13 using the lonca data weighted in the MAIC analysis

Table 132: Variables and values matched in MAIC to COTA<table><tr><th>Treatment (study)</th><th>N/ ESS</th><th>Age <65 (%)</th><th>Male (%)</th><th>Prior lines ≥3 (%)</th><th>HGBL (%)</th></tr><tr><td>Lonca unadjusted (LOTIS-2)</td><td>145.0</td><td>44.8</td><td>58.6</td><td>56.6</td><td>7.6</td></tr><tr><td>Lonca weighted (LOTIS-2)</td><td></td><td></td><td></td><td></td><td></td></tr></table></td><td>Additional row added as per company submission to illustrate loncastuximab matching</td><td>Not a factual error. No change made.</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>Pola+BR (Company values)</td><td>43.0</td><td>50.0</td><td>60.0</td><td>26.0</td><td>12.0</td></tr>
<tr><td>Pola+BR (Hamadani 2022)</td><td>43</td><td><50% (median 67)</td><td>63%</td><td>?</td><td>12%</td></tr>
</table>
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAG report, Section 3.3.3, Table 13, page 49</td>
<td>Please correct “16% of patients in COTA receive subsequent CAR-T therapy …” to “23% of patients in the 3L+ Pola+BR group from COTA receive subsequent CAR-T therapy …”</td>
<td>Correction of patient proportion receiving CAR-T from COTA database for specific 3L+ population of interest, see poster provided by the company</td>
<td>The EAG has updated this value. The EAG had previously used the value reported in the abstract available by Hamadani et al.</td>
</tr>
<tr>
<td>EAG report, Section 3.3.4, Table 16, page 51</td>
<td>Please correct values in Table 16, for OS from “0.67 (0.51, 0.86)” to “0.70 (0.51, 0.86)”

Table 16: Outcomes from MAIC analysis to Chemotherapy using CORAL extension study
<table>
<tr><td>Outcome</td><td>Naïve comparison</td><td>Company MAIC ana</td></tr>
<tr><td>Overall Survival*</td><td>0.69
(0.51, 0.94)</td><td>0.70
(0.51, 0.86)</td></tr>
<tr><td>ORR**</td><td>1.51
(0.91, 2.50)</td><td>1.53
(0.91, 2.54)</td></tr>
</table>
</td>
<td>Correction of HR point estimate</td>
<td>Not a factual error. The EAG values combines the point estimate estimated using the standard approach, with the confidence interval from the bootstrapped approach. No change needed.</td>
</tr>
</table>

<table>
<tr>
<td>EAG report, Section 3.6, page 54
Conclusions of the clinical effectiveness section
EAG report, Section 4.2.3, page 61
EAG comments</td>
<td>Please change from: “Furthermore, the database contains only a small number of included patients (n=44).” to “Furthermore, the database contains only a small number of included 3L+ Pola+BR patients (n=43).”</td>
<td>Correction of Pola+BR 3L+ patient numbers in COTA US electronic database</td>
<td>Text has been added to improve clarity.</td>
</tr>
<tr>
<td>EAG report, Section 4.2.7.2, Table 22, page 82</td>
<td>Please correct the standard error for the base case PFS in Table 22 from “0.01” to “0.011”.
<table>
<tr><th>Scenario</th><th>State</th><th>Utility values</th><th>Standard Error</th></tr>
<tr><td rowspan="3">Base case</td><td>PFS</td><td>0.685</td><td>0.011</td></tr>
<tr><td>Disutility for progressed disease</td><td>-0.056</td><td>0.021</td></tr>
<tr><td>AE disutility</td><td>-0.045</td><td>0.16</td></tr>
</table>
</td>
<td>Correction of standard error</td>
<td>Additional decimal point added</td>
</tr>
<tr>
<td>EAG report, Section</td>
<td>Please change from: “Table 28 shows the mean duration and percentage share of each therapy class included in the post-discontinuation treatment for loncastuximab tesirine, Pola+BR and chemotherapy and the total post-discontinuation costs</td>
<td>Costs differ depending on whether the loncastuximab tesirine arm is compared with</td>
<td>Changes made on section 4.2.8.1 and</td>
</tr>
</table>

<table>
<tr>
<td>4.2.8.1, page 86

EAG report, Section 4.2.8.1, Table 28, page 86</td>
<td>which were highest for chemotherapy arm but similar for loncastuximab tesirine and Pola+BR (Table 26).” to “Table 28 and Table 29 shows the mean duration and percentage share of each therapy class included in the post-discontinuation treatment for loncastuximab tesirine, Pola+BR and chemotherapy and the total post-discontinuation costs which were highest for the Pola+BR arm and loncastuximab tesirine arm in the comparison between loncastuximab tesirine and Pola+BR (Table 28).
Please replace Table 28 with the below tables (Table 28 and 29).
Table 28: Cost of subsequent treatment, loncastuximab tesirine vs Pola+BR
<table>
<tr><th>Regimen</th><th>Chemotherapy</th><th>ASCT</th><th>AlloSCT</th><th>CAR-T</th><th>Averag cost</th></tr>
<tr><td>Loncastuximab tesirine</td><td>54%</td><td>3%</td><td>8%</td><td>11%</td><td>£48,004.</td></tr>
<tr><td>Pola+BR</td><td>54%</td><td>3%</td><td>8%</td><td>11%</td><td>£48,004.</td></tr>
</table>
Abbreviations: AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor; Pola+BR, polatuzumab plus bendamustine and rituximab.

Table 29: Cost of subsequent treatment, loncastuximab tesirine vs chemotherapy</td>
<td>Pola+BR or chemotherapy</td>
<td>reflected in tables 28 and 29</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><th>Regimen</th><th>Chemotherapy</th><th>ASCT</th><th>AlloSCT</th><th>CAR-T</th><th>Average cost</th></tr>
<tr><td>Loncastuximab tesirine</td><td>54%</td><td>3%</td><td>8%</td><td>0%</td><td>£12,180.53</td></tr>
<tr><td>Chemotherapy</td><td>54%</td><td>22%</td><td>8%</td><td>0%</td><td>£18,175.84</td></tr>
</table>
Abbreviations: AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor; RGemOx; rituximab, gemcitabine and oxaliplatin.
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAG report, Section 5.1, Table 34, page 91</td>
<td>
Please correct Table 34 to include the correct QALYs for chemotherapy with 1.2 modifier and to include missing rows:

Table 3: Submitted base-case deterministic cost-effectiveness results, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)
<table>
<tr><th>Severity modifier</th><th>Comparator</th><th>Total costs</th><th>Total QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td rowspan="2">No severity modifier</td><td>Chemotherapy</td><td>[redacted]</td><td>[redacted]</td><td>-</td></tr>
<tr><td>Loncastuximab</td><td>[redacted]</td><td>[redacted]</td><td>£48,986</td></tr>
<tr><td>1.2 severity modifier</td><td>Chemotherapy</td><td>[redacted]</td><td>[redacted]</td><td>-</td></tr>
</table>
Table 4: Submitted base-case deterministic cost-effectiveness results, loncastuximab tesirine vs chemotherapy (with PAS price for loncastuximab tesirine)
</td>
<td></td>
<td>
Not a factual error. QALYs for chemotherapy at 1.2 modifier are [redacted]

Please note the QALY values provided by the company in the adjacent table (current FAC form) for 1.2 and 1.7 modifiers are inaccurate and have been switched around for loncastuximab and chemotherapy.

We have thus added the missing rows but used the values
</td>
</tr>
</table>

	Severity modifier	**Comparator**	**Total costs**	**Total QALYs**	**ICER (£/QALY)**		presented in company's clarification response "v2.0 12052023"
	No severity modifier	Chemotherapy	[redacted]	[redacted]	-		
		Loncastuximab	[redacted]	[redacted]	£48,986		
	1.2 severity modifier	Chemotherapy	[redacted]	[redacted]	-		
		Loncastuximab	[redacted]	[redacted]	£40,821		
	1.7 severity modifier	Chemotherapy	[redacted]	[redacted]	-		
		Loncastuximab	[redacted]	[redacted]	£28,815		

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 27 July**. 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)	Swedish Orphan Biovitrum ('Sobi')
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

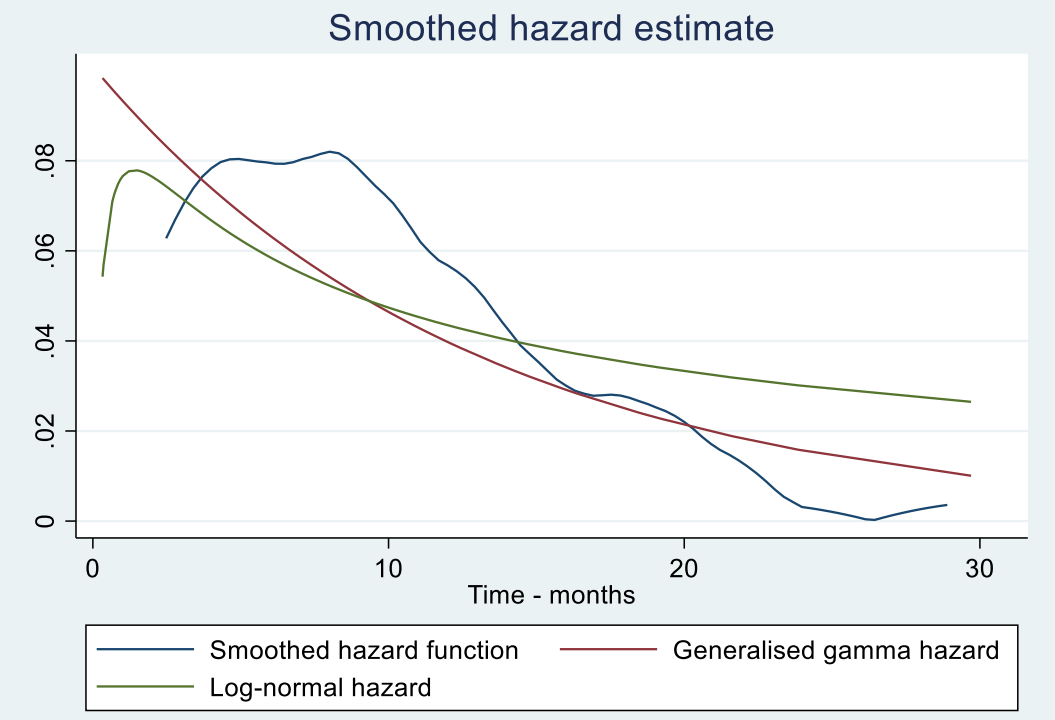
All: Please use the table below to respond to the key issues raised in the EAR.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Concerns over the suitability of the matching-adjusted indirect comparison (MAIC) analyses performed and presented (Sections 3.3.2, 3.3.3, 3.3.4, 4.2.6)	Yes	The Company has used robust methodology to conduct the MAICs and provided the best comparison possible, from the available data. Sample sizes in the MAICs varied, however, for the primary analyses presented (GO29365 extension study polatuzumab plus bendamustine plus rituximab [Pola+BR] and CORAL chemotherapy comparisons) sample sizes were all ≥78, including the estimated effective sample sizes, and this was considered reasonable, particularly in the context of the later line of treatment considered. The Company maintains that an exploration of a population-adjustment analysis including refractory to last therapy when comparing loncastuximab tesirine with Pola+BR, is not suitable or valid because there is a significant discrepancy between the definitions of refractory to last therapy across the two trials (LOTIS 2 and GO29365 extension) which could not be matched. The Company also remains concerned that including International Prognostic Index [IPI] score as well as including the individual components of IPI score (age, Eastern Cooperative Oncology Group [ECOG] status and Ann Arbor stage) results in double-adjustment of the population and is not appropriate. However, an additional analysis to include IPI score is provided in Appendix A: Additional matching-adjusted indirect comparison analyses. The conclusions of these additional analyses do not differ from those of the base-case and demonstrate there is no significant efficacy difference between loncastuximab tesirine and Pola+BR.
Unsupported degree of overall survival (OS) benefit of loncastuximab tesirine over Pola+BR (Sections 3.3.2, 3.3.3, 4.2.6)	Yes	Durable, long-term responses have been demonstrated in LOTIS-2 among heavily pretreated patients. Additional long-term follow-up data (detailed below and in Appendix B: Updated data cut from LOTIS-2) supports the Company position that loncastuximab tesirine has some OS benefit over Pola+BR. The September 2022 data cut (presented in Appendix B: Updated data cut from LOTIS-2) provides additional follow-up on OS, giving a further 13 patient-years of follow-up, with no additional deaths observed. The number of patients observed to be alive at 3 years has increased to 24. Caimi et al presented this data at the

		European Hematology Association (EHA) (1) and explored outcomes by response status. Amongst 36 patients with a complete response, 44% (16/36) and 31% (11/36) were event-free for ≥1 and ≥2 years, respectively, and 61% (22/36) were alive at ≥2 years. All 11 patients with a complete response (CR) who were event-free for ≥2 years were censored due to patient discontinuation from the study. Survival analyses used to inform the model have been rerun using the new data cut, with outputs presented in Appendix C: Updated survival analysis. The Company base case retains the generalised gamma model for extrapolating OS. Clinical advice provided to the Company selected the generalised gamma curve as providing the most reasonable extrapolation. Clinicians also suggested it is reasonable to assume that patients who are progression free at 2 years following treatment initiation, and who have received no new anticancer therapy, can be discharged and regarded as 'cured' (i.e. a normal life expectancy). Therefore, the Company would not expect survival at 10-years to drop off as much as shown by the log-normal curve. This is supported by the additional follow-up provided by the new data cut, which shows no additional deaths and suggests a decreasing hazard function. Figure 1 presents the smoothed hazard estimate from LOTIS-2, alongside the hazard functions estimated by the generalised gamma and log-normal distributions. The generalised gamma function provides a better fit to the observed data in the tail and is expected to produce more realistic extrapolations.

Figure 1: Comparison of observed and estimated hazard functions in LOTIS-2

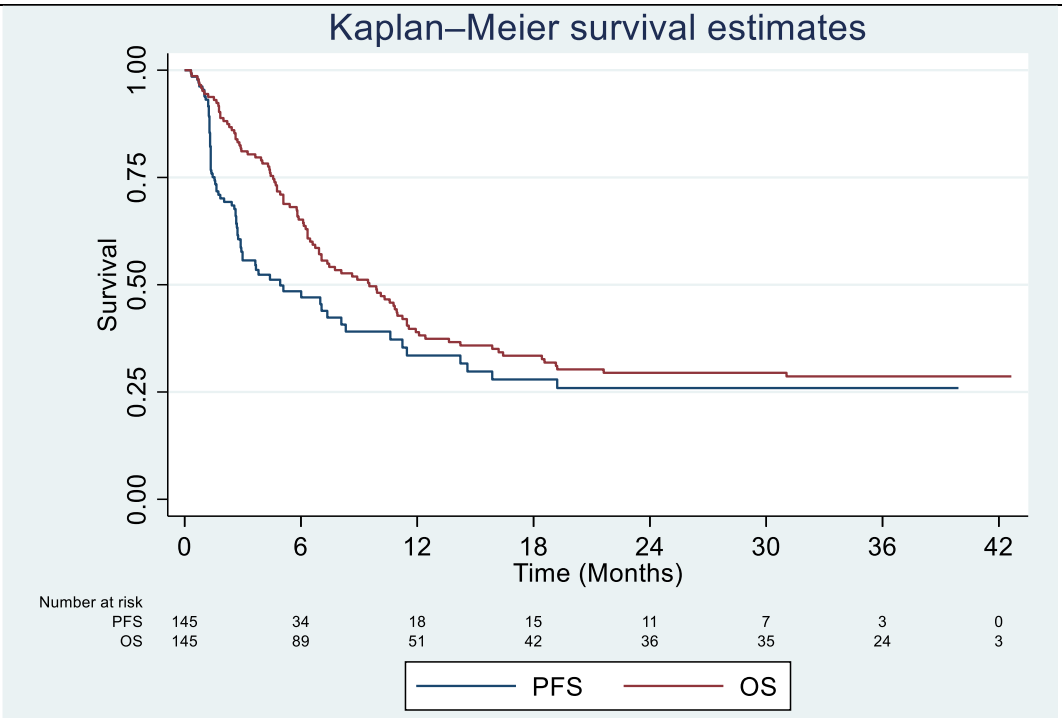


Scenario analyses using the External Assessment Group (EAG)'s preferred analysis have also been presented.

As Kaplan-Meier (KM) curves were not available for the third-line plus (3L+) population in the GO29365 extension study, the extrapolations used for Pola+BR are based on pooled second-line (2L) and 3L+ data, with a hazard ratio (HR) applied for being in 3L+. While the MAICs show minimal difference in OS between loncastuximab tesirine and Pola+BR, there are differences in the model due to differences in the extrapolations. The KM curves from GO29365 show survival of around 35% at 2 years for the 2L+ population, compared to 30% in LOTIS-2 for 3L+. Clinical experts highlighted that line of therapy is a key prognostic factor and outcomes in the 3L+ population for Pola+BR are expected to be lower than in the pooled population.

This is supported by the COTA data (2), which shows much lower survival outcomes for patients treated with Pola+BR in a 3L+ vs 2L setting, with median survival of 7.1 months. The MAIC using the COTA data, which is based on KM data rather than median survival times, showed a HR for OS of 0.69 for loncastuximab tesirine vs Pola+BR. A scenario analysis using the COTA data has been presented in Table 10.

		This is further supported by the Northend et al data (3), which reports real-world experience of using Pola+BR in the UK. As with the GO29365 data, results are not presented for the 3L+ subgroup, however outcomes for patients treated with Pola+BR are worse than seen in the GO29365 study, with a median survival time of 8.1 months. The OS and progression-free survival (PFS) curves from Northend et al have been digitised and parametric survival curves fitted and this data has been used to inform a scenario in the model, with results presented in Table 10. In this scenario, unweighted LOTIS-2 outcomes have been compared to unweighted outcomes from the Northend study. There is uncertainty in the relative efficacy of loncastuximab tesirine and Pola+BR, and in the modelled outcomes for Pola+BR due to the lack of trial evidence for the 3L+ population. However, of the data sources available to inform outcomes for Pola+BR, those used in the model base case are the most optimistic for Pola+BR, and are expected to present a conservative estimate of the cost-effectiveness of loncastuximab tesirine. Using alternative data for Pola+BR results in improved cost-effectiveness for loncastuximab tesirine, and in the EAG scenario assuming equivalent efficacy for loncastuximab tesirine and Pola+BR, loncastuximab tesirine is cost-saving.
Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine (Section 4.2.6)	Yes	As with OS, the PFS data has also been updated using the new data cut. The new data cut provides 0.46 additional years of follow up on PFS, and the impact of the new data cut on extrapolations is minimal. While the MAIC does not show an advantage on PFS for loncastuximab tesirine over Pola+BR when using the 3L+ data from the GO29365 extension study, the extrapolations used in the model lead to a gain in PFS. This is due to the shape of the tails of the PFS curves used for extrapolation. In LOTIS-2, the median PFS was 4.93 months, compared to 6.6 months for the for the overall population in the GO29365 extension, which drops to 6.1 months for the 3L+ population. However, by 18 months PFS in the GO29365 extension has dropped to around 18% for the overall population and would be expected to be lower than this in the 3L+ population. Meanwhile, PFS in LOTIS-2 plateaus at around 25% and this drives the gain in PFS in the economic model. A benefit on PFS is also supported by the additional data sources identified for Pola+BR. The COTA data (2) shows a median PFS for Pola+BR in the 3L+ population of 3.7 months and the Northend et al data (3) shows a median PFS of 4.8 months in a population with 2L and 3L+ patients. The vanishing post-progression survival is a function of the LOTIS-2 survival curves. Figure 2 presents a comparison of PFS and OS from LOTIS-2. In both curves, there a few events after 18 months and both the OS and PFS curves plateau at around 25% survival. **Figure 2: Comparison of PFS and OS in LOTIS-2**

		 Scenario analyses with alternative assumptions around the shape of the PFS curve that exhibit more time in the post-progression state have been explored in scenario analyses (Table 10).
Lack of information for a meaningful extrapolation for PFS of chemotherapy (Section 4.2.6)	Yes	The Company acknowledge that there is a paucity of data to inform the extrapolation of PFS for chemotherapy, however there is little decision uncertainty associated with this. CORAL extension data was also used to extrapolate chemotherapy outcomes in the appraisal of tisagenlecleucel [TA567] (4). The committee's preferred analysis in TA567 was to use a proportional approach between OS and PFS for chemotherapy, apply a ratio of 0.65 to the cumulative hazard, based on the approach taken by Hettle et al (5). Additional scenario analyses modelling PFS for chemotherapy using this approach have been presented. This approach leads to a reduction in the incremental cost-effectiveness ratio (ICER), as PFS is reduced for chemotherapy and patients spend more time in the post-progressions state. Furthermore, the Company reiterates that Pola+BR, and not chemotherapy, should be considered the most relevant comparator within decision-making, which limits the relevance of this issue. This is based on clinical advice received by the Company that many patients at 3L+ will already be refractory to chemotherapy, and therefore, clinicians try to avoid treating patients with another chemotherapy in this line of treatment (6).
For chemotherapy comparison: Inconsistent	Yes	To address this concern, the HR for chemotherapy has been reassessed after the two-stage adjustment to remove the impact of subsequent CAR-T therapy. Adjustment of the OS data from LOTIS-2 was performed in the same way as in previous analyses:

<table>
<tr>
<td>application of two-stage adjustment to remove benefit of chimeric antigen receptor T cells (CAR-T) therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses (Section 4.2.6.2.2)</td>
<td></td>
<td>

A secondary baseline was defined using the time of treatment discontinuation and post-discontinuation survival was estimated
A log-logistic model was fit to this data to assess the impact of CAR-T on survival, including covariates for age, number of prior lines of therapy, response to first and last treatment, ECOG score, disease stage at diagnosis and time to progression
Counterfactual survival times were generated for patients treated with CAR-T.

Once counterfactual survival times had been generated, the loncastuximab tesirine data was reweighted using weights generated for the MAIC comparing to CORAL extension data. The pseudo-individual patient data (IPD) for chemotherapy from CORAL extension was then used to generate a HR for chemotherapy via the reweighted counterfactual survival times from LOTIS-2 using a Cox model.
Table 3 presents the HRs for chemotherapy after the two-stage adjustment has been applied, with and without weights from the MAIC. The HR is slightly reduced compared with the original analysis and the model base case has been updated to use the reweighted HR to estimate outcomes for chemotherapy.

Table 3: OS HRs for chemotherapy after two-stage adjustments, with and without weights
<table>
<tr><th>Scenario</th><th>HR</th><th>Standard error</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr>
<tr><td>Two-stage adjustment, reweighted</td><td>1.430</td><td>0.217</td><td>1.061</td><td>1.926</td></tr>
<tr><td>Two-stage adjustment, unweighted</td><td>1.414</td><td>0.175</td><td>1.108</td><td>1.803</td></tr>
</table>
</td>
</tr>
<tr>
<td>Rate of subsequent autologous stem cell transplantation (autoSCT) therapy in chemotherapy arm (Section 4.2.8.1)</td>
<td>Yes</td>
<td>
The Company maintains that its rate of subsequent autoSCT therapy in the chemotherapy arm is more reflective of proportions seen in clinical practice than proposed by the EAG, and have concerns over the approach taken by the EAG.

The Company’s modelled stem cell transplantation (SCT) rates are based upon the best available information and reflect those seen in a clinical trial – the CORAL extension study. Although the Company acknowledges that the rates may slightly differ in clinical practice, deviating from the rates of subsequent SCT seen in the study while using the efficacy data from the same study would result in significant bias in the economic analysis, as the EAG approach retains the efficacy of SCT while removing the costs.

In order to assess the impact of alternative rates of SCT, two additional scenario analyses have been included and can be considered by the committee. Both CORAL extension studies have reported outcomes separately for those that did
</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>and did not go on to receive an SCT. These curves have been digitised to generate pseudo-IPD by eventual SCT status and analyses separately.

In the first scenario, the analysis performed for ‘Issue 5’ (application of two-stage adjustment) has been repeated to generate OS HRs for patients with and without an eventual SCT separately. The same counterfactual survival times for LOTIS-2 patients have been used, and as baseline characteristics are not reported by eventual SCT status, the same weights have been applied. The same proportion of patients have then been assumed to receive an SCT as was observed in LOTIS-2 (3% AutoSCT, 11% allogenic stem cell transplantation [AlloSCT]) and a weighted HR generated. The HR for patients with and without SCT and the weighted HR are presented in Table 4

Table 4: HRs for chemotherapy by eventual SCT status
<table>
<tr><th></th><th>HR</th><th>SE</th><th>CI</th></tr>
<tr><td>No SCT</td><td>1.767</td><td>0.166</td><td>1.300–2.403</td></tr>
<tr><td>SCT</td><td>0.801</td><td>0.166</td><td>0.533–1.204</td></tr>
<tr><td>Weighted 11% SCT</td><td>1.659</td><td>–</td><td>–</td></tr>
</table>

In the second scenario, outcomes for patients with and without an eventual SCT have been extrapolated separately, and the OS curves for chemotherapy have been generated by weighting these two curves, again assuming the same rates of SCT as observed in LOTIS-2. The results of these scenarios are presented in Table 13.

Both scenarios demonstrate that chemotherapy-treated patients who have received subsequent SCT accrue greater health benefits than those who have not received it. Therefore, the EAG approach, which retains the efficacy of SCT in CORAL extension patients while removing the costs (by lowering the SCT rate), is flawed.

In both scenarios there is an increase in both incremental costs and QALYs, leading to a small reduction in the ICER.

The results of these scenarios should be interpreted with caution, as receipt of subsequent SCT will be correlated with response to treatment received in the extension study, and with baseline fitness. As such, the outcomes for patients that did not receive an SCT cannot be assumed to be equivalent to the outcomes of the CORAL extension study had no patients received an SCT and vice versa.</td>
</tr>
<tr>
<td>Appropriate quality-adjusted life year (QALY)</td>
<td>No</td>
<td>No changes have been made; severity modifiers are applied for each comparison depending on the QALYs generated in the comparison, which aligns with the approach recommended by the EAG.</td>
</tr>
</table>

weighting to adjust for severity (Section 4.2.9)		
Appropriateness of comparator treatments (Table 3 and Section 2.3)	No	Polatuzumab plus rituximab, cyclophosphamide, doxorubicin and prednisoloneat (Pola-R CHP) first-line (1L) was not recommended by National Institute for Health and Care Excellence (NICE), nor standard of care, at the time of the Company submission for loncastuximab tesirine. Whilst the Company acknowledges that the recent positive recommendation by NICE of Pola-R CHP at 1L may impact the use of Pola+BR at later lines, the extent of the impact is highly uncertain and will be dependent on the future front-line uptake of Pola-R CHP. Clinical advice given to the company was that Pola+BR was an appropriate comparator for loncastuximab tesirine. There are limited treatment options at 3L, and clinical input indicates that many patients at this line are chemo-refractory, and clinicians are reluctant to use further lines of chemotherapy, preferring to enter patients into clinical trials or seek compassionate use of bi-specifics if there are no other options available (6).

Additional issues

All: Please use the table below to respond to additional issues in the EAR 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 evaluation (for example, at the clarification stage).

Table 5: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Not applicable			

Abbreviations: EAR, External Assessment Report.

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 6: Changes to the company's cost-effectiveness estimate – comparison with Pola+BR

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 2: Unsupported degree of OS benefit of loncastuximab tesirine over Pola+BR Issue 3: Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine	An interim data cut from LOTIS-2 from March 2022 (7)was used to inform OS and PFS for loncastuximab tesirine.	Clinical data used was updated to the most recent data cut from LOTIS-2, from September 2022 (8).	Original base-case ICER: Dominant Revised ICER: Dominant
No issue applicable	Loncastuximab tesirine PAS price of [redacted] per vial used	Loncastuximab tesirine PAS price of [redacted] per vial used	Original base-case ICER: Dominant Revised ICER: Dominant
Company's revised base case following	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Dominant

technical engagement			

Table 7: Changes to the company's cost-effectiveness estimate – comparison to chemotherapy

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 2: Unsupported degree of OS benefit of loncastuximab tesirine over Pola+BR Issue 3: Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine	An interim data cut from LOTIS-2 from March 2022 was used to inform OS and PFS for loncastuximab tesirine.	Clinical data used was updated to the most recent data cut from LOTIS-2, from September 2022 (8).	Original base-case ICER: £48,986 Revised ICER: £48,961
Issue 2: Unsupported degree of OS benefit of loncastuximab tesirine over Pola+BR Issue 3: Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine	Unweighted LOTIS-2 data used for OS, PFS and TTD in loncastuximab tesirine arm	CORAL extension study weights applied to LOTIS-2 data for OS, PFS and TTD in loncastuximab tesirine arm	Original base-case ICER: £48,986 Revised ICER: £43,654
Issue 5: For chemotherapy comparison: Inconsistent application of two-stage adjustment to	Hazard ratio of 1.49 used for chemotherapy OS and PFS	Hazard ratio of 1.43 used for chemotherapy OS and PFS based on the application of	Original base-case ICER: £48,986 Revised ICER: £52,992

remove benefit of CAR-T therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses		two-stage adjustments	
No issue applicable	Loncastuximab tesirine PAS price of [redacted] per vial used	Loncastuximab tesirine PAS price of [redacted] per vial used	Original base-case ICER: £48,986 Revised ICER: £36,561
Company's revised base case following technical engagement	Incremental QALYs: [redacted]	Incremental costs: [redacted]	ICER: £33,231

Sensitivity analyses around revised base case

The deterministic and probabilistic cost-effectiveness results for the base-case analysis comparing loncastuximab tesirine with Pola+BR are presented in Table 8 and Table 9, respectively. The base-case analysis is based on the latest September 2022 data cut from LOTIS-2 (8).

Table 8: Revised deterministic base-case results, loncastuximab tesirine vs Pola+BR, loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, PAS, patient access scheme; QALY, quality adjusted life-years.

Table 9: Revised probabilistic base-case results, loncastuximab tesirine vs Pola+BR, loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	-
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, PAS, patient access scheme; QALY, quality adjusted life-years.

Figure 3 presents the CEAC for the comparison with Pola+BR. Loncastuximab tesirine is cost-effective in 99% of scenarios at a willingness-to-pay (WTP) threshold of £20,000 per QALY and 100% of scenarios at £30,000 per QALY.

Figure 3: CEAC, vs Pola+BR

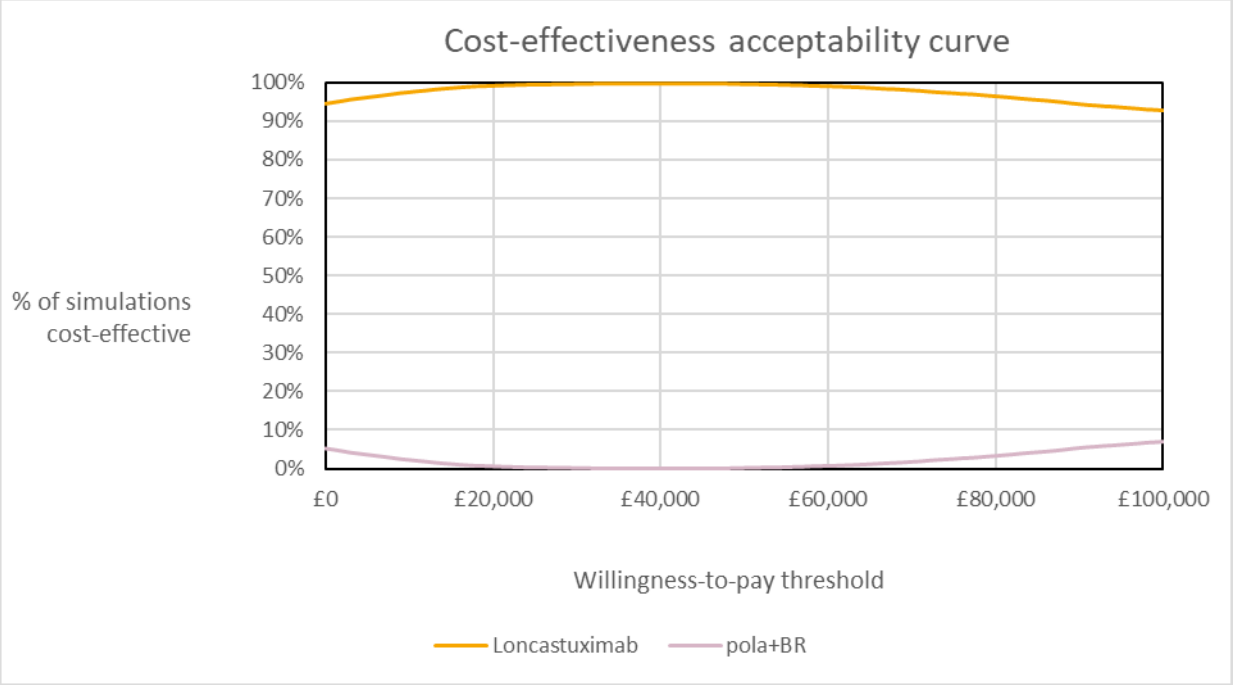


Table 10 presents the outcomes of the additional scenario analyses comparing to Pola+BR run for the technical engagement response.

Table 10: Additional scenario analyses for technical engagement, vs Pola+BR

Scenario	Incremental costs	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	Dominant
EAG base-case	[redacted]	[redacted]	Dominant
Company base-case extrapolations for loncastuximab, assuming equivalence for pola+BR	[redacted]	[redacted]	Dominant
Using COTA data to inform survival analysis	[redacted]	[redacted]	Dominant
Northend et al to inform outcomes for Pola+BR, unweighted LOTIS-2 outcomes for loncastuximab	[redacted]	[redacted]	Dominant
Using log-normal model for PFS	[redacted]	[redacted]	Dominant

The revised deterministic and probabilistic base case results for the comparison against chemotherapy are presented in Table 11 and Table 12, respectively. The revised base case is based on the latest September 2022 data cut from LOTIS-2 (8) and an updated hazard ratio of 1.43 for chemotherapy. In the revised base case, the CORAL extension study weights are applied to the data from LOTIS-2 in the loncastuximab tesirine arm, in line with the preferred assumptions of the EAG.

Table 11: Revised deterministic base-case results, loncastuximab tesirine vs chemotherapy, loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	ICER with severity multiplier
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,231	£27,692

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, PAS, patient access scheme; QALY, quality adjusted life-years.

Table 12: Revised probabilistic base-case results, loncastuximab tesirine vs chemotherapy, loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	ICER with severity multiplier
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	£36,864	£30,720

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained, PAS, patient access scheme; QALY, quality adjusted life-years.

Figure 4 presents the CEAC for the comparison with chemotherapy. This shows a 6% probability of being cost-effectives at a WTP threshold of £20,000 per QALY and 31% at £30,000 per QALY. With the severity weights applied, this becomes 12% and 51% respectively.

Figure 4: CEAC, vs chemotherapy

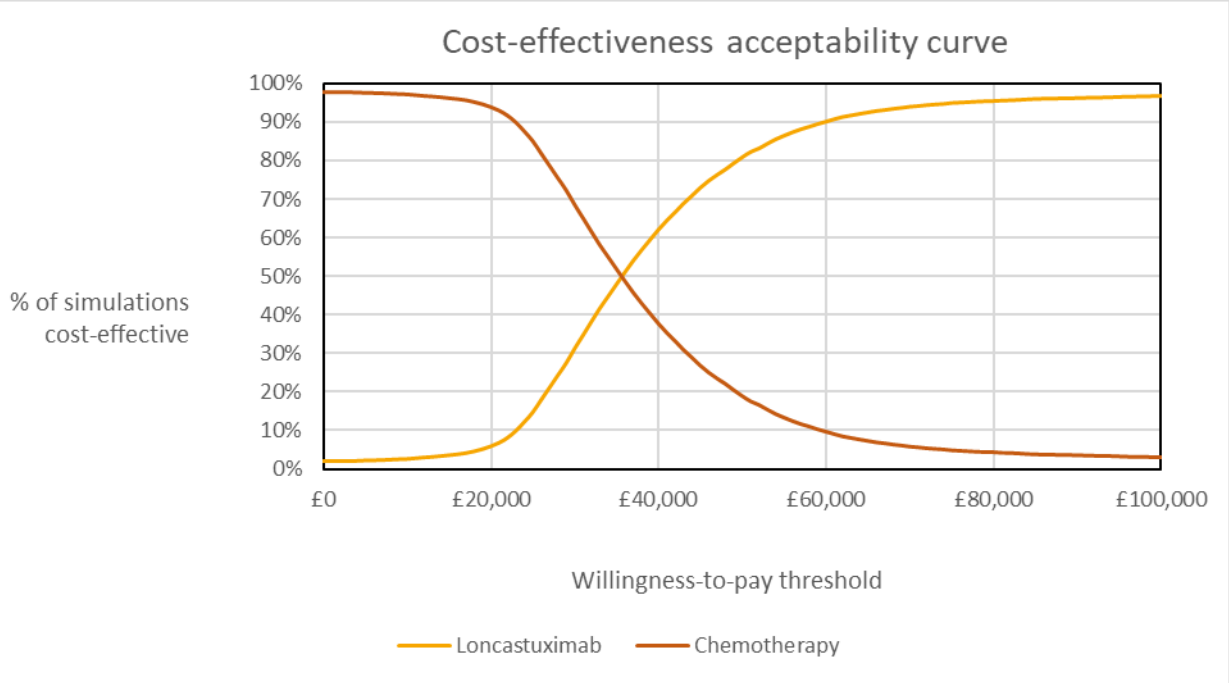


Table 13 presents the outcomes of the additional scenario analyses comparing to chemotherapy run for the technical engagement response.

Table 13: Additional scenario analyses for technical engagement, vs chemotherapy

Scenario	Incremental costs	Incremental QALYs	ICER	ICER with severity weighting
Base-case	[redacted]	[redacted]	£33,231	£27,692
EAG base-case			£55,746	£46,455
Proportional model for OS and PFS			£17,374	£14,478
Weighted HR for chemotherapy, assuming 11% SCT	[redacted]	[redacted]	£32,189	£26,824
Weighted OS extrapolations for chemotherapy, assuming 11% SCT	[redacted]	[redacted]	£31,089	£25,907

Appendix A: Additional matching-adjusted indirect comparison analyses

Additional MAIC analyses have been conducted to address the EAG concerns about the included patients and variables.

Patients with transformed lymphoma were excluded from the GO29365 extension study and therefore, in the company base-case, 29 patients were excluded from the LOTIS-2 dataset when making a comparison with Pola+BR. This yielded a dataset of 116 patients treated with loncastuximab tesirine.

In addition, it was noted that 14 patients in the LOTIS-2 dataset have missing data with respect to primary relapse/refractory status and no response to 1L treatment/time to progressive disease. On the basis that the definition of refractory is of interest in the MAICs and these patients are considered relevant to decision making because they have received at least two prior lines of treatment and are relapsed or refractory to the prior line, these patients were included for the updated Company base-case comparison. For the purpose of the analyses, it was assumed these patients were non-refractory, which was considered a conservative approach.

To explore this assumption and the question of how simultaneously adjusting for both individual components of IPI and the compound IPI score impact the outcomes, sensitivity analyses have been conducted for OS, PFS and overall response rate (ORR). These analyses are summarised in Table 14.

- One sensitivity analysis comprised excluding 29 transformed lymphoma patients and 14 “other” primary refractory patients from the LOTIS-2 dataset (N=102) and using individual components available from the International Prognostic Index (IPI) as well as gender; HGBL status; prior lines and primary refractory status to match patient characteristics (seven variables matched, as per company base-case)

- The second sensitivity analysis excluded patients with transformed disease (N=116 included) and matched all patient characteristics from the base-case with the addition of matching for % of patients with IPI score ≥3 (eight baseline variables matched).

Despite the company concern that including IPI score as well as the individual components of IPI score result in double adjustment of the population, conclusions were unchanged across the analyses compared with the base case, with similar OS, PFS and ORR for patients treated with loncastuximab tesirine or Pola+BR (Table 15). No significant differences between treatments were identified for any of these analyses.

Table 14: Included patients and variables for base-case MAIC and sensitivity analyses comparing loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study)

Treatment (study)	Number of included lonca patients	Age <65	Male	ECOG PS 0-1	HGBL	Prior lines ≥3	Primary refractory or progression / relapse <6 months	Disease stage ≥3	IPI ≥3
Company base-case	116	√	√	√	√	√	√	√	x
Sensitivity analysis: Exclude "other" primary refractory patients†	102	√	√	√	√	√	√	√	x
Sensitivity analysis: Include IPI matching	116	√	√	√	√	√	√	√	√

†Patients whose refractory status after primary treatment was unknown, not evaluable, or missing.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; lonca, loncastuximab tesirine; MAIC, matching-adjusted indirect comparison; Pola+BR, polatuzumab vedotin, bendamustine, and rituximab.

Table 15: Results for company base-case MAIC and sensitivity analyses comparing loncastuximab tesirine (LOTIS-2) vs Pola+BR (GO29365 extension study)

Treatment (study)	Number of included lonca patients	OS HR (95% CI) Unadjusted	OS HR (95% CI) Weighted	PFS HR (95% CI) Unadjusted	PFS HR (95% CI) Weighted	ORR OR (95% CI) Unadjusted	ORR OR (95% CI) Weighted
Company base-case	116	0.94 (0.67, 1.31)	1.00 (0.71, 1.40)	1.24 (0.88, 1.73)	1.24 (0.88, 1.74)	0.97 (0.57, 1.65)	0.92 (0.53, 1.59)
Sensitivity analysis: Exclude "other" primary refractory patients†	102	1.07 (0.76, 1.50)	1.07 (0.75, 1.51)	1.24 (0.88, 1.74)	1.20 (0.85, 1.70)	1.00 (0.58, 1.73)	1.02 (0.58, 1.78)
Sensitivity analysis: Include IPI matching	116	0.94 (0.67, 1.31)	1.00 (0.71, 1.40)	1.24 (0.88, 1.73)	1.39 (0.99, 1.95)	0.97 (0.57, 1.65)	0.91 (0.53, 1.57)

†Patients whose refractory status after primary treatment was unknown, not evaluable, or missing.

Abbreviations: CI, confidence interval; HR, hazard ratio; lonca, loncastuximab tesirine; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; PFS, progression-free survival; Pola+BR, polatuzumab vedotin, bendamustine, and rituximab.

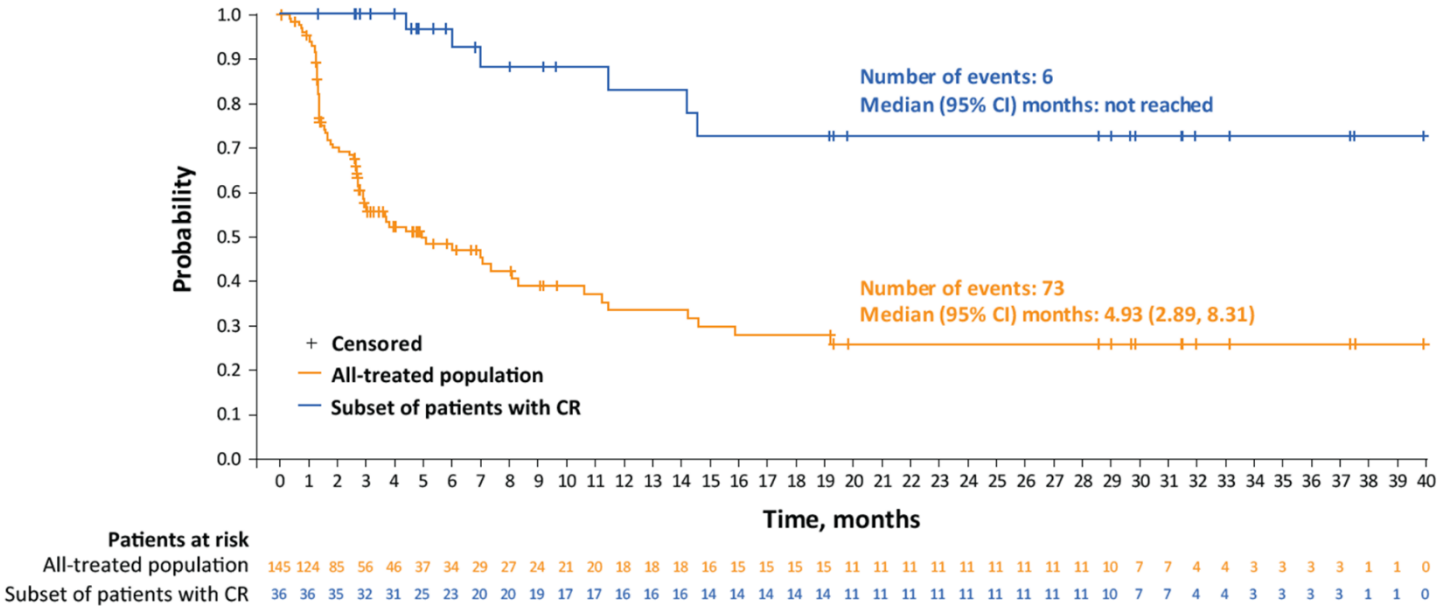
Appendix B: Updated data cut from LOTIS-2

Loncastuximab tesirine continued to demonstrate durable responses after long-term follow-up. As of final data cut off (September 2022), 70 (48.3%) of 145 patients achieved response and 36 (24.8%) patients achieved complete response (CR); 16 (44%) and 11 (31%) of the 36 CR patients were event-free for ≥1 and ≥2 years, respectively (1).

Progression-free survival

Figure 5 presents the clinical activity of loncastuximab tesirine measured by PFS as assessed by independent reviewer and presented as a KM curve in the all-treated population (N=145) and the subset of patients with a best response of a CR (n=36). As of final data cut off (September 2022), the median PFS was 4.93 months (95% CI: 2.89, 8.31) (1).

Figure 5: Kaplan-Meier plot of PFS in the all-treated population and the subset of patients with a CR (September 2022 data cut)

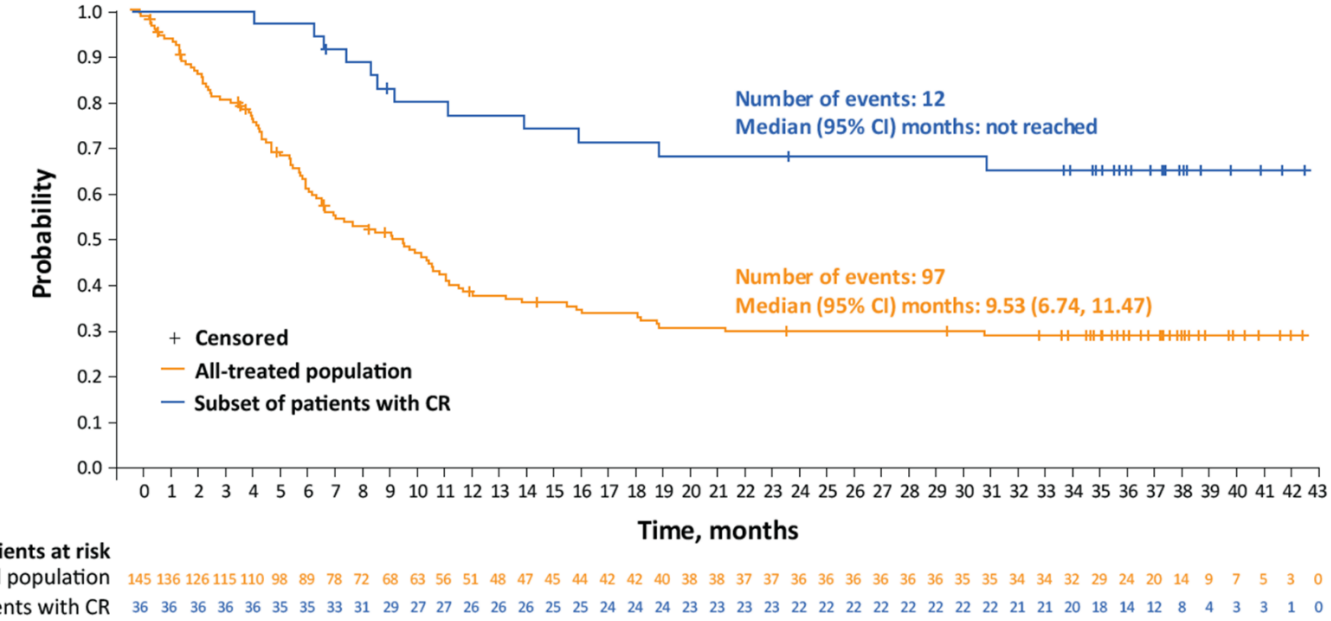


Source: Caimi 2023 (1).
Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; PFS, progression-free survival.

Overall survival

Figure 6 presents the clinical activity of loncastuximab tesirine, measured by OS as a KM curve in the all-treated population (N=145) and the subset of patients with a best response of a CR (n=36). As of final data cut off (September 2022), the median OS was 9.53 months (95% CI: 6.74, 11.47) (1).

Figure 6: Kaplan-Meier plot of OS in the all-treated population and the subset of patients with a CR (September 2022 data cut)



Source: Caimi 2023 (1).
Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; OS, overall survival.

Other clinical outcomes

A summary of the efficacy outcomes from the final data cut (September 2022) is presented in Table 16.

Table 16: LOTIS-2 efficacy outcomes (September 2022 data cut)

Outcome	All-treated population (N=145)
Primary endpoint: ORR	
Best Overall Response (n [%])	
Complete response	36 (24.8)
Partial response	34 (23.4)
ORR (CR + PR)	70 (48.3)
95% CI for ORR	(39.9, 56.7)
95% CI for CR	(18.0, 32.7)
Key secondary endpoints	
CRR (%[95%CI])	24.8 (18.0, 32.7)
Median DOR (months [95%CI])	13.37 (6.87, NE)
Median PFS (months [95%CI])	4.93 (2.89, 8.31)
Median OS (months [95%CI])	9.53 (6.74, 11.47)

Source: Caimi 2023 (1), Sobi final CSR 2023 (8).
Abbreviations: CI, confidence interval; CR, complete response; CRR, complete response rate; CSR, clinical study report; DOR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

Loncastuximab tesirine demonstrated a strong safety profile. Most treatment-emergent adverse events (TEAEs) were Grade ≤3, with minimal number of Grade 4 or 5 TEAEs. Toxicities were generally reversible and manageable with dose delays/reductions in most patients. No new safety concerns were identified during the long-term follow-up.

Appendix C: Updated survival analysis

Updated survival analysis was carried out based on the more recent LOTIS-2 data cut from September 2022. The outputs of the updated survival analyses for the base case used for loncastuximab and scenario analyses for loncastuximab and Pola+BR are presented in this section.

Loncastuximab survival analyses

Table 17: Outputs of the log-logistic model used in the two-stage adjustments

	Coefficient	SE	LCI	UCI
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]
PFS time	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines				
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
Response to first line				
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]
Response to last line				
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
Stage at diagnosis				
Stage II	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
gamma	[redacted]	[redacted]	[redacted]	[redacted]

Table 18: Parameters and goodness-of-fit statistics for loncastuximab tesirine OS, unweighted

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	440.0	448.9
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	468.0	473.9
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	436.0	441.9
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	478.4	481.4
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	445.4	451.3
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	447.6	453.5
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Table 19: Parameters and goodness-of-fit statistics for loncastuximab PFS, unweighted

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	326.2	335.1
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	372.5	378.5
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	344.4	350.3
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	384.0	386.9
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	346.4	352.3
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	351.0	357.0
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Table 20: Parameters and goodness-of-fit statistics for loncastuximab OS, weighted to match the CORAL extension studies using two-stage adjustment

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	230.8	237.9
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	248.1	252.8
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	231.1	252.8
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	250.4	252.8
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	232.7	237.5
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	234.3	239.1
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Table 21: Parameters and goodness-of-fit statistics for loncastuximab PFS, weighted to match the CORAL extension studies

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	162.5	169.6
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	186.6	191.4
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	175.8	180.5
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	186.8	189.2
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	172.0	176.8
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	174.4	179.1
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Table 22: Parameters and goodness-of-fit statistics for loncastuximab OS, weighted to match GO29365

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	328.6	336.8
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	343.6	349.1
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	301.3	306.8
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	352.1	345.8
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	308.7	314.2
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	309.8	315.3
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Table 23: Parameters and goodness-of-fit statistics for loncastuximab PFS, weighted to match GO29365

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	256.4	264.7
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	284.3	289.8
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	255.8	261.3
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	291.4	294.2
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	256.8	262.3
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	259.4	264.9
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Table 24: Parameters and goodness-of-fit statistics for loncastuximab OS, weighted to match COTA

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	345.1	354.0
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	369.7	375.7
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	277.5	283.5
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	381.2	384.2
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	287.7	293.7
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	291.0	297.0
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Table 25: Parameters and goodness-of-fit statistics for loncastuximab PFS, weighted to match COTA

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	262.0	270.9
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	304.1	310.0
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	252.1	258.0
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	316.7	319.7
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	255.5	261.4
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	259.7	265.7
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

Pola+BR survival analyses

Data from Northend et al (3) was used to inform the efficacy of Pola+BR in a scenario analysis. The survival analysis outputs for OS and PFS, based on curves digitised from Northend et al, are reported in Table 26 and Table 27, respectively.

Table 26: Parameters and goodness-of-fit statistics for Pola+BR OS, Northend et al (3)

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	280.3	289.0
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	285.7	291.5
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	287.5	293.3
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	285.6	288.5
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	278.8	284.6
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	281.7	287.5
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; OS, overall survival; SE, standard error; UCI, upper confidence interval.

Table 27: Parameters and goodness-of-fit statistics for Pola+BR PFS, Northend et al (3)

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
Generalised gamma	Constant	[redacted]	[redacted]	[redacted]	[redacted]	342.9	351.6
	ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
	kappa	[redacted]	[redacted]	[redacted]	[redacted]		
Weibull	Constant	[redacted]	[redacted]	[redacted]	[redacted]	362.1	367.8
	Ln(p)	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Constant	[redacted]	[redacted]	[redacted]	[redacted]	358.8	364.6
	gamma	[redacted]	[redacted]	[redacted]	[redacted]		
Exponential	Constant	[redacted]	[redacted]	[redacted]	[redacted]	360.2	363.0
Lognormal	Constant	[redacted]	[redacted]	[redacted]	[redacted]	347.8	353.6
	Ln(sigma)	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	Constant	[redacted]	[redacted]	[redacted]	[redacted]	353.2	359.0

	Parameter	Coefficient	SE	LCI	UCI	AIC	BIC
	Ln(gamma)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LCI, lower confidence interval; PFS, progression-free survival; SE, standard error; UCI, upper confidence interval.

References

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Single Technology Appraisal

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Clinical expert statement and technical engagement response form

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- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

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Thank you for your time.

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Part 1: Treating diffuse large B-cell lymphoma and high-grade 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	Andrea Kuhnl
2. Name of organisation	King's College Hospital London
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 diffuse large B-cell lymphoma and high-grade B-cell lymphoma? ☒ A specialist in the clinical evidence base for diffuse large B-cell lymphoma and high-grade B-cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ 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.	

8. What is the main aim of treatment for diffuse large B-cell lymphoma and high-grade B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
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)	
10. In your view, is there an unmet need for patients and healthcare professionals in diffuse large B-cell lymphoma and high-grade B-cell lymphoma?	
11. How is diffuse large B-cell lymphoma and high-grade B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA649]?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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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 EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Concerns over the suitability of the matching-adjusted indirect comparison (MAIC) analyses performed and presented (Sections 3.3.2, 3.3.3, 3.3.4, 4.2.6) • The MAIC analyses offer little improvement over a naïve comparison in terms of accounting for differences due to lack of information available on the target studies and small sample sizes. Any estimates of effect size are unlikely to be solely attributable to the treatment received. • For comparison to Pola+BR using GO29365, most MAIC inputs come from a wider trial population, not the desired 3L+ population. This comparison is based on crude methodology using median survival times, as no other information is available. • The company has not performed requested MAIC analysis for Pola+BR comparison. The EAG is	• Agree with concerns about the suitability of the MAIC analyses, due to small sample size and missing data in the target population. In particular, lack of adequate data from the COTA database does not allow to account for important differences. I.e. an incidence of only 6% of patients with bulky disease in LOTIS-2 will likely be significantly higher in the RW setting. • Median survival times are indeed problematic as main efficacy endpoint for comparison. In a 3L+ setting where many patients have fast progressing disease and the treatment is expected to achieve long-term remission in far less than 50% of patients, the median PFS may predominantly reflect the speed of progression of non-responders (impacted by baseline risk factors not adequately

concerned with the company's rationale for the inclusion of patients and variables in the MAIC analysis.	adjusted for) rather than the likelihood of prolonged remissions of responding patients (as the clinically meaningful parameter). • We did not find justification by the company why requested MAIC analysis has not been performed which needs to be provided. • Given the importance of the factor 'response to last line' in the 3L+ setting, it is highly unsatisfactory that this variable is not adjusted for. The company justifies the exclusion of this variable with the difference in variable definitions and the impact of different definitions on outcome. However, they provide evidence from the front-line setting, where outcome is indeed significantly different between primary progressing or early relapsing patients, but this cannot be directly applied to the 3L+ setting. Inclusion of the variable 'refractoriness to 1L' does not substitute for 'response to last line'.
Unsupported degree of overall survival (OS) benefit of loncastuximab tesirine over Pola+BR (Sections 3.3.2, 3.3.3, 4.2.6) • Company OS extrapolations are too optimistic. • There is a lack of evidence from MAIC analyses to support the difference in effect for OS between loncastuximab tesirine and Pola+BR.	• Agree that the long-term OS extrapolations were too optimistic and the lognormal assumption of 6% 10-y OS is more appropriate. • Agree with assumption of similar OS between lonca-T vs Pola-BR.
Company progression-free survival (PFS) extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine (Section 4.2.6)	• Agree with the concern of the generalised gamma model being slightly too optimistic and the numbers at risk are too small to provide clear evidence of a plateau. However, it seems plausible that a plateau would start to appear at around 24-30 months (12 months

• For comparison to Pola+BR, the company base case predicts a PFS benefit which is not supported by the indirect comparison.	after last dose of treatment), and therefore the lognormal curve might be too pessimistic.
Lack of information for a meaningful extrapolation for PFS of chemotherapy. (Section 4.2.6)	The proposed assumption is probably reasonable given the strong association of PFS and OS in the 3L+ setting for chemotherapy.
For chemotherapy comparison: Inconsistent application of two-stage adjustment to remove benefit of CAR-T therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses (Section 4.2.6.2.2) • Whilst two-stage adjustment is applied in cost-effectiveness analysis, this is not done in clinical sections. The EAG believes that applying two-stage adjustment prior to calculating hazard ratios and MAIC weights would reduce the relative benefit of loncastuximab tesirine as measured by a hazard ratio.	Agree that HRs should have been calculated after 2-stage adjustment and that this would likely result in reduced benefit of lonca-T.
Rate of subsequent autoSCT therapy in chemotherapy arm (Section 4.2.8.1) • EAG considers that the proportions of patients in the chemotherapy arm who receive chemotherapy as 4th line (subsequent therapy) is too high and unlikely to be reflective of proportions seen in clinical practice.	A rate of 54% of 3L chemotherapy patients receiving a 4th line of chemotherapy is unrealistically high and should rather be estimated in the range of 20%. The estimated proportion of patients undergoing subsequent autoSCT in the chemotherapy arm should be similar as for the lonca-T group, ~3%
Appropriate QALY weighting to adjust for severity (section 4.2.9) • The company base case analysis for Pola+BR indicates that a severity weighting does not apply for this appraisal whilst the chemotherapy comparison	Severity weighting should not apply since Pola BR is the more appropriate comparator.

proposes that a 1.2x QALY weighting is justified. The EAG believes the appropriate QALY weighting should be based on the analysis from a comparator treatment considered the most relevant for this appraisal.	
Appropriateness of comparator treatments (Table 3 and Section 2.3)	Uncertainty about the future role of pola-BR as comparator after introduction of pola-R-CHP in 1L; however, there is currently no alternative comparator treatment that would provide a more accurate approximation.
Are there any important issues that have been missed in EAR?	When IPI was replaced with individual components for adjustment, the 2 IPI factors “elevated LDH” and “involvement of 2+ extranodal sites” were not included, even though prognostically significant in the 3L setting. Given the concerns of the current MAIC analysis to adequately account for differences, inclusion of these 2 factors might be considered.

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

From the presented data, no firm conclusion can be drawn regarding the effectiveness of lonca-T against comparator treatments in 3L+ LBCL.

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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Part 1: Treating diffuse large B-cell lymphoma and high-grade 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	Cathy Burton
2. Name of organisation	Leeds Teaching Hospitals NHS Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with diffuse large B-cell lymphoma and high-grade B-cell lymphoma? ☒ A specialist in the clinical evidence base for diffuse large B-cell lymphoma and high-grade B-cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ 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.	N/A

8. What is the main aim of treatment for diffuse large B-cell lymphoma and high-grade B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	For most patients, the main aim will be to be cured of lymphoma. If refractory/relapse/poor performance score, main aim may still be to cure lymphoma or to control disease/relieve symptoms.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	At least a partial response – clinically, radiologically and metabolically – reduction by 50% or more but aiming for complete (metabolic) response
10. In your view, is there an unmet need for patients and healthcare professionals in diffuse large B-cell lymphoma and high-grade B-cell lymphoma?	Yes, 25% of patients relapse and more difficult to treat with more intensive treatment required at relapse. Difficult to predict at outset which patients would benefit from intensive/alternative treatments. Need to identify molecular targets so can give targeted treatment with less off target effects. Need to predict who would benefit from intensive treatments such as transplant, CAR-T cell therapy.
11. How is diffuse large B-cell lymphoma and high-grade B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	R-Pola-CHP is first line for patients IPI 2 or above since earlier this year. R-CHOP (4-6 cycles) for those IPI score 0 or 1 Clinical trials – REMoDLA Currently second line is CAR-T cell therapy if prompt relapse (within 12 months), otherwise salvage chemo and autograft. Currently third line is CAR-T cell therapy (at any time of relapse). Bi-specific antibody, glofitimab, available on EAMS. Currently undergoing NCIE review. Bi-specifics and more targeted treatment s available through clinic trials BSH guidelines Pathway well defined but changed significantly in England over last 6 months Technology expands number of effective lines of treatment for patients
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will be used a line of treatment in current care of DLBCL/HGBCL

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Will be further line of iv outpatient treatment, may allow patients to be eligible for other lines of therapy, eg CAR-T cell therapy Should be used in secondary care by haematologists caring for lymphoma patients Staff need to be trained in the administration of drug and potential side effects on chemo day care unit but no specialist equipment required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	An additional option rather than palliative care esp for those less likely to be eligible for CAR-T cell therapy due to poor performance status/co-morbidites and an alternative treatment for those that have relapsed post CAR-T cell therapy/bi-specifics Has potential to increase QoL above palliative care
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No as long as felt patient able to tolerate treatment
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Equivalent to current care and perhaps easier if patients respond so performance status improves

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Can continue as long as well tolerated, no significant debilitating side effects. No additional testing required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Should be included in QALY
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Addresses unmet need of further treatment option for patients heavily pretreated as an alternative to palliative care
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Main side effects are weight gain and oedema which can also lead to shortness of breath due to fluid accumulation in the lungs
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, most important outcome would be PFS, which was measured in trial as well as ORR and OS.

• 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?	Short FU to predict long term response No adverse effects as predicted
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 [TA649]?	No
23. How do data on real-world experience compare with the trial data?	There is real world date on BR-Pola published by Townsend et al. Real world experience is changing as now R-Pola-CHP available front line which will impact on use of BR-Pola in subsequent lines of treatment
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	No

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Concerns over the suitability of the matching-adjusted indirect comparison (MAIC) analyses performed and presented (Sections 3.3.2, 3.3.3, 3.3.4, 4.2.6) • The MAIC analyses offer little improvement over a naïve comparison in terms of accounting for differences due to lack of information available on the target studies and small sample sizes. Any estimates of effect size are unlikely to be solely attributable to the treatment received. • For comparison to Pola+BR using GO29365, most MAIC inputs come from a wider trial population, not the desired 3L+ population. This comparison is based on crude methodology using median survival times, as no other information is available. • The company has not performed requested MAIC analysis for Pola+BR comparison. The EAG is	Not an expert on MAIC analyses but think analysis should have included well recognised variables from IPI. Not clear why LDH and number of extranodal sites not included, this information should have been accessible. Also bulk vs non-bulk disease. Lots of variability in variables used so makes comparison difficult. Median survival times not ideal and direct comparison with 3L+ population agree not used.

concerned with the company's rationale for the inclusion of patients and variables in the MAIC analysis.	
Unsupported degree of overall survival (OS) benefit of loncastuximab tesirine over Pola+BR (Sections 3.3.2, 3.3.3, 4.2.6) • Company OS extrapolations are too optimistic. • There is a lack of evidence from MAIC analyses to support the difference in effect for OS between loncastuximab tesirine and Pola+BR.	Agree too optimistic, OS benefit likely equivalent to PR-Pola, difference not supported
Company progression-free survival (PFS) extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine (Section 4.2.6) • For comparison to Pola+BR, the company base case predicts a PFS benefit which is not supported by the indirect comparison.	Would suggest curve for PFS sits between gamma (black) and lognormal (brown). Gamma likely too optimistic but not unreasonable to suggest plateau to some extent and therefore between two curves is plausible.
Lack of information for a meaningful extrapolation for PFS of chemotherapy. (Section 4.2.6)	Think very difficult to extrapolate PFS for chemo
For chemotherapy comparison: Inconsistent application of two-stage adjustment to remove benefit of CAR-T therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses (Section 4.2.6.2.2) • Whilst two-stage adjustment is applied in cost-effectiveness analysis, this is not done in clinical sections. The EAG believes that applying two-stage adjustment prior to calculating hazard ratios and MAIC weights would reduce the relative benefit of loncastuximab tesirine as measured by a hazard ratio.	Think two stage adjustment could have some clinical relevance as 2 different clinical questions, Lonca-T as bridge to CAR-T cell therapy or used post CAR-T cell therapy but I am not sure if it can be used in this way if result is to impact on benefit of CAR-T cell therapy.

Rate of subsequent autoSCT therapy in chemotherapy arm (Section 4.2.8.1) • EAG considers that the proportions of patients in the chemotherapy arm who receive chemotherapy as 4th line (subsequent therapy) is too high and unlikely to be reflective of proportions seen in clinical practice.	Agree too high and does not reflect clinical practice, rate of auto would be very low
Appropriate QALY weighting to adjust for severity (section 4.2.9) • The company base case analysis for Pola+BR indicates that a severity weighting does not apply for this appraisal whilst the chemotherapy comparison proposes that a 1.2x QALY weighting is justified. The EAG believes the appropriate QALY weighting should be based on the analysis from a comparator treatment considered the most relevant for this appraisal.	Agree QALY weighting to be applied according to comparator
Appropriateness of comparator treatments (Table 3 and Section 2.3)	Comparators appropriate. As mentioned above, R-Pola-CHP use upfront will alter use of BR-Pola downstream but for the purposes of this appraisal, BR-Pola correct comparator.
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Remains unmet need for many DLBCL/HGBCL patients after 2 or more lines of therapy

Lonca-T provides an additional line of treatment, mainly after CAR-T cell therapy

Lonca-T is well tolerated, outpatient treatment with limited additional delivery burden

Lonca-T is of survival benefit for those patients whom palliative care is the alternative

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ID3943: Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies.

External Assessment Group Critique of Company Technical Engagement Response

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Declared competing interests of the authors

None

Introduction

The company technical engagement response is structured to respond to eight of the key issues raised in the original EAG report. This EAG critique follows the same structure and responds the new information presented for each issue. It concludes with the presentation of EAG base case analysis and some selected scenario analyses. This report is complemented by the EAG cPAS appendix which applies confidential discounts for competitor health technologies into the economic analyses.

Issue 1: Concerns over the suitability of the matching-adjusted indirect comparison (MAIC) analyses performed and presented (Sections 3.3.2, 3.3.3, 3.3.4, 4.2.6)

In response to the EAG's concerns about the parameters and patients included in the MAIC analysis for the comparison between loncastuximab tesirine and polatuzumab plus bendamustine rituximab (Pola+BR), using data from LOTIS-2 and GO29365, the company have presented the output from additional MAIC analyses. It appears that these MAIC analyses use the previous March 2022 data-cut rather than the latest September 2022 data-cut which is mentioned in later TE responses.

Given the lack of potential variables that were available for matching, the EAG had requested that a maximal set of variables be used adding in IPI stage, however even this analysis would be at high risk of bias.

In addition, at the previous clarification response stage, the company included an additional 14 patients in the MAIC from LOTIS-2 who had an "other" classification for primary refractory status. This was not requested by the EAG and so the EAG asked the company to remove these patients.

In the TE submission, the company provided two analyses, one where the "other" primary refractory patients were excluded, and a second where the maximal set of variables has been used. The company has not provided an analysis where both of these adjustments are applied simultaneously.

The EAG presents the key weighted output from the analyses in Table 1. The company has not provided Kaplan-Meier plots for the time-to-event outcomes, so the EAG is unable to establish whether the hazard ratios presented give an accurate

representation of the difference between the treatments across the follow-up period. Neither has the company provided effective sample sizes (ESS), preventing any assessment of comparative reliability of the analyses, but it is reported that each has an ESS of over 78.

The sensitivity analyses which omits the "other" primary refractory patients reports a minor difference in OS suggesting loncastuximab might be inferior, whilst the analysis which includes IPI as a matching variable finds a sizeable difference in favour of Pola+BR for PFS, where the 95% confidence interval almost excludes the point of no difference.

Table 1: Output from company's additional MAIC analyses

Analysis	Starting N for loncastuximab tesirine	OS HR (95% CI) Weighted	PFS HR (95% CI) Weighted	ORR OR (95% CI) Weighted
Company base-case	116	1.00 (0.71, 1.40)	1.24 (0.88, 1.74)	0.92 (0.53, 1.59)
Sensitivity analysis: Exclude "other" primary refractory patients	102	1.07 (0.75, 1.51)	1.20 (0.85, 1.70)	1.02 (0.58, 1.78)
Sensitivity analysis: Include IPI matching	116	1.00 (0.71, 1.40)	1.39 (0.99, 1.95)	0.91 (0.53, 1.57)

It remains possible that an analysis combining the changes requested by the EAG would estimate loncastuximab tesirine to be inferior for both OS and PFS relative to Pola+BR. Furthermore, the company have not implemented the output from these MAIC analyses into the economic model so their impact on the cost-effectiveness is unknown. Ultimately, the relative effect of loncastuximab tesirine compared to Pola+BR remains unknown due to the lack of direct comparison data and a high uncertainty associated with all available indirect comparisons. These limitations extend to the comparison with chemotherapy, and it is plausible that the indirect comparisons presented in this appraisal are no more reliable than a naïve, unadjusted comparison.

Issue 2: Unsupported degree of overall survival (OS) benefit of loncastuximab tesirine over Pola+BR (Sections 3.3.2, 3.3.3, 4.2.6)

The original company submission critiqued by the EAG used time-to-event outcomes that were based on indirect comparisons using the March 2022 data-cut from LOTIS-2 for loncastuximab tesirine. In this TE response, the company have presented updated output from LOTIS-2, however this is provided without any accompanying indirect comparison analyses which prevents any conclusions of relative benefit from being made.

The EAG shows an overlayed comparison of the PFS and OS plots in Figure 1.

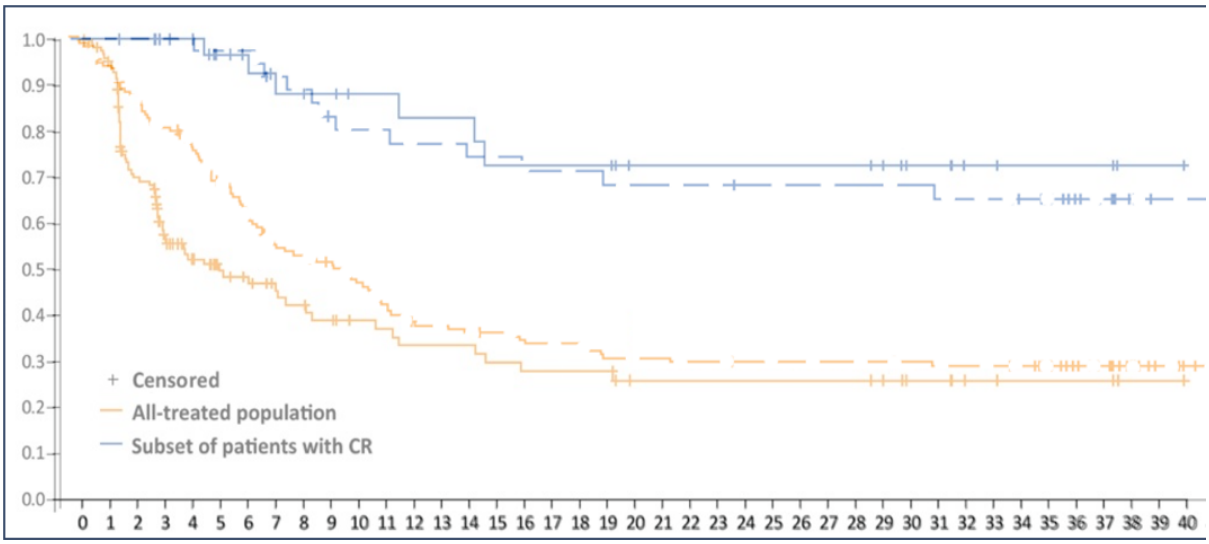

Figure 1: Comparison of new follow-up from LOTIS-2, with dashed line for OS and solid line for PFS

The EAG is concerned with the reliability of this new information, as for the CR population, the OS curve falls below the PFS curve. Furthermore, there are also more OS events (12 and 97) than PFS events (6 and 73) in both groups, which is unexpected given that the definition of a PFS event usually includes OS events. The EAG also notes different patterns of censoring across PFS and OS, for which no reason is provided.

The company reports that survival models fitted to output from indirect comparisons using the September 2022 data-cut have been used in the economic model. The EAG is wary of using analyses from the TE economic model when there are clear issues with the data feeding into the PFS and OS outcomes.

Based on the latest data, in support of the company's economic modelling, clinicians consulted by the company stated that a number of patients could be considered cured, and would have a normal life expectancy, if they were to remain progression-

free at 2 years and received no further anti-cancer therapy. In contrast, the EAG's clinical expert was of the view that "almost all patients will relapse and it… it is most unlikely that any or very few isolated patients will be 'cured' of their disease."

The company's approach to modelling OS for loncastuximab tesirine in comparison to Pola+BR was to use a generalised gamma extrapolation of MAIC-weighted LOTIS-2 data. For Pola+BR, the company used a generalised gamma extrapolation of data from GO29365.

The company supports this choice of model through presentation of a smoothed hazard rate plot, however this plot is not really fit for this purpose on its own due to the range of smoother settings for the line representing the observed data.

The EAG presents the output of the company's OS assumptions in Figure 2, where a small benefit in favour of loncastuximab tesirine is apparent. The company state this is justified as the comparison to GO29365 is biased against loncastuximab tesirine as the LOTIS-2 trial includes no second line patients, some of whom were included in GO29365. The company supports this with comparisons to RWE use of Pola+BR however the EAG has already advised against this approach, and does not recommend comparing RWE to trial data.

The EAG maintain their preference to use a log-normal extrapolation for loncastuximab tesirine and assume equivalent between the two treatments, which is more consistent with the hazard ratios yielded from the MAIC analyses. The choice of data-cuts has minimal impact on the EAG's base case given the assumption of equivalence.

Figure 2: Company base case OS curves for loncastuximab tesirine vs Pola+BR

Issue 3: Company PFS extrapolations are too optimistic and result in a vanishing post-progression survival health state for loncastuximab tesirine (Section 4.2.6)

The EAG's original concerns with the company's modelling of PFS were that it modelled a large benefit for loncastuximab tesirine over Pola+BR, which was inconsistent with the PFS hazard ratio, and resulted in lack of post-progression survival health state for loncastuximab tesirine beyond 15 years. The company reports that it has updated the PFS data used in the MAIC and economic model to now be based on the September 2022 data-cut. The additional data have little impact, and the company maintains its use of independent generalised gamma extrapolations for MAIC-weighted LOTIS-2 data and GO29365 data (Figure 3). The EAG notes that the large benefit for loncastuximab tesirine is not supported by the hazard ratios estimated by models fitted to the data. Hence the EAG again prefer to use a log-normal extrapolation for loncastuximab tesirine and assume equivalence across the two treatments.

Figure 3: Company base case PFS curves for loncastuximab tesirine vs Pola+BR

Issue 4: Lack of information for a meaningful extrapolation for PFS of chemotherapy (Section 4.2.6)

For the comparison to chemotherapy, the company compared LOTIS-2 data to data from the CORAL extension study, however the CORAL extension lacked any PFS data for the chemotherapy patients. The company's preferred approach is to extrapolate the MAIC-weighted LOTIS-2 PFS data and apply the OS hazard ratio to obtain a PFS extrapolation for chemotherapy (HR=1.43). The company explore an alternative approach which applies a ratio of 0.65 between PFS and OS cumulative hazard for chemotherapy, as was done in TA567 which also used CORAL extension study data. This results in a reduced mean PFS time for chemotherapy relative to the company's base case. Whilst this is a plausible alternative, the uncertainty remains very high. The EAG is unable to explore any alternative scenarios and, in the EAG base case, persists with the assumptions of the company's base case.

Issue 5: For chemotherapy comparison: Inconsistent application of two-stage adjustment to remove benefit of chimeric antigen receptor T cells (CAR-T) therapies in some LOTIS-2 patients across clinical and cost-effectiveness analyses (Section 4.2.6.2.2)

Previously, the company had applied a two-stage adjustment to remove the benefit of CAR-T therapy from patients in LOTIS-2, as clinical expert advice stated it was unlikely that patients receiving chemotherapy would receive CAR-T therapy. However this adjustment was only applied into the economic model, and not the results of the clinical section. The EAG also requested that the adjustment be applied prior to MAIC weights being calculated.

The company present this new analysis, however have not provided complete detailed output. The new model reports a hazard ratio of 1.43 (95% CI: 1.06, 1.93) in favour of loncastuximab tesirine, which is lower than the company's original OS hazard ratio of 1.49 (95% CI: 1.16, 1.96). This result has been carried forward into the economic model, and the EAG welcomes this revision.

Issue 6: Rate of subsequent autologous stem cell transplantation (autoSCT) therapy in chemotherapy arm (Section 4.2.8.1)

The company maintains the use of subsequent autoSCT following chemotherapy as observed in the CORAL extension study. In the TE response the company acknowledges that the rates "may slightly differ" in routine use, having previously stated that "this rate is higher" than is expected in clinical practice. The EAG rejects the company's preferred value as implausible, and maintains its original choice to use the same value used for loncastuximab tesirine as per the previous EAG base case.

Issue 7: Appropriate quality-adjusted life year (QALY) weighting to adjust for severity (Section 4.2.9)

No new information has been provided.

Issue 8: Appropriateness of comparator treatments (Table 3 and Section 2.3)

No new information has been provided.

Revised cost-effectiveness analyses results

The EAG's main assumptions remain unchanged for Pola+BR. The impact of the company's revised analysis on EAG's preferred assumptions are presented in Table 2.

Table 2: EAG's preferred assumptions, loncastuximab tesirine vs Pola+BR

Assumptions	Incremental costs	Incremental QALYs	Incremental QALYs (severity-modified)	ICER*	ICER* (severity-modified)
Company's revised base-case	[redacted]	[redacted]	[redacted]	**Dominant**	**Dominant**
EAG's Preferred Assumptions					
EAG 01: Loncastuximab OS changed to log-normal	[redacted]	[redacted]	[redacted]	SW: £319,971	SW: £319,971
EAG 02: Loncastuximab PFS changed to log-normal	[redacted]	[redacted]	[redacted]	Dominant	Dominant
EAG 03: Pola+BR OS set equal to Loncastuximab	[redacted]	[redacted]	[redacted]	Dominant	Dominant
EAG 04: Pola+BR PFS set equal to Loncastuximab	[redacted]	[redacted]	[redacted]	Dominant	Dominant
EAG base-case	[redacted]	[redacted]	[redacted]	**Loncastuximab cost-saving**	**Loncastuximab cost-saving**

*Dominant ICER – loncastuximab less costly, more effective; Cost-saving – loncastuximab less costly but less effective (or zero QALY benefits)

Note on severity modifier: The EAG has maintained the company's approach to 're-calculate' the QALY weight for each of the EAG's preferred assumptions. This is because expected QALYs - a key input parameter in calculating QALY shortfalls, varies depending on the model assumption.

Table 3: Revised EAG deterministic base-case results, loncastuximab tesirine vs Pola+BR, updated loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Loncastuximab tesirine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Loncastuximab cost-saving

Table 4 Revised EAG probabilistic base-case results, loncastuximab tesirine vs Pola+BR, updated loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	-
pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	Loncastuximab cost-saving

Table 5: EAG's preferred assumptions, loncastuximab tesirine vs chemotherapy

Assumptions	Incremental costs	Incremental QALYs	Incremental QALYs (severity-modified)	ICER*	ICER* (severity-modified)
Company's revised base-case	[redacted]	[redacted]	[redacted]	£33,231	£27,692
EAG's Preferred Assumptions					
EAG 01: OS distribution changed from Gen Gamma to Lognormal	[redacted]	[redacted]	[redacted]	£46,317	£38,598
EAG 05: AutoSCT subsequent therapy changed from 22% to 3%	[redacted]	[redacted]	[redacted]	£39,687	£33,072
EAG base-case	[redacted]	[redacted]	[redacted]	£55,746	£46,455

Table 6: Revised EAG deterministic base-case results, loncastuximab tesirine vs chemotherapy, updated loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,746

Table 7: Revised EAG probabilistic base-case results, loncastuximab tesirine vs chemotherapy, updated loncastuximab tesirine PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-
Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]	£60,800