Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

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 Roche:**
   a. Full submission
   b. Pola-BR scenario analysis
   c. Company response regarding second-line use of Pola-BR
   d. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Response
   b. Appendix

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Lymphoma Action

4. **Expert personal perspectives** from:
   a. Dr Cathy Burton – clinical expert, nominated by Roche
   b. Dr Sridhar Chaganti - clinical expert, nominated by Roche
   c. Peter Clark – CDF clinical lead

5. **External Assessment Report** prepared by SHTAC
   a. External Assessment Report
   b. EAG addendum – critique of company Pola-BR scenario analysis
   c. EAG additional analysis pre-ACM1

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

Company evidence submission

February 2025

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Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ABC	activated B-cell-like
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criterion
ALT	alanine transaminase
ASCT	autologous stem-cell transplant(ation)
ASH	American Society of Hematology
AST	aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BIC	Bayesian information criterion
BMI	Body Mass Index
BNF	British National Formulary
BR	bendamustine and rituximab
BSA	body surface area
BSH	British Society for Haematology
CAR	chimeric antigen receptor
CCOD	clinical cut-off date
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone
CHP	cyclophosphamide, doxorubicin and prednisone
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatine clearance
CRR	complete response rate
CRS	cytokine release syndrome
CSR	clinical study report

Abbreviation	Definition
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DA-EPOCH-R	dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab
DHL	double-hit lymphoma
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOCR	duration of complete response
DOR	duration of objective response
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
EBV	Epstein–Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQol 5-Level 5-Dimension Questionnaire
ESMO	European Society for Medical Oncology
FACT-Lym LymS	Functional Assessment of Cancer Therapy−Lymphoma Subscale
FL	follicular lymphoma
GCB	germinal centre B-cell like
GemOx	gemcitabine and oxaliplatin
GHS/QoL	global health status/quality of life
Glofit	glofitamab
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRQoL	health-related quality-of-life
HSCT	haematopoietic stem cell transplant

Abbreviation	Definition
HTA	health technology assessment
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
ICF	Informed Consent Form
ICU	Intensive Care Unit
IHC	immunohistochemistry
ILD	interstitial lung disease
IPI	International Prognostic Index
IRC	Independent Review Committee
IRR	infusion-related reaction
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
KM	Kaplan-Meier
LBCL	large B-cell lymphoma
LY	life years
LYG	life years gained
MA	marketing authorisation
MALT	mucosa-associated lymphoid tissue
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NAE	neurological adverse events
NALT	new anti-lymphoma therapy
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NE	not estimable
NHB	net health benefit
NHL	non-Hodgkin lymphoma
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit

Abbreviation	Definition
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PCR	polymerase chain reaction
PD	progressive disease
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PK	pharmacokinetic
PN	peripheral neuropathy
Pola-R-CHP	polatuzumab vedotin, rituximab, doxorubicin, cyclophosphamide and prednisolone
Pola-BR	polatuzumab vedotin, bendamustine and rituximab
PPS	post-progression survival
PR	partial response
PRO	patient-reported outcome
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
PSSRU	Personal Social Services Research Unit
PT	preferred term
QALY	quality-adjusted life year
QoL	quality-of-life
Q3	third quarter
RA	rheumatoid arthritis
R/R	relapsed/refractory
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
R-CODOX-M/R-IVAC	rituximab, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/rituximab, ifosfamide, etoposide and high-dose cytarabine
R-DECC	rituximab, dexamethasone, etoposide, chlorambucil and lomustine
R-DHAP	dexamethasone, cytarabine and cisplatin
RECIST	Response Evaluation Criteria in Solid Tumours
R-ESHAP	rituximab, etoposide, methylprednisolone, cytarabine and cisplatin
R-GDP	rituximab, gemcitabine, dexamethasone and cisplatin
R-Gem	rituximab and gemcitabine

Abbreviation	Definition
R-ICE	rituximab, ifosfamide, carboplatin and etoposide
R-P-MitCEBO	rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin and vincristine
SACT	systemic anti-cancer therapy
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCT	stem cell transplant
SD	stable disease
SLL	small lymphocytic lymphoma
SLR	systematic literature review
SMR	standardised mortality ratio
SOC	standard-of-care
TCR	T-cell receptor
TLS	tumour lysis syndrome
TTD	time-to-deterioration
TTOT	Time-to-off-treatment
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTP	willingness-to-pay
β2-MG	β2 microglobulin
1L	first-line
2L	second-line
3L	third-line
4L	fourth-line

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

1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation, specifically for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplantation (ASCT) who have progressed during or after one prior treatment only (i.e. **for patients in the second-line [2L] setting**). The proposed position in the R/R DLBCL pathway is narrower than the marketing authorisation ([redacted]) for the reasons outlined below:

- **The available evidence for glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx)**: it was not possible to conduct robust ITCs vs. comparators identified in the NICE scope that are used in the third-line and beyond (3L+) setting (axicabtagene ciloleucel, loncastuximab tesirine, epcoritamab) (see Section 2.10). This is due to either an absence of aggregated data to enable matching or significant imbalances remaining in matched populations, which when adjusted for would result in a very small effective sample size, rendering the ITCs highly uncertain. Furthermore, while a propensity score analysis vs. glofitamab monotherapy can be conducted due to the availability of individual patient data, the outcomes from this analysis are highly uncertain due to a small effective sample size.

  However, a comparison against rituximab plus gemcitabine and oxaliplatin (R-GemOx), to reflect rituximab-chemotherapy as identified in the NICE scope as a 2L comparator, is feasible as data are available from the pivotal Phase III study, STARGLO, which investigated the safety and efficacy of Glofit-GemOx compared with R-GemOx in R/R DLBCL patients who were ineligible for transplant after receiving at least one prior therapy. Although the enrolled population was broad by including both 2L and 3L+ patients approximately two-thirds of patients received Glofit-GemOx or R-GemOx as a second-line treatment, therefore restricting to this setting is not limited by small patient numbers.

- **Relevance to NHS clinical practice**: UK clinical experts have confirmed that the greatest unmet need in R/R DLBCL is in the 2L setting, where treatment for patients who are transplant-ineligible is limited to R-GemOx. This regimen is widely acknowledged as an ineffective treatment option for 2L patients and is offered to allow patients to progress to more effective treatments in the 3L setting. This view is supported by UK real-world data from patients treated with R/R DLBCL after 1L therapy, which showed that median progression-free survival (PFS) and median overall survival (OS) in patients not eligible for transplant was 4.27 months and 6.94 months, respectively (1). Therefore, there is an urgent need for effective treatments that can achieve a complete response and offer a survival benefit. Clinical experts confirmed to the company that if Glofit-GemOx were to be reimbursed for the entire R/R DLBCL population as per the marketing authorisation, the use of the regimen would primarily be in the 2L given the lack of effective treatments and availability of glofitamab monotherapy for 3L+ patients (TA927), and therefore optimising the reimbursement population to 2L patients addresses the unmet need and aligns with intended clinical practice for this regimen.

- **Optimising cost-effectiveness:** Given the limitations and challenges in conducting robust ITCs in the 3L+ setting, restricting the population to 2L only where the evidence is strongest reduces uncertainties in the analysis and allows for the most robust case for the cost-effectiveness of Glofit-GemOx to be considered.

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: • after 1 systemic therapy when autologous stem cell transplant is not suitable or • after 2 or more systemic therapies	Adults with relapsed or refractory diffuse large B-cell lymphoma: • after 1 systemic therapy when autologous stem cell transplant is not suitable	The proposed reimbursement population is narrower than the full market authorisation for the reasons highlighted above, i.e.: • A feasibility assessment confirmed that ITCs vs. regimens in the 3L setting (axicabtagene ciloleucel, loncastuximab tesirine and epcoritamab) are not possible due to an absence of aggregated data or significant imbalances remaining in adjusted populations. Restricting to the 2L setting is supported by where the available evidence base is most robust (i.e. 2/3 of patients received Glofit-GemOx or R-GemOx in the 2L setting in STARGLO) • UK clinical experts confirmed that the greatest unmet need in R/R DLBCL is in the 2L setting and this is where Glofit-GemOx would be mainly prescribed if reimbursed, regardless of the

			broader marketing authorisation, therefore the 2L population is of greatest relevance to NHS clinical practice • Restricting to 2L only patients allows for the most robust case for the cost-effectiveness of Glofit-GemOx to be considered
Intervention	Glofitamab with gemcitabine and oxaliplatin	In line with NICE scope	
Comparator(s)	After 1 systemic therapy and when autologous stem cell transplant is not suitable: • Rituximab in combination with one or more chemotherapy agents such as: o R-GemOx (rituximab, gemcitabine, oxaliplatin) o R-Gem (rituximab, gemcitabine) o R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine) o (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine) o BR (bendamustine, rituximab) • Polatuzumab vedotin with rituximab and bendamustine After 2 or more systemic therapies:	After 1 systemic therapy and when autologous stem cell transplant is not suitable: • Rituximab in combination with gemcitabine and oxaliplatin (R-GemOx)	The company does not consider Pola-BR to be a relevant comparator for 2L R/R DLBCL (see section 1.3.2.1.2). The rationale for excluding Pola-BR from the analysis is based on: • UK clinical expert opinion, which states that Pola-BR is very rarely used in the 2L today (0-10% estimated), due to the approval of Pola-R-CHP in 1L DLBCL and BlueTeq restrictions to re-expose patients to polatuzumab (as indicated by an absence of data demonstrating re-treatment with polatuzumab), plus a reluctance to prescribe bendamustine-containing

	• Rituximab in combination with one or more chemotherapy agents such as:
	  ○ R-GemOx (rituximab, gemcitabine, oxaliplatin)
	  ○ R-Gem (rituximab, gemcitabine)
	  ○ R-P-MitCEBO (rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine)
	  ○ (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine)
	  ○ BR (bendamustine, rituximab)
	• Polatuzumab vedotin with rituximab and bendamustine (only when stem cell transplantation is not suitable)
	• Axicabtagene ciloleucel
	• Glofitamab
	• Loncastuximab tesirine (only if previously treated with polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated)
	• Epcoritamab (only if they have had polatuzumab vedotin, or if polatuzumab vedotin is contraindicated or not tolerated)
			regimens in this setting as this may preclude the use of T-cell effector therapies (CAR-T, bispecific monoclonal antibodies) in later lines
			• Market share data obtained by the company supports clinical expert opinion as this demonstrates an increased use of 1L Pola-R-CHP over 2024, with market share increasing from [redacted] at the start of 2024 to [redacted] at the latest readout in October 2024. Over the same period, the market share for Pola-BR decreased from [redacted] to just [redacted]
			
			Consequently, Roche considers Pola-BR to no longer be a relevant comparator for R/R DLBCL and therefore R-GemOx remains the sole comparator for the current appraisal.
			
			The comparison for rituximab in combination with chemotherapy is reflected by R-GemOx only as this is the standard of care for 2L transplant-ineligible DLBCL, and UK clinical experts confirmed that this regimen is

			representative of all R-chemo regimens in terms of efficacy and safety outcomes. Due to the restriction of reimbursement to 2L patients, the 3L comparators are no longer relevant.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	In line with NICE scope	
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 and cost of biosimilar and generic products should be taken into account.	In line with NICE scope	

Special considerations including issues related to equity or equality	None specified	In line with NICE scope	

1.2 Description of the technology being evaluated

The technology being appraised is described in Table 2. See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Technology being evaluated

UK approved name and brand name	Glofitamab (Columvi) in combination with gemcitabine and oxaliplatin
Mechanism of action	Glofitamab is a full-length, fully humanised IgG1 bispecific monoclonal antibody that recognises and binds bivalently to CD20 expressed on the surface of B-cells, and monovalently to CD3 in the T-cell receptor (TCR) complex expressed on the surface of T-cells. By simultaneously binding to CD20 on the B-cell and CD3 on the T-cell, glofitamab mediates the formation of an immunological synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B-cells (2). The CD3-binding region of glofitamab is fused to one of the CD20-binding regions in a head-to-tail fashion via a flexible linker; this head-to-tail fusion format is designed to increase potency and stabilise the T-cell-target-cell immune synapse (2, 3). The immunoglobulin G format of glofitamab prolongs its half-life, while the silent Fc region is designed to avoid the activation of nonspecific immunomodulatory anti-tumour effects (2, 3). Gemcitabine is a nucleoside analogue that becomes incorporated into nascent DNA of cells undergoing DNA replication (4). Oxaliplatin is a platinum-based alkylating compound that causes inter- and intra-strand cross-links in DNA (5). While gemcitabine and oxaliplatin are cytotoxic chemotherapies, they have not been shown to inhibit anti-tumour cytotoxic T lymphocyte function. Rather, the GemOx regimen can modulate the tumour immune microenvironment to enhance the immunogenicity of tumours, thus supporting its combination with a T-cell engaging therapy such as glofitamab (6-10). In addition, gemcitabine has been shown to upregulate CD20 in DLBCL cell lines. This effect leads to increased cell surface rituximab binding concentrations as well as enhanced rituximab-mediated complement-dependent cytotoxicity (11). CD20 upregulation by gemcitabine could similarly lead to increased CD20-bispecific antibody-binding capacity of the tumour.
Marketing authorisation/CE mark status	A type II variation to include glofitamab in combination with GemOx in the product licence was submitted to the EMA on 29th July 2024.

	A positive CHMP opinion is anticipated in [redacted], and a UK marketing authorisation (MA) is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The MHRA granted conditional approval for glofitamab as monotherapy for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy on 16th October, 2023. The proposed additional indication is as follows: [redacted]
Method of administration and dosage	**Premedication and prophylactic medications** To reduce the risk of cytokine release syndrome (CRS), 20 mg IV dexamethasone premedication should be administered at least 60 minutes prior to the administration of obinutuzumab and glofitamab; dexamethasone premedication will be required after Cycle 3 for patients who experienced CRS with the previous dose; oral analgesic/anti-pyretic and anti-histamine should be administered at least 30 minutes before all infusions of obinutuzumab and glofitamab. **Pre-treatment with obinutuzumab** All patients must receive a single 1000 mg dose of obinutuzumab on Cycle 1, Day 1 (7 days prior to initiation of glofitamab treatment). This is to deplete circulating B cells and thereby reduce the risk of CRS. Obinutuzumab should be administered as an intravenous (IV) infusion at 50 mg/h. The rate of infusion can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h. **Glofitamab posology** After completion of pre-treatment with obinutuzumab on Cycle 1, Day 1, glofitamab must be administered as an IV infusion according to the dose step-up schedule leading to the recommended dose of 30 mg. Each cycle is 21 days. The glofitamab dose step-up schedule is detailed below: • On Cycle 1, Day 8, 2.5 mg of glofitamab is administered over 4 hours; on Cycle 1, Day 15, 10 mg of glofitamab is administered over 4 hours; • On Cycle 2, Day 1, 30 mg of glofitamab is administered over a period of 4 hours; • If the patient experienced CRS with their previous dose, the duration of infusion may be extended to up to 8 hours. • On Cycles 3–12, Day 1, 30 mg of glofitamab may be shortened to 2 hours at the discretion of the treating physician, if the previous infusion was well tolerated. If the patient experienced CRS with the previous dose, the duration of infusion should be maintained at 4 hours

	Gemcitabine/oxaliplatin posology • On Cycle 1, Day 2, 1000 mg/m^2 of gemcitabine and 100 mg/m^2 of oxaliplatin are administered IV. • On Cycles 2–8, Day 1 or 2 (per local practice), 1000 mg/m^2 of gemcitabine and 100 mg/m^2 of oxaliplatin are administered IV. **Dose modifications and treatment interruptions** No dose modifications of glofitamab, obinutuzumab, rituximab, or gemcitabine were permitted in the STARGLO protocol. Oxaliplatin dose could be reduced as per usual clinical practice. If a glofitamab dose delay resulted in a treatment-free interval of 6 weeks or longer, obinutuzumab pre-treatment was re-initiated 7 days prior to resuming glofitamab treatment, and step-up dosing of glofitamab was required for the first cycle after the dose delay.
Additional tests or investigations	Patients must be monitored for signs and symptoms of potential CRS during all glofitamab infusions and for 24 hours after completion of the first infusion of glofitamab on Cycle 1, Day 8. Patients should be monitored and evaluated for tumour flare at critical anatomical sites. Patients at risk of tumour lysis syndrome (TLS) should be monitored closely by appropriate laboratory and clinical tests for electrolyte status, hydration and renal function. No additional requirements are needed for the administration of glofitamab other than those already required for the administration of other conventional cancer treatments.
List price and average cost of a course of treatment	List price: • £687.00 (2.5 mg vial) • £2,748 (10 mg vial)
Patient access scheme (if applicable)	[redacted] (simple discount)

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

1.3.1.1 Incidence and Prevalence

Non-Hodgkin lymphoma (NHL) consists of a heterogeneous group of lymphoproliferative disorders arising from the lymphoid system, and is the most prevalent haematological malignancy (12, 13). Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease and is the most common histologic subtype of NHL, accounting for up to 40% of all newly diagnosed NHL cases (14). In the UK, an estimated 4,870 people are diagnosed with DLBCL (not otherwise specified [NOS]) each year (15). The UK prevalence per 100,000 population is estimated at 39.6, with the 10-year prevalence estimated at 26,000 cases (16). The natural behaviour of the aggressive lymphomas, such as DLBCL, is characterised by faster progression and reduced survival compared with indolent NHL (17).

The incidence of DLBCL increases with age, with the disease typically occurring in adults aged over 60 years (especially the 65–74 years age group) (14, 18). In the UK, the median age at diagnosis for DLBCL patients is 70.2 years (19). Nevertheless, DLBCL can also occur in younger patients, including young adults and children (20). Elderly patients with DLBCL have a poorer prognosis and inferior outcomes compared with younger patients with DLBCL, even with similar treatment (21). The disease symptoms (e.g. fever, recurrent night sweats, weight loss and/or local effects of lymph node enlargement), as well as those of bone marrow failure, along with treatment-related side effects, often lead to impairments in aspects of health-related quality of life (HRQoL), including physical functioning and fatigue (22). Initial treatment aims to be curative; however, about 10–15% of patients are refractory to the first-line (1L) standard of care - rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); and a further 20–30% of patients relapse after a period of remission (23).

1.3.1.2 Pathophysiology

DLBCL has distinct morphology, immunophenotype and genetic features with various subtypes defined in the 2016 World Health Organization (WHO) Classification (24). DLBCL is a neoplasm of large B-lymphoid cells that shows a diffuse growth pattern. Morphologically, the disease is characterised by complete or partial effacement of the nodal architecture by sheets of large atypical lymphoid cells. Immunophenotypically, the disease is characterised by the expression of pan B-cell antigens (cluster of differentiation [CD]19, CD20, CD22, CD79a) and surface and/or cytoplasmic immunoglobulin expression (25).

DLBCL arises from centroblasts or immunoblasts and is associated with genetic abnormalities that are relatively specific to the disease. Although there is no single somatic genetic change that defines the disease, the majority of cases have alterations in the immunoglobulin-heavy genes (26). The most frequently dysregulated genes include *BCL6* (rearrangement in 35−40% of cases; mutation in 5' noncoding region in 70%), *BCL2* (translocation in 15%; amplification in 24%) and *cMYC* (5−15%) (27). Gene expression profiling has identified gene expression patterns that lead to further subtypes of the disease that have different oncogenic pathways, including germinal centre B-cell and activated B-cell-like (ABC) subgroups (28). As such, DLBCL is a heterogeneous disease with a number of histological, proteomic and molecular subsets with distinctive prognostic profiles, including cell of origin (germinal centre B-cells and ABC), double-expressor DLBCL, defined as overexpression of MYC and BCL2 proteins, and double- or triple-hit lymphoma, defined as a dual translocation of *MYC* together with *BCL2* and/or *BCL6* (29-33).

1.3.1.3 Diagnosis and staging

According to the British Society for Haematology (BSH) (34) and the NICE NHL Diagnosis and Management Guidelines (35), DLBCL is diagnosed through surgical biopsy, usually of an involved lymph node or extranodal site. Histological evaluation is performed in accordance with the WHO classification of lymphoid neoplasms, which categorises lymphomas on the basis of cytology, immunophenotype, and genetic and clinical features (24). A morphological diagnosis of DLBCL should be confirmed by immunohistochemistry or flow cytometry. If there is a low level of confidence in the diagnosis, for example owing to a small biopsy specimen or if the putatively neoplastic population has a normal phenotype by immunohistochemistry, demonstration of B-cell monoclonality by polymerase chain reaction-based methods should be considered (36).

For patients diagnosed with DLBCL, the extent of the disease is evaluated by staging, which is crucial to determine the best therapeutic option and predict prognosis. DLBCL can be classified into one of four disease stages according to the Ann Arbor (Table 3) and/or Lugano Staging Classification (Table 4) (36-38). The Ann Arbor staging classification is used routinely to classify the extent of disease on the basis of the distribution and number of involved sites, as well as the presence or absence of extranodal involvement and constitutional symptoms. A consensus study developed by the clinical and imaging working groups of the International Conference of Malignant Lymphomas (Lugano classification) recommends fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) scan as the gold standard for staging patients with DLBCL (37, 39).

Table 3: Ann Arbor staging classification

Stage	
I	Involvement of a single lymphatic region (I) or localised involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localised involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

Source: Tilly et al. 2015 (36).

Table 4: Lugano staging classification

Stage	Involvement	Extranodal status
Limited		
Stage I	One 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[a]	II as above with ‘bulky’ disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: extent of disease is determined by positron emission tomography-computed tomography for avid lymphomas and computed tomography for non-avid lymphomas. The tonsils, Waldeyer's ring and spleen are considered nodal tissue.

[a]Whether Stage II 'bulky' disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Source: Cheson et al. 2014 (37).

1.3.1.4 Prognostic factors

The most commonly used prognostic index for aggressive NHL, including DLBCL, is the International Prognostic Index (IPI). This index is based on five clinical features that are independent predictors of OS:

- Age (≤ 60 versus > 60 years)
- Serum lactate dehydrogenase (normal versus elevated) level
- ECOG performance status (0 or 1 versus 2–4)
- Ann Arbor stage (I or II versus III or IV)
- Number of extranodal sites (0 or 1 versus 2–4).

On the basis of the number of negative prognostic features present at the time of diagnosis (age > 60 years, elevated serum lactate dehydrogenase, ECOG performance status ≥ 2, stage III/IV disease, > 1 extranodal sites of disease), four discrete risk groups were identified before rituximab was introduced, with 5-year OS ranging from 26% to 73% (Table 5) (40).

Sehn *et al*. confirmed the validity of the IPI for DLBCL in the rituximab era in a cohort of 365 patients treated with the R-CHOP regimen (the current standard of care treatment for DLBCL) (41). However, the IPI was able to distinguish only three rather than four risk groups in the original IPI. The authors proposed a revised IPI by redistributing the IPI factors into three prognostic groups: 'very good' (0 risk factors), 'good' (1–2 factors) and 'poor' (3–5 factors). The 4-year OS was 94%, 79% and 55% in the three groups, respectively. Although the original IPI remains valid in the R-CHOP era, it now has more limited ability to predict patients who will experience a particularly aggressive course, because even the 'high-risk' group has a 4-year OS greater than 50% (42).

Table 5: The International Prognostic Index (IPI)

IPI			
Number of risk factors	**Risk group**	**5-year OS, %(Without rituximab)**	**3-year OS, %(With rituximab)**
0 or 1	Low risk	73	91

2	Low–intermediate risk	51	81
3	Intermediate–high risk	43	65
4 or 5	High risk	26	59
Revised IPI			
Number of risk factors	**Risk group**	**–**	**4-year OS, %(With rituximab)**
0	Very good	–	94
1 or 2	Good	–	79
3, 4 or 5	Poor	–	55

IPI, International Prognostic Index; OS, overall survival.

Source: International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) for 5-year OS (40), Vaidya and Witzig (2014) for 3-year OS (42), Sehn et al. 2007 for 4-year OS (41).

DLBCL has a multiplicity of prognostic profiles. Evidence suggests that bulky disease is an adverse prognostic factor and the ABC subtype of DLBCL has been shown to be associated with a more aggressive clinical course than the germinal centre B-cell subtype (43). Individual biomarkers assessed by immunohistochemistry or gene expression profiling have been identified as having prognostic significance in DLBCL, such as *TP53* mutations (44), *MYC* rearrangement and *BCL2* expression (45), although the introduction of rituximab to standard chemotherapy seems to ameliorate the negative prognostic impact of *BCL2* expression (46). 'Double-hit' lymphomas, with dual translocations involving both *MYC* and *BCL2* or *BCL6* genes, have a particularly aggressive clinical course and poor response to standard chemotherapy (42). Cell-of-origin profiles (ABC/germinal centre B-cell like [GCB]) do not currently influence treatment choices, even though retrospective analyses have suggested worse outcomes in patients with ABC sub-type compared with the GCB subtype (47).

Evaluation of prognostic markers in practice is difficult because their use is not integrated into standard treatment pathways, but some evidence suggests that IPI score has predictive value in several subgroups (29, 31, 48, 49). Thus, the unmet need in such a heterogeneous disease cannot be defined by only one biological or clinical risk factor; there are patients at low risk according to IPI score who have poor outcomes owing to biological risk factors (e.g. ABC, double-hit lymphoma [DHL]) and patients who are low risk according to biological risk factors who have poor outcomes owing to IPI clinical risk factors. Patients with the poorest outcomes with current therapies are those who are high risk both in terms of biological factors and high IPI score. After adjusting for biological risk factors of severity, IPI scores remain an important indicator of disease severity and prognosis (49).

1.3.1.5 Risk factors

For the vast majority of patients, the aetiology of DLBCL is unknown. Factors thought to potentially incur increased risk include hereditary and acquired immunodeficiencies, such as human immunodeficiency virus (HIV) and rheumatoid arthritis (RA), and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases (50). Exposure to a variety of environmental factors, including pesticides, may also play a role (51), and a subset of DLBCL cases is associated with Epstein–Barr virus (EBV) (52). DLBCL often arises *de novo* but it can also represent a malignant progression or transformation of a less aggressive lymphoma (e.g. follicular lymphoma [FL], chronic lymphocytic leukaemia [CLL], small lymphocytic lymphoma [SLL] and mucosa-associated lymphoid tissue lymphoma [MALT]) (53). It is estimated that 10−15% of patients are refractory to standard 1L treatment for DLBCL (no response or relapse within 12 months) and 20−25% of patients will relapse within 12−18 months (54). B-symptoms and high levels of β2 microglobulin (β2-MG) have also been reported to be risk factors for R/R DLBCL (55).

1.3.1.6 Clinical signs and symptoms

Although DLBCL is often asymptomatic, it may be associated with constitutional symptoms, such as non-specific 'B-symptoms', including fever, recurrent night sweats and weight loss, and/or local effects of lymph node enlargement and bone marrow failure (14, 56). DLBCL is marked by rapidly growing tumours in the lymph nodes, spleen, liver, bone marrow or other organs. As such, patients with DLBCL typically present with rapidly enlarging masses at nodal or extranodal sites. This results in damage to the involved and surrounding tissues and organs and requires immediate treatment. The swollen nodes can form large lumps, known as bulky disease (14, 56). The majority of cases (60%) originate in the lymph nodes, with the remaining (40%) presenting at extranodal sites (57). The most common extranodal sites are the gastrointestinal tract, head and neck, and skin and soft tissue. Bone marrow is involved in 10–30% of cases (36). Relapsed DLBCL is characterised by the appearance of any new lesion after a complete response (CR) to treatment along with the return of symptoms (enlarged lymph nodes, night sweats, unexplained fever and unintentional weight loss), while refractory DLBCL is characterised by progressive disease or no response from the start of previous treatment (58).

1.3.1.7 Quality of life

Without treatment, DLBCL has an aggressive natural history and is fatal, with a median survival of less than a year (59). The clinical course can be debilitating owing to

constitutional symptoms, local symptoms of lymphadenopathy and bone marrow failure that may lead to infections, anaemia and thrombocytopenia. Most patients present with advanced disease (Stage III or IV) and adverse prognostic features (e.g. risk scores of 2–5 on the IPI). Approximately 60% of patients with DLBCL can be cured with 1L standard of care chemoimmunotherapy; the remaining 40% of patients will either relapse or be refractory to 1L treatment, or will die owing to treatment-related complications (54, 60).

Many patients with DLBCL treated with 1L chemoimmunotherapy experience treatment-related adverse events (AEs). These AEs include peripheral neuropathy (PN), nausea, neutropenia, constipation, fatigue, anaemia, and alopecia (61). Patients treated with a greater number of cycles of chemotherapy reported increased symptoms (pain, neuropathy and dyspnoea) compared with patients treated with a lower number of cycles (62). Among higher-risk populations, less than half of patients experience long-term remission after 1L chemoimmunotherapy. For these populations in clinical trial settings, the 10-year PFS rate following standard 1L chemoimmunotherapy was 36.5%, with a corresponding 10-year OS rate of 43.5% (63).

Relapsing or being refractory to 1L treatment remains a major cause of morbidity and mortality for patients with DLBCL. Most relapses occur within 24 months of starting treatment (60, 64) and the majority of patients with relapsed or refractory (R/R) disease have poor outcomes (65-67). Patients who require 2L and subsequent lines of therapy have a particularly poor prognosis, and experience disease progression with an increased risk of side effects of treatments (68). Salvage therapy for R/R DLBCL is limited by a patient's ability to tolerate the therapy and the limited efficacy of treatment.

Disease symptoms, along with treatment-related side effects, often lead to impairments in aspects of HRQoL, including physical functioning and fatigue (22, 61). More patients with DLBCL experience anxiety and depression than their counterparts in the general population; younger patients reported higher anxiety scores, whereas older patients reported higher depression scores over time (69). Reduced HRQoL has also been reported in younger versus older survivors of DLBCL relative to the age-matched normative population (70). Findings suggest that men may be impacted more by DLBCL than women, as reported in a recent study by Paunescu *et al.*, whereby women with DLBCL had significantly higher scores on the post-traumatic growth inventory than men at one year post diagnosis. This indicated more positive changes and self-improvement in women than men (62). However, women had significantly worse physical functioning than men at 1 year post-diagnosis (62). At the same time point, patients with comorbidities had increased physical fatigue and symptom

burden, increased emotional impact, mental fatigue and depression, and reduced physical functioning and global health status compared with patients without comorbidities (62).

1.3.2 Current treatment practice in the UK

Approximately 80% of patients with DLBCL receive treatment in the 1L setting, and around 60% can be cured with rituximab in combination with cyclophosphomide, doxorubicin, vincristine and prednisolone (R-CHOP), which has been the standard of care for over 20 years (49, 55). Pola-R-CHP (replacement of vincristine in the R-CHOP regimen with polatuzumab vedotin) was approved in January 2023 for the 1L treatment of patients with DLBCL and IPI score of 2 to 5 [TA874] and is now standard-of-care in these patients (59). In the POLARIX registration phase III study, Pola-R-CHP demonstrated a clinically meaningful absolute improvement in 2-year PFS of 6.5% (76.7% [95% confidence interval (CI): 72.7, 80.8] vs. 70.2% [95% CI: 65.8, 74.6] for Pola-R-CHP and R-CHOP, respectively, at 2 years), and a statistically significant hazard ratio (HR) for PFS of 0.73 (95% CI: 0.57, 0.95; p=0.02) (67). As such, the approximate 60% 1L cure rate cited above is expected to increase in the coming years.

Guidance published in January 2024 on the management of newly diagnosed large B-cell lymphoma from the British Society of Haematology (BSH) recommends R-CHOP for patients with advanced stage disease and an IPI score of 0-1 and Pola-R-CHP or R-CHOP for IPI 2-5 (71).

More intensive chemoimmunotherapy regimens such as rituximab with cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide and high dose cytarabine (R-CODOX-M/R-IVAC) may be considered in younger patients (≤50 years) with good performance status and IPI 3-5. There is no standard-of-care for patients with ‘double-hit’ lymphomas; however, 1L treatment may be intensified in selected younger patients, including dose-adjusted etoposide with R-CHOP (DA-EPOCH-R), or R-CODOX-M/R-IVAC (71).

1.3.2.1 2L treatments

The proportion of patients receiving 2L and 3L treatments can be estimated using the UK’s Haematological Malignancy Research Network (HMRN) database, which captures data from around 4 million people in the Yorkshire and Humber region, and records around 2,400 new haematological malignancies per year. According to current HMRN data, 31% of patients are estimated to receive 2L treatment, and 18% of 2L-treated patients are estimated to receive 3L treatment (68). For patients who are not cured with 1L therapy, 2L treatment will depend

largely on whether the patient is eligible for high-dose chemotherapy and autologous stem-cell transplantation (ASCT), as ASCT is only available for young, fit patients who demonstrate chemosensitive disease (4). Approximately 50% of patients requiring 2L treatment will be eligible for high-dose chemotherapy (54, 72).

1.3.2.1.1 Patients eligible for ASCT

Young and fit patients who relapse following 1L treatment may be eligible for high-dose salvage chemotherapy (e.g. R-DHAP, R-ICE, R-GDP, R-ESHAP) and, upon evidence of a partial or complete response (~50%), consolidation with ASCT (73). However, there is no standardised guidance on the criteria for selecting patient for ASCT and methods for selecting patients for this treatment route may differ across UK centres (74)). In general, patients will need to be young enough (e.g. aged <70 years) and fit enough to tolerate high dose chemotherapy with low levels of comorbidities (e.g. acceptable cardiac and renal function, ECOG performance score <2).

Patients who do not respond to 1L systemic therapy or who have early relapse (<12 months of completion of 1L treatment; approximately 75% of patients at first relapse (75)) may be candidates for autologous CAR-T therapy in the 2L setting if they are ASCT-eligible (axicabtagene ciloleucel [TA895]) (76). High dose chemotherapy with ASCT consolidation remains an option for fit patients who relapse ≥12 months following 1L systemic therapy.

CAR T-cell therapy

CAR T-cell therapy is a treatment in which T-cells are collected from patients by apheresis, genetically engineered to express receptors that bind to tumour antigens, and then returned to the patient so their T-cells can act against their cancer (77). Axicabtagene ciloleucel (axi-cel; Yescarta®) is a CAR T-cell therapy that is directed against the CD19 protein, which is present on malignant B-cells. This therapy is approved in the UK for the treatment of adults with DLBCL that is refractory to or has relapsed within 12 months of 1L immunochemotherapy. In April 2023, NICE made a recommendation that axi-cel should be made available under a Managed Access Agreement via the Cancer Drugs Fund for this indication (TA895) (76). Use of axi-cel in this indication is restricted to patients who are transplant-eligible, based on the eligibility criteria for the registrational study, ZUMA-7 (78, 79). Lisocabtagene maraleucel (liso-cel; Breyanzi®), another CD19-directed autologous CAR T-cell therapy, is currently being assessed by NICE in the same indication, in transplant-eligible patients (TA10778) (76).

1.3.2.1.2 Patients ineligible for ASCT

Approximately 50% of patients with R/R disease are ineligible for high dose chemotherapy and ASCT consolidation in the 2L setting (54, 72). The NICE scope for this appraisal identifies R-chemo and Pola-BR as relevant comparators in this patient population. Alternatively, these patients may also be suitable candidates for clinical trials.

I. Rituximab-chemotherapy (R-GemOx)

Patients with R/R DLBCL who are ineligible for ASCT may be suitable for 2L rituximab-based immunochemotherapy. Although there are a number of chemotherapy backbones that can be combined with rituximab, R-GemOx is the standard-of-care regimen in UK clinical practice due to its tolerability, even among elderly patients, as confirmed by UK clinical experts at a recent advisory board. Moreover, R-GemOx is considered to be representative of other rituximab-based immunochemotherapy regimens used in the 2L setting in terms of efficacy and safety (80). The efficacy and safety of R-GemOx in patients with R/R DLBCL were established in a series of phase II studies published between 2007 and 2013. While these studies recruited low numbers of patients and were uncontrolled, they consistently demonstrated the favourable toxicity profile of the regimen (81-84).

Studies in patients with one or more prior lines of therapy reported findings as follows:

- In El Gnaoui et al., 46 patients (33 patients with DLBCL) were treated with rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2, and oxaliplatin 100 mg/m^2 every 14 days. The median duration of exposure was 16 weeks. The CR rate was 73% in patients with DLBCL. The median time to progression in DLBCL patients was 24 months, and 2-year event-free survival (EFS) in this population was 42% (81). The median OS for DLBCL was not reported.
- In Lopez et al., 35 patients were treated with rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2, and oxaliplatin 100 mg/m^2 every 2-3 weeks; patients treated later in the study were treated every 3 weeks. Patients were treated for a median of 4 cycles (range, 2-8 cycles). The CR rate was 34% and median OS was 9.1 months. The study noted that its population was older than that treated in the El Gnaoui study and had higher risk features (82).
- In Corazzelli et al., 32 patients (16 with DLBCL) were treated with rituximab 375 mg/m^2, gemcitabine 1200 mg/m^2, and oxaliplatin 120 mg/mg^2 every 2 weeks. The majority of patients received complete therapy (6 cycles). CR rate in DLBCL was 56%; survival was not reported specific to DLBCL (84).

- In Mounier et al., 49 patients with DLBCL were treated as in the El Gnaoui study. The median age of patients was 69 years, 88% of patients had stage III/IV disease, 35% of patients had received prior ASCT, and 74% of patients were in first relapse (other patients had primary refractory disease or were in second relapse). Low rates of renal toxicity (1 patient) and febrile neutropenia (4% of cycles) were reported. At the primary analysis time point, an ORR of 61% and CR rate of 44% was achieved. The median PFS was 5 months and median OS was 11 months. The most common toxicities during treatment were haematologic in 98% of patients, including grade 3 thrombocytopenia in 44% of patients, grade 4 neutropenia in 42% of cycles, and 33% receiving at least one red blood cell transfusion. A dose reduction of oxaliplatin was required in 45% of patients who had at least grade 2 neuropathy. Only two patients discontinued treatment due to toxicity; one treatment related death, thrombotic microangiopathy attributed to gemcitabine, was reported (83).

In a retrospective study of R-GemOx in ASCT-ineligible patients with R/R DLBCL (n=196) where data were collected over a period of 15 years, the most significant AEs were found to be grade 3–4 haematological toxicities (31% of patients). Consistent with the original studies, no grade ≥ 3 renal toxicities were reported (85), thus supporting the use of R-GemOx in patients who cannot tolerate intensive treatment.

Although R-GemOx is well tolerated, survival outcomes with this regimen are poor, with five-year survival rates of only 13.9% (83). Therefore, there remains a significant unmet need for treatment options that offer a survival benefit for 2L R/R DLBCL patients. In line with this, at a recent advisory board, UK clinical experts commented that R-GemOx is used in ASCT-ineligible patients as a ‘stepping stone’ to access approved 3L treatments (axi-cel [TA872] (86), glofitamab monotherapy [TA927] (87), epcoritamab [TA954] (88), loncastuximab tesirine [TA947] (89)). However, some patients will not be able to receive 3L treatments because of declining health or death due to progressive disease before further treatment can be initiated (90).

II. Pola-BR

Polatuzumab vedotin (Polivy®), a CD79b-targeted antibody-drug conjugate, in combination with bendamustine and rituximab (Pola-BR) is indicated for the treatment of adult patients with R/R DLBCL who are not candidates for ASCT and is recommended by NICE in this indication (TA649, September 2020) (91). In the pivotal phase Ib/II study, GO29365, Pola-BR was shown to offer a significant PFS and OS benefit relative to BR alone in R/R DLBCL

patients (92). The efficacy of Pola-BR was subsequently confirmed in an extended cohort of 106 DLBCL patients who had received ≥ 1 prior line of prior therapy (93).

At a recent advisory board, UK lymphoma experts commented that Pola-BR is now rarely used in the 2L setting and its use at this point in the pathway will continue to decline due to several important clinical considerations (80). First is the sequencing of polatuzumab vedotin in the treatment pathway, since polatuzumab vedotin is now available in combination with R-CHP (Pola-R-CHP) as 1L treatment for DLBCL (87). In the registrational study for Pola-BR (GO29365), Pola-BR was evaluated in patients without prior exposure to polatuzumab vedotin, and no subsequent studies have attempted to re-challenge patients who have received polatuzumab vedotin in prior lines of therapy. For this reason, Blueteq criteria for Pola-BR in R/R DLBCL state that patients must not have received prior treatment with polatuzumab unless polatuzumab was given as a bridging treatment for CAR T-cell therapy from which the patient has relapsed (79).

Recent UK market research conducted by Roche between September and November 2024 has estimated the market share of Pola-R-CHP in 1L treatment of DLBCL to be [redacted]. This is corroborated by actual market share data obtained by Roche, which has demonstrated an increase in the use of this regimen over 2024 – from [redacted] of patients between January and March 2024 to [redacted] of patients between August and October 2024. Since polatuzumab vedotin may only be used once in the treatment pathway, the gain in Pola-R-CHP market share has led to a sharp decrease in the use of Pola-BR in the 2L; market share data has shown a decrease in its use from [redacted] in January-March 2024 to just [redacted] in the August-October 2024 data read out (which is similar to shares seen in June to August and July to September, which was [redacted] in both read outs).

In addition to 1L usage, UK clinical experts have highlighted the lymphotoxic effects of bendamustine as another rationale for reducing the use of Pola-BR in the 2L setting. Emerging data suggests reduced efficacy of subsequent T-cell engaging therapies, including CAR T-cell therapy and bispecific antibodies (important 3L+ treatment options in DLBCL), in patients with prior bendamustine treatment:

- A recent retrospective study examined the potential effect of prior bendamustine exposure on response to CAR T-cell therapy in patients with R/R large B-cell lymphoma (LBCL) (94). Patients exposed to bendamustine within the past 9 months had lower mean absolute lymphocyte counts (0.7 $x10^9$/L vs. 1.0 $x10^9$/L, p=0.004), CD3+ cells (0.5 $x10^9$/L vs. 0.7 $x10^9$/L, p=0.006) and platelet counts (125 $x10^9$/L vs. 179 $x10^9$/L, p=0.004) at apheresis than patients naïve to bendamustine. In addition,

prior exposure was associated with lower (14.4 vs. 28.6 cells/mL) and more delayed (17 vs. 13 days) absolute CAR T-cell expansion relative to naïve patients. Overall and CR rates were higher in patients naïve to bendamustine (72% and 51% vs. 57% and 41%, respectively; p=0.018). These data are consistent with another recent retrospective study that assessed the impact of prior bendamustine treatment on outcomes in patients with R/R LBCL one year after receiving CAR T-cell therapy (95). PFS in patients who had received bendamustine was 46%, compared with 73% in patients naïve to bendamustine. The frequency of relapse was higher in patients who had received bendamustine (75%) compared with patients naïve to bendamustine (60%).

- A recent UK real-world study evaluated the efficacy and tolerability of bispecific antibodies in the 3L+ treatment of patients with LBCL (96). Among patients treated with glofitamab, prior exposure to bendamustine (n=84) was associated with an inferior CR rate (CRR) (20% [95% CI: 11%-31%]) compared with patients without prior exposure (n=44) (36% [95% CI: 22%-52%]) (p=0.05). The negative impact of bendamustine was greater when given within 6 months prior to glofitamab (CRR: 9% [95% CI: 2-21] vs. 38% [95% CI: 19-59], respectively).

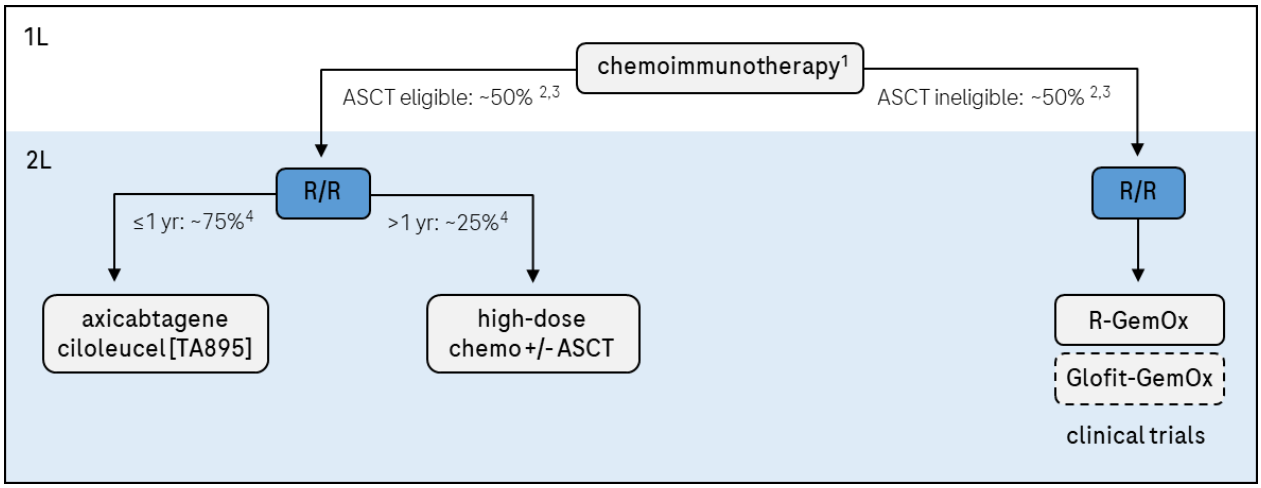
Given the considerations above, Roche expects the use of 2L Pola-BR to decrease further throughout 2025. Since Glofit-GemOx is expected to receive its marketing authorisation in Q3, Roche considers Pola-BR to no longer be a relevant comparator for R/R DLBCL. Therefore, R-GemOx remains the sole comparator for the current appraisal.

1.3.3 Disease management pathway

The proposed treatment pathway and position of Glofit-GemOx is summarised below (Figure 1).

It is proposed that the combination of 12 cycles of glofitamab and 8 cycles of gemcitabine and oxaliplatin may be used in the 2L DLBCL setting in patients who are not eligible for ASCT, which accounts for approximately 50% of patients who relapse following 1L chemoimmunotherapy (54, 72). This is supported by UK clinical experts consulted by the Company at a recent advisory board (90), who agreed there is an unmet need for a 2L therapy in transplant-ineligible patients since current treatments are ineffective and are only used as a ‘stepping stone’ to reach commissioned 3L treatment options. In addition, many transplant-ineligible patients treated with current options may be too frail or die from progression before 3L treatments become an option (90).

Figure 1: Current 1L and 2L treatment pathway for DLBCL patients, including Glofit-GemOx positioning



[1]R-CHOP for IPI 0-5 or Pola-R-CHP for IPI 2-5 [TA874] (87)
[2]Sarkozy and Sehn, 2019 (72)
[3]Sehn and Gascoyne, 2015 (54)
[4]Westin and Sehn, 2022 (75)

For patients who receive 2L R-GemOx as shown in Figure 1 and relapse, the main subsequent treatment options include:

- Axicabtagene ciloleucel [TA872] (86)
- Loncastuximab tesirine [TA947], only if previously treated with polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated (79, 89)
- Epcoritamab [TA954], if polatuzumab vedotin has been used previously or is contraindicated or not tolerated (79, 88)
- Glofitamab monotherapy [TA927] (87)

1.4 Equality considerations

At a recent advisory board, UK clinical experts agreed that there are limited or no equality considerations for Glofit-GemOx as it is expected that this regimen could be implemented in any haemato-oncology treatment unit where bispecific antibodies and R-GemOx are currently used (80).

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

Table 6: Clinical effectiveness evidence

Study	STARGLO; GO41944; NCT04408638
Study design	A phase III, international, open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)
Population	Adult patients with R/R DLBCL after ≥1 line of systemic therapy who are not eligible for autologous stem cell transplant.
Intervention(s)	Pre-treatment with a single dose of obinutuzumab. Eight (21-day) cycles of glofitamab (Glofit) in combination with gemcitabine and oxaliplatin (GemOx), followed by up to four cycles of glofitamab monotherapy.
Comparator(s)	Up to eight (21-day) cycles of rituximab (R) in combination with gemcitabine and oxaliplatin (GemOx).
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	This pivotal study provided key clinical efficacy and safety data supporting the modelling.
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life
All other reported outcomes	Duration of response Pharmacokinetics

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Study design

STARGLO (GO41944) is an international, phase III, open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) versus rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) in patients with R/R DLBCL. Eligible patients were adults with R/R DLBCL not otherwise specified (NOS) after ≥1 line of systemic therapy who were not eligible for ASCT and with an ECOG score of 0–2.

Patients were randomised in a 2:1 ratio to the Glofit-GemOx (n=183) and R-GemOx (n=91) study arms. Prior to randomisation, patients were stratified based on outcome of last systemic therapy (relapsed or refractory disease) and lines of previous systemic therapy (1 or ≥2) (Figure 2). Relapsed disease in this study was defined as disease that recurred following a response that lasted ≥ 6 months after completion of the last line of therapy. Refractory disease was defined as disease that did not respond to or that progressed < 6 months after completion of the last line of therapy. For number of previous lines of systemic therapy, CAR T-cell plus bridging therapy was counted as one line of therapy and local therapies (e.g., radiotherapy) were not considered a line of therapy.

All patients were treated in 21-day cycles. Posology was as follows:

- Patients randomised to the Glofit-GemOx arm were pre-treated with a single IV dose (1000 mg) of obinutuzumab 7 days before the first dose of glofitamab (Day 1, Cycle 1), to deplete circulating B-cells and thus reduce the risk of cytokine release syndrome (CRS). Glofitamab was administered IV in a step-up schedule; 2.5 mg on Day 8 of Cycle 1, 10 mg on Day 15 of Cycle 1, and 30 mg on Day 1 of Cycles 2-12. This schedule is identical to that of glofitamab monotherapy for 3L+ R/R DLBCL (previous appraisal, TA927). Gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) were administered IV on Day 2 of Cycle 1 and Day 1 or 2 (per local practice) of subsequent cycles, up to Cycle 8.
- Patients randomised to the R-GemOx arm received IV rituximab (375 mg/m^2) on Day 1 of each cycle, up to 8 cycles. Gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) were administered IV on Day 2 of Cycle 1 and Day 1 or 2 (per local practice) of subsequent cycles, up to Cycle 8.

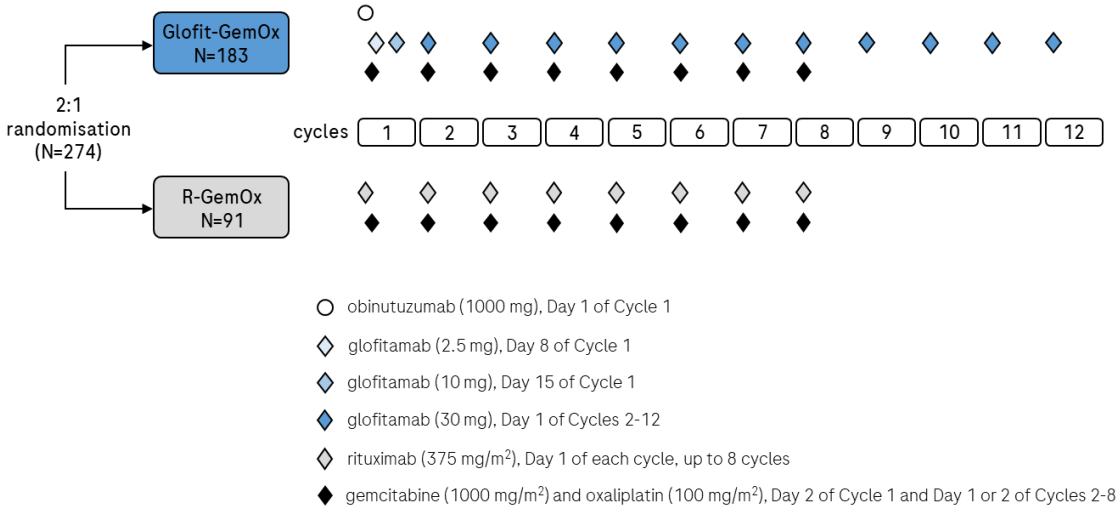
The primary efficacy endpoint was OS, and key secondary endpoints included PFS, CR rate and duration of CR (DOCR). All secondary endpoints were evaluated by an Independent Review Committee (IRC).

A pre-specified OS interim analysis was conducted with data from the date of first patient enrolled (23 February 2021) to the clinical cut-off date (CCOD) of 29 March 2023, when approximately 70% of OS events (97 events) had occurred. Since the study met its primary efficacy endpoint at this time point, with a pre-specified O'Brien–Fleming boundary for statistical significance of p=0.0148, the interim analysis became the primary analysis. This company submission includes trial data from the primary analysis at the CCOD of 29 March 2023. Efficacy and safety data are also provided from an updated analysis, representing an additional 10.5 months of clinical follow-up (CCOD of 16 Feb 2024) when all patients had completed study treatment and the 2L subgroup (patients with only 1 prior systemic therapy) from this analysis.

As the study met its primary endpoint at the primary analysis, all statistical power was consumed in this analysis. Thus, p-values calculated for the updated analysis are descriptive. At the primary analysis, the statistical significance of the primary endpoint and key secondary endpoints were assessed in a hierarchical manner in the order of PFS, CR rate, DOCR. The statistical significance level was recalculated based on the 101 primary endpoint events that had actually occurred by the primary analysis, with statistical significance declared if the two-sided p-value was 0.0174 or less. Key secondary endpoints would be significant if the p-value was 0.03244 or less.

The design schema of the STARGLO study is shown in Figure 2.

Figure 2: STARGLO (GO41944) study design schema



2.3.2 Summary of study methodology

Table 7: Methodology of STARGLO study

	STARGLO (GO41944)
Settings and locations of data collection	274 patients were enrolled at 62 study sites in 13 countries: **Countries, number of patients (centres)** • Australia, 30 (6) • Belgium, 3 (2) • Switzerland, 3 (2) • China, 80 (8) • Germany, 6 (3) • Denmark, 6 (2) • Spain, 16 (5) • France, 20 (5) • United Kingdom, 16 (5) • Republic of Korea, 37 (6) Poland, 18 (5) • Taiwan, 14 (3) • USA, 25 (10)
Trial design	Phase III, open-label, multicentre, active-control, randomised study
Eligibility criteria	**Inclusion criteria** • Age ≥18 years at time of signing the informed consent form (ICF) • Histologically confirmed DLBCL (NOS) • R/R disease, defined as follows: ○ Relapsed: disease that had recurred following a response that lasted 6 months after completion of the last line of therapy ○ Refractory: disease that did not respond to, or that progressed < 6 months after, completion of the last line of therapy

	○ Patients who discontinued last line of therapy before sufficient time for a response assessment (for example, due to toxicity) were assessed for refractoriness based on the previous line of therapy. • At least one (≥ 1) line of prior systemic therapy: ○ Patients may have undergone ASCT prior to recruitment ○ CAR T-cell plus bridging therapy were counted as one line of therapy ○ Local therapies (e.g., radiotherapy) were not considered as lines of therapy. • Patients who had failed only one prior line of therapy and were not a candidate for high-dose chemotherapy followed by ASCT by meeting at least one of the following criteria: ○ Left ventricular ejection fraction ≤ 40% ○ Creatinine clearance (CrCl) or glomerular filtration rate ≤ 45 mL/min ○ Eastern Cooperative Oncology Group (ECOG) Performance Status of ≥ 2 ○ Age ≥ 70 years ○ Patient refused high-dose chemotherapy and/or transplant ○ Patient had insufficient response to pre-transplant chemotherapy to be able to proceed to transplant ○ Other comorbidities or criteria that precluded the use of transplant based on local practice standards or in the investigator's opinion. The rationale for transplant ineligibility had to be recorded in the electronic Case Report Form (eCRF). • At least one bi-dimensionally measurable (≥ 1.5 cm) nodal lesion, or one bi-dimensionally measurable (≥ 1 cm) extranodal lesion, as measured on CT scan • ECOG Performance Status of 0, 1, or 2 • Negative SARS-CoV-2 antigen or PCR test within 7 days prior to enrolment • Adequate renal function, defined as an estimated CrCl ≥ 30 mL/min • For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures • For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm **<u>Exclusion criteria</u>** • Patients who had failed only one prior line of therapy and were a candidate for stem cell transplantation • History of transformation of indolent disease to DLBCL • High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, and high-grade B-cell lymphoma NOS, as defined by 2016 WHO guidelines (24) • Primary mediastinal B-cell lymphoma • Primary or secondary central nervous system (CNS) lymphoma at the time of recruitment or history of CNS lymphoma

	• Current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease • History of other malignancy that could affect compliance with the protocol or interpretation of results • Significant or extensive cardiovascular disease such as New York Heart Association Class III or IV cardiac disease or Objective Assessment Class C or D, myocardial infarction within the last 3 months, unstable arrhythmias, or unstable angina • Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrolment or any major episode of infection (as evaluated by the investigator) within 4 weeks prior to the first study treatment • Diagnosis with SARS-CoV-2 infection within 30 days prior to the first study treatment, including asymptomatic SARS-CoV-2 infection • Documented SARS-CoV-2 infection within 6 months of first study treatment. Patients may have been eligible if they had no persistent respiratory symptoms, no evidence of lung infiltrates on chest CT, and had a negative PCR during the 30 days prior to first study treatment. • Known history of HIV seropositive status. For patients with unknown HIV status, HIV testing was performed at screening if required by local regulations. • Prior solid organ transplantation • Prior allogeneic stem cell transplant • Active autoimmune disease requiring treatment • Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 18 months after the final dose of study treatment **Exclusion criteria related to medications** • Prior treatment with glofitamab or other bispecific antibodies targeting both CD20 and CD3 • Prior treatment with R-GemOx or GemOx • Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent; stable low-dose or short high-dose courses of steroid administration were permissible
Trial drugs and concomitant medications	**Trial drugs** Note: all treatment cycles were 21 days in length. **Obinutuzumab** • 7 days prior to first dose of glofitamab • Single 1000 mg IV dose administered on Day 1 of Cycle 1 **Glofitamab** • Step-up dosing; 2.5 mg administered on Day of Cycle 1, 10 mg on Day 15 of Cycle 1, and 30 mg on Day 1 of cycles 2-12 • Administered before gemcitabine and oxaliplatin in cycles 2-8 **Rituximab** • 375 mg/m^2 administered IV on Day 1 of cycles 2-8

	• Administered before gemcitabine and oxaliplatin **Gemcitabine** • 1000 mg/m^2 administered IV on Day 2 of Cycle 1 and Day 1 or 2 of cycles 2-8 (per local practice) • Administered after glofitamab/rituximab • Administered before oxaliplatin on the same day **Oxaliplatin** • 100 mg/m^2 administered IV on Day 2 of Cycle 1 and Day 1 or 2 of cycles 2-8 (per local practice) • Administered after glofitamab/rituximab • Administered after gemcitabine on the same day **Dose modifications** • No dose modifications of glofitamab, obinutuzumab, rituximab, or gemcitabine were permitted, but dose interruptions were permitted • Dose modification of oxaliplatin was permitted: o Reduced to 75 mg/m^2 in patients where persistent grade 2 neurosensory events did not reduce to grade 1 by the time of the next oxaliplatin dose. Other treatments were continued. If a patient had a grade 2 neurosensory event at the time of the subsequent dose, oxaliplatin was withheld and other treatments continued o Reduced to 75 mg/m^2 in patients where grade 3 neurosensory events reduced to grade 1 by the time of the next oxaliplatin dose. If a patient had a grade 2 neurosensory event at the time of the subsequent dose, oxaliplatin was withheld and other treatments continued o For persistent grade 3 neurosensory events that did not recover to at least grade 1 by the time of the next scheduled oxaliplatin dose, or for recurrent grade 3 events, oxaliplatin was permanently discontinued. o For grade 4 neurosensory events, oxaliplatin was permanently discontinued. **Concomitant medications** **Permitted concomitant medications:** • Prophylactic granulocyte colony-stimulating factor was mandated during cycles 1−2 in both groups, and was optional thereafter at the investigator's discretion • Oral contraceptives with a failure rate of < 1% per year • Hormone-replacement therapy • IL-6 inhibitor (tocilizumab), corticosteroids (methylprednisolone or dexamethasone) or other therapies at the discretion of the investigator to manage CRS • Treatment of haemophagocytic lymphohistiocytosis (HLH) according to published recommendations and/or institutional practice

	• Anti-infective prophylactic medicines for fungal, viral, bacterial and Pneumocystis infections, e.g. anti-SARS-CoV-2 antibodies • When dexamethasone was required in the protocol, if dexamethasone was available or the patient had an intolerance to dexamethasone, methylprednisolone, prednisone, or prednisolone were possible alternatives after consultation with the Medical Monitor. **Prohibited concomitant medications:** • Investigational, unlicensed, or unapproved agents • Administration of live vaccines • Cytotoxic chemotherapy other than study treatments intended for treatment of lymphoma • CNS prophylaxis • Radiotherapy for treatment of lymphoma • Immunotherapy other than study treatments for treatment of lymphoma • Immunosuppressive therapy (except medications indicated per protocol, including corticosteroids and tocilizumab) • Hormone therapy (other than contraceptives, hormone-replacement therapy, or egestrol acetate) ○ Adjuvant endocrine therapy for non-metastatic hormone receptor-positive breast cancer was permitted • Biologic or targeted agents for treatment of lymphoma • Herbal therapies intended as treatment of lymphoma • Any therapies intended for the treatment of lymphoma, whether approved by local regulatory authorities or investigational
Primary outcome	**Primary endpoint:** Overall survival (OS), defined as the time from randomisation to date of death from any cause.
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** Note: All response assessments were based on the 2014 Lugano Response Criteria. • Progression-free survival (PFS), defined as the time from randomisation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the: Independent review committee (IRC) and Investigator • Complete response (CR) rate, defined as the proportion of patients whose best overall response is a CR on positron emission tomography/computed tomography (PET/CT) during the study, as determined by the IRC and Investigator • Objective response rate (ORR), defined as the proportion of patients whose best overall response is a partial response (PR) or a CR during the study, as determined by the IRC and Investigator • Duration of objective response, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression, or death from any cause, whichever occurs first • Duration of CR, defined as the time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first

	• Time to deterioration in physical functioning and fatigue, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire (EORTC QLQ-C30) and in lymphoma symptoms, as measured by the Functional Assessment of Cancer Therapy−Lymphoma subscale (FACT-Lym LymS)
	
	Exploratory objectives:
	• Descriptive summary statistics of patient-reported outcomes and the change from baseline by treatment arm at each assessment for the following:
	  ○ All remaining scales of the EORTC QLQ-C30
	  ○ FACT-Lym LymS subscale
	• Characterisation of patients who become hematopoietic stem cell transplant (HSCT) candidates after study therapy and are treated with autologous or allogeneic HSCT, including:
	  ○ Incidence of autologous and allogeneic HSCT after study therapy
	  ○ Survival post-HSCT, defined as the time from date of transplantation to date of death from any cause
	• Characterisation of patients who receive chimeric antigen receptor (CAR) T-cell therapy after study therapy and are treated with CAR T-cell therapy, including:
	  ○ Incidence of treatment with CAR T-cell therapy
	  ○ Survival post-CAR-T-cell therapy, defined as the time from date of CAR T-cell infusion to date of death from any cause
	
	Safety objectives:
	• Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0), including CRS, with severity determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading criteria (97)
	• Change from baseline in targeted vital signs
	• Change from baseline in targeted clinical laboratory test results
	• Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events
	
	Safety exploratory objectives:
	• Day 100 non-relapse mortality, defined as the incidence of death not related to disease progression within 100 days of transplantation
	• Day 100 non-relapse mortality, defined as the incident of death not related to disease progression within 100 days of CAR T-cell therapy
	• Incidence and severity of CRS
	• Incidence and severity of immune effector cell-associated neurotoxicity syndrome (ICANS)

Pre-planned subgroups	• Sex • Age group (<65, ≥ 65)

	• Ethnicity (Hispanic or Latino, not Hispanic or Latino, not stated or unknown) • Race (Asian, Black or African American, White, unknown) • Enrolment by geographical region (Europe, North America, rest of the world) • Baseline BMI (kg/m^2) (<25%, 25-<50%, 50-<75%, 75-100%) • Baseline ECOG (0, 1, 2, unknown) • Lines of previous systemic therapy for DLBCL (1 or ≥2) • Prior CAR-T therapy (yes, no) • Response to last line of therapy (relapsed or refractory) • Refractory to any line of therapy (yes, no) • Refractory to first line of therapy (yes, no) • Relapsed or refractory to any prior platinum therapy (refractory, relapsed, unknown) • Relapsed or refractory to any prior anti-CD20 therapy (refractory, relapsed, unknown) • Primary refractory or relapse within 1 year after initial diagnosis date (yes, no) • Primary refractory or relapse within 12 months after 1L therapy (yes, no) • Early relapse from ASCT (PD ≤ 12 months from completion) (yes, no, no prior ASCT) • Double refractory to any prior anti-CD20 and anthracycline based regimen (refractory, relapse (no refractory), unknown) • Initial diagnosis (ABC, GCB, non-GCB, unclassified) • Ann Arbor staging at study entry (stage I, stage II, stage III, stage IV, unknown) • Prior ASCT (yes, no) • IPI score at study entry (CRF or derived) (0,1,2,3,4,5) • Double expresser (MYC and BCL2 overexpression (yes, no)) • Bulky disease ≥ 10 cm (yes, no, unknown) • Cell of origin (ABC, GCB, non-GCB (by IHC + non-GCB unclassified), unknown)

2.3.3 Patient demographics and baseline characteristics

The study had completed enrollment at the time of the CCOD of the primary analysis (29 March 2023); therefore, patient demographics and other baseline characteristics remained essentially unchanged at the CCOD for the updated analysis (16 February 2024).

The baseline demographic data and disease characteristics were generally well balanced between patients who received Glofit-GemOx and those who received R-GemOx for most parameters (Table 8). At recent advisory boards, a panel of UK lymphoma experts agreed that the demographics and baseline characteristics of the STARGLO population was broadly generalisable to the UK treatable 2L, transplant-ineligible DLBCL population (80, 90).

At baseline, the median age of patients in both treatment arms was 68.0 years, and the majority were ≥ 65 years of age (Glofit-GemOx, 63.4%; R-GemOx, 61.5%). Patients were predominantly male (57.4% and 58.2% of the Glofit-GemOx and R-GemOx populations, respectively). In total, 47.0% of patients enrolled in the Glofit-GemOx arm and 56.0% of patients enrolled in the R-GemOx arm were Asian, and 44.8% and 36.3% of patients enrolled, respectively, were White (Table 8).

In the Glofit-GemOx and R-GemOx treatment arms, 89.4% and 90.9% of patients had an ECOG PS of 0 or 1, respectively. An ECOG PS of 2 was reported in 10.6% of patients in the Glofit-GemOx arm and in 9.1% of patients in the R-GemOx arm.

The majority of patients had advanced stage disease at study entry, with an Ann Arbor Stage of III-IV reported in 67.2% of patients in the Glofit-GemOx arm, and in 76.9% of patients in the R-GemOx arm. Bulky disease (≥ 10 cm) was reported in 12.6% of patients in the Glofit-GemOx arm and 15.4% of patients in the R-GemOx arm.

A similar proportion of patients in the Glofit-GemOx (57.9%) and R-GemOx (51.6%) arms were refractory to their first line of therapy; 61.2% of Glofit-GemOx treated patients and 59.3% of R-GemOx treated patients were refractory to their last line of therapy, and 68.3% of patients in the Glofit-GemOx arm and 63.7% of patients in the R-GemOx arm were refractory to any prior therapy. Only one previous line of systemic therapy for R/R DLBCL had been given to 62.8% of patients in the Glofit-GemOx arm and to 62.6% of patients in the R-GemOx arm; 37.2% and 37.4% of patients, respectively, had received ≥ 2 lines of systemic therapy for R/R DLBCL (Table 8).

The most common reasons for transplant ineligibility was patient refused transplant (Glofit-GemOx; 35.5%; R-GemOx; 33.0%), age (Glofit-GemOx; 34.4%; R-GemOx; 27.5%), age ≥ 70 years (Glofit-GemOx; 8.2%; R-GemOx; 14.3%), and insufficient response to salvage therapy (Glofit-GemOx; 9.3%; R-GemOx; 11.0%). Similarly, of 115 patients in Glofit-GemOx arm and 57 patients in R-GemOx arm with one prior line of therapy, the most common reason for not being a candidate for transplant was age (Glofit-GemOx: [redacted] patients [redacted]; R-GemOx: [redacted] patients [redacted]), age ≥ 70 years (Glofit-GemOx; [redacted] patients [redacted]; R-GemOx; [redacted] patients [redacted]) and patient refusal (Glofit-GemOx: [redacted] patients [redacted]; R-GemOx: [redacted] patients [redacted]).

Demographic and baseline disease characteristics are also presented for the subpopulation of patients who received 1 prior line of therapy for DLBCL (referred to as the 2L subpopulation hereafter) (Table 9). Baseline demographic and disease characteristics

[redacted]. However, as would be expected in a subgroup treated in an earlier line of therapy, [redacted]; the proportion of patients refractory to last line of therapy was [redacted]% in the 2L subgroup versus [redacted]% in the ITT, and the proportion of patients refractory to any line of prior therapy was [redacted]% and [redacted]%, respectively.

Table 8: Summary of demographic and baseline disease characteristics (whole population; STARGLO)

Characteristic	R-GemOx Population n=91	Glofit-GemOx Population n=183	Total ITT Population n=274
Age, years			
Median	68.0	68.0	68.0
Min–Max	22–88	20–84	20–88
< 65, n (%)	35 (38.5)	67 (36.6)	102 (37.2)
≥ 65, n (%)	56 (61.5)	116 (63.4)	172 (62.8)
Sex, n (%)			
Female	38 (41.8)	78 (42.6)	116 (42.3)
Male	53 (58.2)	105 (57.4)	158 (57.7)
Race, n (%)			
Asian	51 (56.0)	86 (47.0)	137 (50.0)
Black or African American	1 (1.1)	2 (1.1)	3 (1.1)
White	33 (36.3)	82 (44.8)	115 (42.0)
Unknown	6 (6.6)	13 (7.1)	19 (6.9)
ECOG PS at baseline, n (%)			
0	44 (50.0)	72 (40.0)	116 (43.3)
1	36 (40.9)	89 (49.4)	125 (46.6)
2	8 (9.1)	19 (10.6)	27 (10.1)
Geographic region, n (%)			
Europe	26 (28.6)	62 (33.9)	88 (32.1)
North America	10 (11.0)	15 (8.2)	25 (9.1)
Rest of the world	55 (60.4)	106 (57.9)	161 (58.8)
Number of previous lines of systemic therapy for DLBCL, n (%)			
1	57 (62.6)	115 (62.8)	172 (62.8)
≥ 2	34 (37.4)	68 (37.2)	102 (37.2)
Relapsed/refractory to last line of therapy, n (%)			
Refractory	54 (59.3)	112 (61.2)	166 (60.6)
Relapsed	37 (40.7)	71 (38.8)	108 (39.4)
Relapse or refractory to any prior therapy, n (%)			
Refractory	58 (63.7)	125 (68.3)	183 (66.8)
Relapsed	33 (36.3)	58 (31.7)	91 (33.2)
Relapse or refractory to first line of prior therapy, n (%)			
Refractory	47 (51.6)	106 (57.9)	153 (55.8)

Relapsed	44 (48.4)	77 (42.1)	121 (44.2)
Relapse or refractory to any prior anti-CD20 therapy, n (%)			
Refractory	55 (60.4)	117 (63.9)	172 (62.8)
Relapse (no refractory)	34 (37.4)	64 (35.0)	98 (35.8)
Unknown	2 (2.2)	2 (1.1)	4 (1.5)
Ann Arbor Staging at study entry, n (%)			
Stage I-II	20 (22.0)	60 (32.8)	80 (29.2)
Stage III-IV	70 (76.9)	123 (67.2)	193 (70.4)
Unknown	1 (1.1)	0	1 (0.4)
Patients who received prior ASCT			
No	88 (96.7)	175 (95.6)	263 (96.0)
Yes	3 (3.3)	8 (4.4)	11 (4.0)
Patients who received prior CAR-T therapy, n (%)			
No	83 (91.2)	170 (92.9)	253 (92.3)
Yes	8 (8.8)	13 (7.1)	21 (7.7)
Patients with bulky disease ≥ 10cm, n (%)			
No	76 (83.5)	160 (87.4)	236 (86.1)
Yes	14 (15.4)	23 (12.6)	37 (13.5)
Cell of origin, n (%)			
GCB	29 (31.9)	60 (32.8)	89 (32.5)
Non-GCB (by IHC + non-GCB unclassified)	[redacted]	[redacted]	[redacted]
ABC	[redacted]	[redacted]	[redacted]
Unknown	12 (13.2)	20 (10.9)	32 (11.7)

Source: STARGLO_updated_CSR

Table 9: Summary of demographic and baseline disease characteristics (2L subpopulation; STARGLO)

Characteristic	R-GemOx Population n=57	Glofit-GemOx Population n=115	Total 2L Population n=172
Age, years			
Median	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]
< 65, n (%)	[redacted]	[redacted]	[redacted]
≥ 65, n (%)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
ECOG PS at baseline, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
Europe	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Rest of the world	[redacted]	[redacted]	[redacted]

Relapsed/refractory to last line of therapy, n (%)								
Refractory	[redacted]		[redacted]		[redacted]			
Relapsed	[redacted]		[redacted]		[redacted]			
Relapse or refractory to any prior therapy, n (%)								
Refractory	[redacted]		[redacted]		[redacted]			
Relapsed	[redacted]		[redacted]		[redacted]			
Relapse or refractory to first line of prior therapy, n (%)								
Refractory	[redacted]		[redacted]		[redacted]			
Relapsed	[redacted]		[redacted]		[redacted]			
Relapse or refractory to any prior anti-CD20 therapy, n (%)								
Refractory	[redacted]		[redacted]		[redacted]			
Relapse (no refractory)	[redacted]		[redacted]		[redacted]			
Unknown	[redacted]		[redacted]		[redacted]			
Ann Arbor Staging at study entry, n (%)								
Stage I-II	[redacted]		[redacted]		[redacted]			
Stage III-IV	[redacted]		[redacted]		[redacted]			
Patients who received prior ASCT								
No	[redacted]		[redacted]		[redacted]			
Yes	[redacted]		[redacted]		[redacted]			
Patients who received prior CAR-T therapy, n (%)								
No	[redacted]		[redacted]		[redacted]			
Yes	[redacted]		[redacted]		[redacted]			
Patients with bulky disease ≥ 10cm, n (%)								
No	[redacted]		[redacted]		[redacted]			
Yes	[redacted]		[redacted]		[redacted]			
Cell of origin, n (%)								
GCB	[redacted]		[redacted]		[redacted]			
Non-GCB (by IHC + non-GCB unclassified)	[redacted]		[redacted]		[redacted]			
ABC	[redacted]		[redacted]		[redacted]			
Unknown	[redacted]		[redacted]		[redacted]			

Source: Global Access Evidence Team

The participant flow and details on patient study and treatment withdrawal for STARGLO is presented in Appendix B.

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

All patients with R/R DLBCL enrolled in the study were included in the intent-to-treat (ITT) population. The analysis populations are defined in Table 10.

Table 10: Definitions of STARGLO analysis populations

Population	Definition
ITT	All patients randomised in the study

PRO-evaluable	All patients who had a baseline and at least one post-baseline assessment. PRO-evaluable population was used for descriptive analyses of visit summary and change from baseline analyses. All randomised patients (ITT) were used for completion analyses and time-to-deterioration analyses
Safety-evaluable	Patients who received any amount of any study treatment, whether prematurely withdrawn from the study or not
PK-evaluable population	All patients who received at least one dose of study treatment in the Glofit-GemOx arm and had at least one post-dose concentration result
Immunogenicity population	All patients who had at least one pre-dose and one post-dose ADA (anti-drug antibody) assessment

For all efficacy analyses (including PRO-evaluable), patients were grouped according to the treatment assigned at randomisation. For all safety analyses, patients were grouped according to the treatment actually received (patients with any dose of glofitamab or obinutuzumab were analysed in the Glofit-GemOx arm). Hypothesis tests were two-sided, unless otherwise indicated. The type I error (α) for this study was 0.05 (two-sided).

2.4.1 Determination of sample size

The primary objective of this study was to evaluate the efficacy of Glofit-GemOx relative to R-GemOx in patients with R/R DLBCL as measured by OS. Assuming a median OS of 11 months in the R-GemOx arm based on the median OS reported in the largest multi-site phase II study of R-GemOx (83) and other similar clinical trials (82, 84), and a randomisation ratio of 2:1, 138 events were required to detect a between-group difference of 7.3 months in median OS (HR=0.6), assuming an exponential distribution of OS using a log-rank test with 80% power and a two-sided α of 0.05. A target total population of 270 patients was specified based on the above statistical assumptions and taking into account an estimated annual dropout rate of 2%.

2.4.2 Efficacy endpoints

The analysis population for the efficacy analyses consisted of all randomised patients (ITT population), with patients grouped according to their assigned treatment.

The primary objective of this study was to evaluate the efficacy of Glofit-GemOx relative to R-GemOx in patients with R/R DLBCL as measured by OS. The key secondary endpoints were tested hierarchically as assessed by the IRC: PFS, best overall CR rate (based on response including PET/CT data) and DOCR (based on response including PET/CT data). Other secondary efficacy endpoints included best ORR, duration of objective response (DOR) and time to deterioration in physical functioning and fatigue, as measured by the

European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire (EORTC QLQ-C30) and in lymphoma symptoms, as measured by the Functional Assessment of Cancer Therapy−Lymphoma subscale (FACT-Lym LymS). Exploratory endpoints based on patient-reported outcomes (PROs) are discussed in section B.2.4.3.

To control the overall type I error rate at a two-sided 0.05 level of significance, a hierarchical testing procedure was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. The definitions and analysis methodology of these endpoints are summarised in Table 11.

Table 11: STARGLO efficacy endpoint definitions and analysis methodology

Endpoint	Definition	Analysis methodology	Analysis population
Primary efficacy endpoint			
OS	Time from randomisation to death from any cause	• Treatment comparison made using a two-sided level 0.05 stratified log-rank test • Randomisation stratification factors were previous lines of systemic therapy for DLBCL (1 vs. ≥ 2) and outcome of last systemic therapy (relapsed vs. refractory) • The Kaplan-Meier method was used to estimate the median OS, if reached, and OS distribution for each treatment arm. • The Brookmeyer-Crowley methodology (98) was used to construct the 95% CI for the median OS for each treatment arm • Cox proportional-hazards models were used to estimate the stratified hazard ratio and its 95% CI	ITT
Secondary efficacy endpoints			
PFS	Time from randomisation to the first occurrence of disease progression, or death due to any cause, whichever occurred first	• Assessed by the IRC and by the Investigator • Same methodologies as detailed for OS	ITT
CR rate	Proportion of patients whose best	• Assessed by the IRC and by the Investigator	ITT

	overall response was a CR on PET/CT during the study	• Measured according to 2014 Lugano response criteria (99) • CR rate estimate and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm • Treatment arms were compared using the Cochran-Mantel-Haenszel test stratified by the randomisation stratification factors	
DOCR	Time from the date of the first occurrence of CR until the first date that progressive disease or death was documented, whichever occurred first	• The methodologies detailed for OS were used for the duration of response analyses, except that the analyses were not stratified	ITT
ORR rate	Proportion of patients whose best overall response was a PR or a CR during the study	• Assessed by the IRC and by the Investigator • Same methodologies as detailed for CR rate	ITT
DOR	Time from the date of the first occurrence of an objective response (PR or CR) until the first date that progressive disease or death was documented, whichever occurred first	• The methodologies detailed for OS were used for the duration of response analyses, except that the analyses were not stratified	ITT
Time to deterioration in physical functioning and/or fatigue	Time from randomisation to the first occurrence of a 10-point or more decrease	• Based on EORTC QLQ-C30 questionnaire • Visit summary and change from baseline analyses, and mixed-effects repeated measures modelling at each time point were performed by treatment arm • Time to deterioration analysis was also performed	PRO-evaluable
Time to deterioration in lymphoma-specific symptoms	Time from randomisation to the first occurrence of a 3-point or more decrease	• Based on FACT-Lym-LymS questionnaire • Visit summary and change from baseline analyses, and mixed-effects repeated measures modelling at	PRO-evaluable

		each time point were performed by treatment arm • Time to deterioration analysis was also performed	

2.4.3 Patient-reported outcomes (PROs)

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS) were the PRO scales analysed in the PRO-evaluable population.

The EORTC QLQ-C30 is a validated, reliable self-report measure (97). It consists of 30 questions that assess five domains of patient functioning (physical, emotional, role, cognitive and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status/quality of life (GHS/QoL) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Scores are transformed to a 0–100 scale, with higher scores on the five domains and GHS/QoL reflecting a good HRQoL and higher scores on the symptom scales and single items reflecting poor HRQoL.

The 15-item FACT-Lym LymS was developed to assess HRQoL in patients with NHL. The FACT-Lym LymS enables assessment of the changes from baseline with respect to B-symptoms and impact on HRQoL caused by symptom worsening or alleviation and treatment toxicity. The scale range is 0–60, with a higher score reflecting better HRQoL. The validity and reliability of the FACT-Lym LymS for patients with NHL has been established (90).

The EORTC QLQ-C30 and FACT-Lym LymS assessments were performed at baseline and every 3 months during the post treatment follow-up. The scales were scored according to the user manual. Summary statistics and changes from baseline scores were calculated for all time points. The proportion of patients who reported changes from baseline or exceeding the minimal important difference for each measure was also reported.

For the EORTC QLQ-C30, time to deterioration in physical functioning and/or fatigue was defined as the time from randomisation to the first documentation of a 10-point or more decrease. For the FACT-Lym LymS, time to deterioration in lymphoma-specific symptoms was defined as the time from randomisation to the first documentation of a 3-point or more decrease.

2.4.4 Safety reporting and analyses

All safety analyses were based on the safety-evaluable population, defined as patients who received any amount of any study treatment, whether prematurely withdrawn from the study or not, grouped according to treatment received. Safety was assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) was summarised with descriptive statistics.

All verbatim AE terms were mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Other than AEs of CRS, which were graded according to ASTCT CRS Consensus Grading (97), the AE severity grading scale for the NCI CTCAE v5.0 were used for assessing AE severity. All AEs, serious AEs (SAEs), AEs leading to death, AEs of special interest (AESIs), and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent AEs) were summarised by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade was used in the summaries. Deaths and cause of death were summarised. Definitions of AEs, SAEs and AESIs are provided in Table 12.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data were displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests was used to summarise the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs were summarised.

Table 12: STARGLO safety event definitions

Safety data	Methods of analysis
AEs	AEs included: • Any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, regardless of whether it is considered to be related to the medicinal product • Any new disease or exacerbation of an existing disease • Recurrence of an intermittent medical condition not present at baseline • Any deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug • AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment
SAEs	SAEs included AEs meeting the following criteria: • Fatal • Life-threatening • Requires or prolongs in-patient Hospitalisation • Results in persistent or significant disability/incapacity • Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug • Significant medical event in the Investigator's judgment SAEs were required to be reported by the Investigator to the sponsor immediately (no more than 24 hours after learning of the event)
AESIs	AESIs included: • Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice • Suspected transmission of an infectious agent by the study drug AESIs specific for glofitamab: • Grade ≥ 2 CRS • Grade ≥ 2 neurologic adverse event • Any suspected haemophagocytic lymphohistiocytosis • Tumour lysis syndrome (TLS) (minimum grade 3 by definition) • Febrile neutropenia (minimum grade 3 by definition) • Grade ≥ 2 AST, ALT or total bilirubin elevation • Any grade disseminated intravascular coagulation (minimum grade 2 by definition) • Grade ≥ 2 tumour inflammation/flare • Any grade pneumonitis or interstitial lung disease (ILD) • Colitis of any grade AESIs specific for obinutuzumab: • Secondary malignancies • TLS • Serious infections • Serious neutropenia • Serious infusion-related reactions (IRRs) Non-serious AESIs were required to be reported by the Investigator to the sponsor immediately (no more than 24 hours after learning of the event).

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of the STARGLO study was performed using established risk of bias tools recommended for HTA submissions. A summary is presented in Table 13.

Table 13: STARGLO clinical effectiveness evidence quality assessment

Study question	STARGLO (GO41944)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?*	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

2.6 Clinical effectiveness results of the relevant studies

Pivotal efficacy data supporting this submission were derived from the primary analysis of the STARGLO trial, which reported efficacy and safety data collected from the date of first patient enrolled (23 February 2021) to the CCOD of 29 March 2023, and the updated analysis, which represented an additional 10.5 months of clinical follow-up when all patients had finished study treatment. Longer follow-up data from the latter analysis were used in the health economic modelling for the submission. In this section, efficacy data is provided for both the whole population (1 or ≥ 2 prior lines of therapy) and the subpopulation with only 1 prior line of therapy (2L subpopulation).

2.6.1 Primary efficacy endpoint

At the pre-specified interim analysis (which became the primary analysis), the median follow-up time for OS was 11.3 months. There was a 41% reduction in the risk of death in patients treated with Glofit-GemOx compared to patients treated with R-GemOx: stratified HR=0.59 (95% CI: 0.40, 0.89; log-rank p-value of 0.01). Median OS was not reached (95% CI: 13.8, NE) in the Glofit-GemOx arm and was 9.0 months (95% CI: 7.3, 14.4) in the R-GemOx arm (Table 14).

The OS benefit in the Glofit-GemOx arm was maintained at the updated analysis (median follow-up of 20.7 months, with a 38% reduction in the risk of death compared to patients

treated with R-GemOx (stratified HR=0.62; 95% CI: 0.43, 0.88; log-rank p-value of 0.006). Median OS in the Glofit-GemOx and R-GemOx arms was 25.5 months (95% CI: 18.3, NE) and 12.9 months (95% CI: 7.9, 18.5), respectively. At 24 months, OS rates were 52.8% (95% CI: 44.8%, 60.7%) in the Glofit-GemOx arm and 33.5% (95% CI: 22.2%, 44.9%) in the R-GemOx arm.

The OS benefit of Glofit-GemOx compared with R-GemOx was observed early and consistently, as evidenced by separation of Kaplan–Meier (KM) curves in the updated analysis as early as 3 months (**Figure 3**), with a potential plateau in the Glofit-GemOx curve emerging at around 24 months.

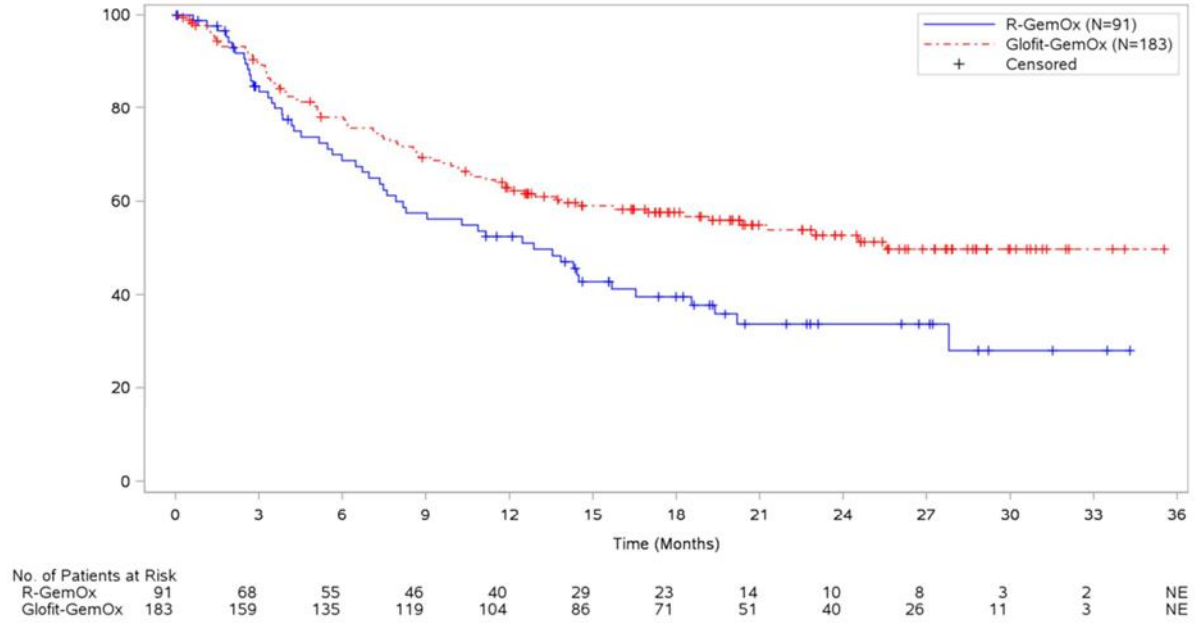
At the updated analysis, the OS benefit was similar in the 2L subpopulation (median follow-up of 20.2 months), with a 33% reduction in the risk of death compared to patients treated with R-GemOx (stratified HR=0.67; 95% CI: 0.41, 1.07; log-rank p-value of 0.092), though this subgroup analysis was underpowered to demonstrate a statistically significant difference. Median OS was not reached (95% CI: 20.4, NE) in the Glofit-GemOx arm and was 15.7 months (95% CI: 10.3, NE) in the R-GemOx arm. At 24 months, OS rates were 58.6% (95% CI: 48.9%, 68.3%) in the Glofit-GemOx arm and 40.0% (95% CI: 24.9%, 55.1%) in the R-GemOx arm. Although the difference in OS between Glofit-GemOx and R-GemOx did not reach statistical significance in the 2L subpopulation, there is clear separation of the Kaplan-Meier curves, favouring Glofit-GemOx (**Figure 4**) and improved efficacy of this regimen compared with R-GemOx is supported by the significant improvements in PFS and CR rate (Sections 2.6.2.1 and 2.6.2.2, respectively).

Table 14: Summary of OS data (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
Primary analysis (median follow-up: 11.3 months)		
Median, months (95% CI)	9.0 (7.3, 14.4)	NE (13.8, NE)
Stratified HR (95% CI)	0.59 (0.40, 0.89)	
p-value* (log-rank)	0.011	
Updated analysis (median follow-up: 20.7 months)		
Median, months (95% CI)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
Stratified HR (95% CI)	0.62 (0.43, 0.88)	
p-value* (log-rank)	0.006	
2L subpopulation	**n=57**	**n=115**
Updated analysis (median follow-up: 20.2 months)		
Median, months (95% CI)	15.7 (10.3, NE)	NE (20.4, NE)
Stratified HR (95% CI)	0.67 (0.41, 1.07)	
p-value* (log-rank)	0.092	

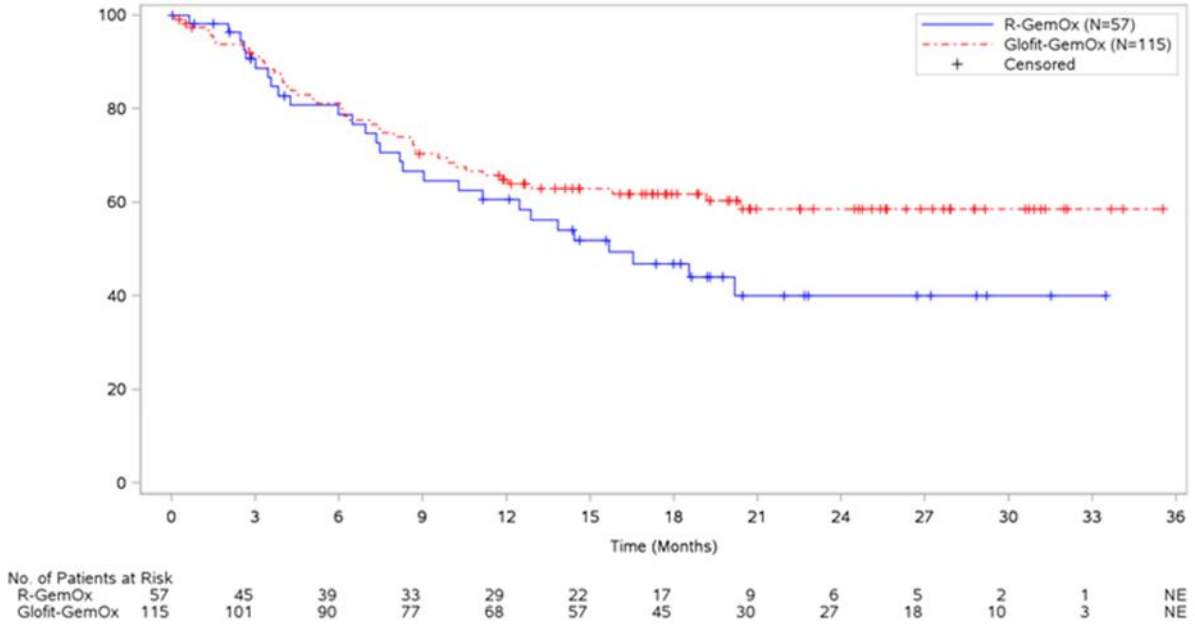
*p-value is alpha controlled at the primary analysis and descriptive at updated analysis.
Source: STARGLO_primary_CSR, STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

Figure 3: Kaplan-Meier plot of OS, whole population, updated analysis (STARGLO)



Source: Update_CSR_Study_GO41944

Figure 4: Kaplan-Meier plot of OS, 2L subpopulation, updated analysis (STARGLO)



Source: post-hoc outputs for the 2L subpopulation

2.6.2 Key secondary efficacy endpoints

At the primary analysis, STARGLO met the pre-specified hierarchically tested key secondary endpoints of IRC-assessed PFS and IRC-assessed CR rate.

2.6.2.1 Progression-free survival

At the primary analysis (median follow-up of 7.2 months), there was a statistically significant and clinically meaningful increase in IRC-assessed PFS with a 63% reduction in the risk of a PFS event in Glofit-GemOx treated patients compared to R-GemOx treated patients (stratified HR=0.37 (95% CI: 0.25, 0.55), log-rank p-value < 0.000001). Median PFS was 12.1 months (95% CI: 6.8, 18.3) in the Glofit-GemOx arm and 3.3 months (95% CI: 2.5, 5.6) in the R-GemOx arm (Table 15).

At the updated analysis (median follow-up of 15.7 months), the risk of a PFS event was reduced by 60% in the Glofit-GemOx arm relative to the R-GemOx arm (stratified HR=0.40; 95% CI: 0.28, 0.57; log-rank p-value <0.000001). Median PFS was 13.8 months (95% CI: 8.7, 20.5) in the Glofit-GemOx arm and 3.6 months (95% CI: 2.5, 7.1) in the R-GemOx arm (Table 15). At 12 months, PFS rates were 51.7% (95% CI: 44.0%, 59.4%) in the Glofit-GemOx arm and 25.2% (95% CI: 13.6%, 36.9%) in the R-GemOx arm.

In the 2L subpopulation (median follow-up of 15.5 months), the risk of a PFS event was reduced by 59% in the Glofit-GemOx arm relative to the R-GemOx arm (stratified HR=0.41; 95% CI: 0.25, 0.67; log-rank p-value 0.006). Median PFS was 20.4 months (95% CI: 9.2, NE) in the Glofit-GemOx arm and 5.6 months (95% CI: 3.0, 13.1) in the R-GemOx arm (Table 15) and the 12-month PFS rates were 54.9% (95% CI: 45.3%, 64.6%) in the Glofit-GemOx arm and 33.0% (95% CI: 15.8%, 50.2%) in the R-GemOx arm.

Kaplan-Meier PFS analyses of the whole population (Figure 5) and the 2L subpopulation (Figure 6) demonstrate an early benefit of Glofit-GemOx compared with R-GemOx, as evidenced by the separation of the curves as early as 1 month, and the PFS rates in the Glofit-GemOx arm were consistently numerically higher at all time points in landmark analyses. A potential plateau in the PFS curves for Glofit-GemOx is emerging at around 21 months.

Table 15: Summary of IRC-assessed PFS data (STARGLO)

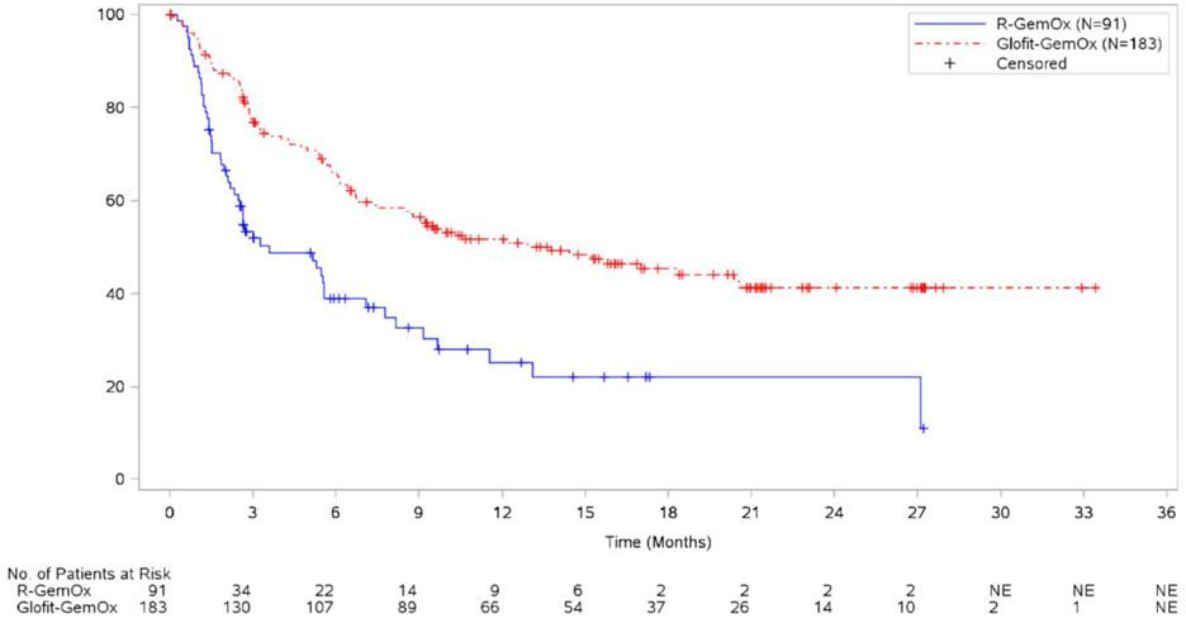
	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
Primary analysis (median follow-up: 7.2 months)		
Median, months (95% CI)	3.3 (2.5, 5.6)	12.1 (6.8, 18.3)
Stratified HR (95% CI)	0.37 (0.25, 0.55)	
p-value* (log-rank)	<0.000001	
Updated analysis (median follow-up: 15.7 months)		
Median, months (95% CI)	3.6 (2.5, 7.1)	13.8 (8.7, 20.5)
Stratified HR (95% CI)	0.40 (0.28, 0.57)	
p-value* (log-rank)	<0.000001	

2L subpopulation	n=57	n=115
Updated analysis (median follow-up: 15.5 months)		
Median, months (95% CI)	5.6 (3.0, 13.1)	20.4 (9.2, NE)
Stratified HR (95% CI)	0.41 (0.25, 0.67)	
p-value* (log-rank)	0.0002	

*p-value is alpha controlled at the primary analysis and descriptive at updated analysis.

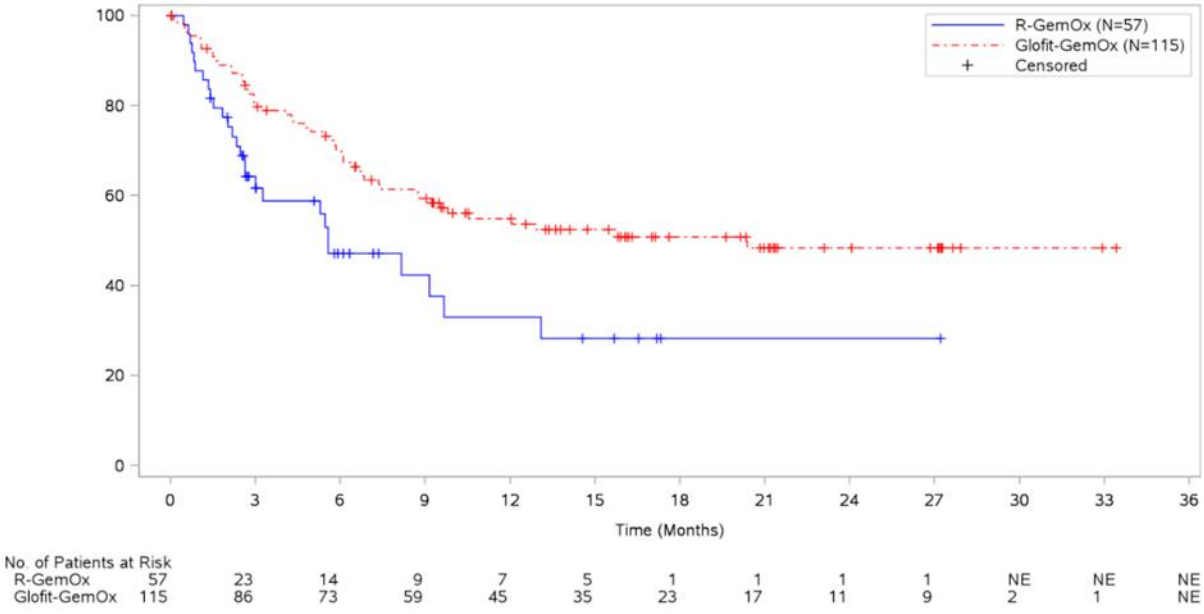
Source: STARGLO_primary_CSR, STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

Figure 5: Kaplan-Meier plot of IRC-assessed PFS*, whole population (STARGLO)



*censored before NALT
Source: Update_CSR_Study_GO41944

Figure 6: Kaplan-Meier plot of IRC-assessed PFS*, 2L subpopulation (STARGLO)



*censored before NALT
Source: post-hoc outputs for the 2L subpopulation

2.6.2.2 Complete response rate

At the primary analysis, there was a statistically significant and clinically meaningful increase in IRC-assessed CR rate in Glofit-GemOx treated patients (50.3%; 95% CI: 42.8, 57.7) compared to R-GemOx treated patients (22.0%; 95% CI: 14.0, 31.9) with a difference of 28.3% (95% CI: 16.3, 40.3) and a Cochran-Mantel-Haenszel (CMH) test p-value < 0.0001 (Table 16).

At the updated analysis, the CR rate was 33.2% greater (95% CI: 20.9, 45.5; p-value < 0.0001) in the Glofit-GemOx arm (58.5%; 95% CI: 51.0, 65.7) compared with the R-GemOx arm (25.3%; 95% CI: 16.8, 35.5). This trend was also observed in the 2L subpopulation, where the CR rate was 35.4% greater (95% CI: 19.5%, 51.3%; p-value < 0.0001) in the Glofit-GemOx arm (63.5%; 95% CI: 54.0, 72.3) relative to the R-GemOx arm (28.1%; 95% CI: 17.0, 41.5) (Table 16).

Table 16: Summary of IRC-assessed CR rate (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
Primary analysis		
% CR rate (95% CI)	22.0 (14.0, 31.9)	50.3 (42.8, 57.7)
% difference in CR rates (95% CI)	28.3 (16.3, 40.3)	
p-value* (Cochran-Mantel-Haenszel)	<0.0001	
Updated analysis		
% CR rate (95% CI)	25.3 (16.8, 35.5)	58.5 (51.0, 65.7)
% difference in CR rates (95% CI)	33.2 (20.9, 45.5)	
p-value* (Cochran-Mantel-Haenszel)	<0.0001	
2L subpopulation	**n=57**	**n=115**
Updated analysis		
% CR rate (95% CI)	28.1 (17.0, 41.5)	63.5 (54.0, 72.3)
% difference in CR rates (95% CI)	35.4 (19.5, 51.3)	
p-value* (Cochran-Mantel-Haenszel)	<0.0001	

*p-value is alpha controlled at the primary analysis and descriptive at updated analysis.
Source: STARGLO_primary_CSR, STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

2.6.2.3 Duration of complete response

At the primary analysis, follow-up for IRC-assessed DOCR was immature (median follow-up 6.4 months) and with CR in 92 patients in the Glofit-GemOx arm and 20 patients in the R-GemOx arm. DOCR was 14.4 months (95% CI: 14.4, NE) in Glofit-GemOx treated patients and could not be estimated in R-GemOx treated patients (NE; [95% CI: 6.4, NE]). The HR was 0.59 (95% CI: 0.19, 1.83), which did not meet the threshold for statistical significance, with an unstratified log-rank p-value of 0.3560 (Table 17; Figure 7).

At the updated analysis, with median follow-up of 13.1 months, median DOCR was not reached in the Glofit-GemOx treated patients with CR (n=107; 95% CI: NE) and was 24.2 months (95% CI: 6.9, NE), in the R-GemOx treated patients with a CR (n=23), with a HR of 0.59 (95% CI: 0.25, 1.35) and an unstratified log-rank p-value of 0.2040 (Table 17; Figure 8).

Table 17: Summary of IRC-assessed DOCR (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population		
Primary analysis	**n=20**	**n=92**
Median, months (95% CI)	NE (6.4, NE)	14.4 (14.4, NE)
Unstratified HR (95% CI)	0.59 (0.19, 1.83)	
p-value* (log-rank)	0.3560	
Updated analysis	**n=23**	**n=107**
Median, months (95% CI)	24.2 (6.9, NE)	NE (NE, NE)
Unstratified HR (95% CI)	0.59 (0.25, 1.35)	
p-value* (log-rank)	0.2040	
2L subpopulation		
Updated analysis	**n=16**	**n=73**
Median, months (95% CI)	NE (6.5, NE)	NE (NE, NE)
Unstratified HR (95% CI)	0.57 (0.21, 1.54)	
p-value* (log-rank)	0.2574	

*p-value is alpha controlled at the primary analysis and descriptive at updated analysis.
Source: STARGLO_primary_CSR, STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

The IRC-assessed benefit in DOCR seen in the Glofit-GemOx arm was observed from 6 months, as evidenced by separation of KM curves (Figure 7, Figure 8) and further stratified analyses showed continued numerically higher IRC-assessed DOCR rates in the Glofit-GemOx arm compared to the R-GemOx arm at 9, 12, 15, and 18-month landmark analyses.

In the 2L subpopulation, median DOCR was not reached in Glofit-GemOx treated patients with CR (n=73, 95% CI: NE) nor in R-GemOx treated patients with CR (n= 16; 95% CI: 6.5, NE), with a HR of 0.57 (95% CI: 0.21, 1.54) and an unstratified log-rank p-value of 0.2574 (Table 17; Figure 9).

Figure 7: Kaplan-Meier plot of IRC-assessed DOCR, whole population, primary analysis (STARGLO)

Figure 8: Kaplan-Meier plot of IRC-assessed DOCR, whole population, updated analysis (STARGLO)

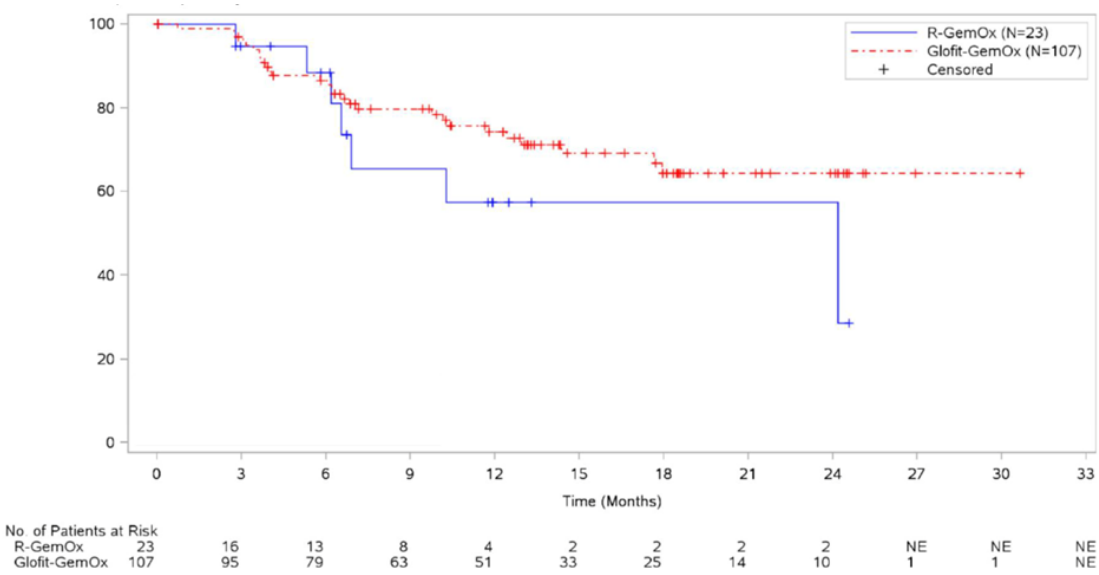
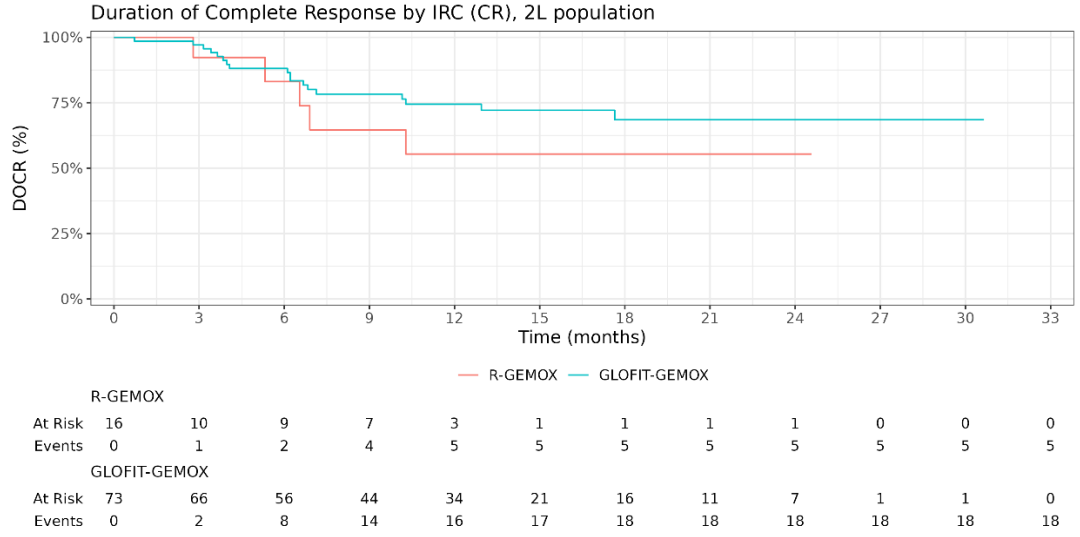


Figure 9: Kaplan-Meier plot of IRC-assessed DOCR, 2L subpopulation, updated analysis (STARGLO)



2.6.3 Patient-reported outcomes

Completion rates for all questionnaires were high (>90%) at baseline in both treatment arms and remained more than [redacted] until treatment completion. Completion rates dropped due to treatment completion and early discontinuation to below [redacted] and continued to decline during long-term follow-up, as expected due to attrition.

At the updated analysis, [redacted] patients ([redacted]) in the Glofit-GemOx arm and [redacted] patients ([redacted]) in the R-GemOx arm had [redacted] deterioration in physical functioning.

The median time to deterioration in physical functioning was 23.0 months (95% CI: 10.3, NE) in the Glofit-GemOx arm and 18.0 months (95% CI: 8.6, NE) in the R-GemOx arm with a stratified HR=[redacted] (95% CI: [redacted]).

A clinically meaningful deterioration in fatigue [redacted] ([redacted]) in the Glofit-GemOx arm and [redacted] patients ([redacted]) in the R-GemOx arm. The median time to deterioration in fatigue in the Glofit-GemOx arm was 1.6 months in the Glofit-GemOx arm (95% CI: 1.4, 3.1) and 1.4 months in the R-GemOx arm (95% CI: 1.0, 4.2) with a stratified HR=0.93 (95% CI: 0.67, 1.30), indicating that increases in fatigue occurred at similar time points for both arms while on treatment.

[redacted] patients ([redacted]) in the Glofit-GemOx arm and [redacted] patients ([redacted]) in the R-GemOx arm experienced a clinically meaningful deterioration in lymphoma-specific symptoms. The median time to deterioration in lymphoma-specific symptoms was 6.2 months in the Glofit-GemOx arm (95% CI: 3.3, 8.3) and 4.5 months in the R-GemOx arm (95% CI: 3.0, 12.5) with a stratified HR=1.02 (95% CI: 0.71, 1.45) (Table 18).

Overall, there were no clinically meaningful differences in median time to deterioration in physical functioning, fatigue and lymphoma-specific symptoms between arms, demonstrating that Glofit-GemOx does not add additional burden in these domains.

Table 18: Summary of patient-reported outcomes (STARGLO)

	R-GemOx n=91	Glofit-GemOx n=183
Time to confirmed deterioration in physical functioning – EORTC QLQ-C30		
Median, months (95% CI)	18.0 (8.6, NE)	23.0 (10.3, NE)
Stratified HR (95% CI)	[redacted]	
Time to confirmed deterioration in fatigue – EORTC QLQ-C30		
Median, months (95% CI)	1.4 (1.0, 4.2)	1.6 (1.4, 3.1)
Stratified HR (95% CI)	0.93 (0.67, 1.30)	
Time to confirmed deterioration in lymphoma-specific symptoms – FACT-Lym LymS		
Median, months (95% CI)	4.5 (3.0, 12.5)	6.2 (3.3, 8.3)
Stratified HR (95% CI)	1.02 (0.71, 1.45)	

Source: STARGLO_updated_CSR

2.7 Subsequent treatments used in the relevant studies

New anti-lymphoma therapy (NALT), including radiotherapy and/or systemic therapies, were not permitted during study therapy but could be administered after patients had discontinued or completed study treatment. NALT decision-making was at the discretion of the investigator.

At the updated analysis, in the whole population, the total number of patients receiving NALTs was lower in the Glofit-GemOx arm (46/183 patients [25.1%]) compared to the R-GemOx arm (52/91 [57.1%]) (Table 19). In addition, the total number of patients receiving NALTs prior to IRC-assessed PD was lower in the Glofit-GemOx arm (9/183 patients [4.9%]) compared to the R-GemOx arm (19/91 [20.9%]). As expected, median time to NALT or death was greater in the Glofit-GemOx arm (13.8 months [95% CI: 10.2, 23.6]) compared to the R-GemOx arm (3.7 months [95% CI: 3.3, 7.1]).

The most frequently administered NALTs in the Glofit-GemOx and R-GemOx arms, respectively, were:

- CAR T-cell therapy: 4.4% vs. 13.2%.
- Chemotherapy (non-intensive): 8.7% vs. 16.5%
- Chemotherapy (intensive): 3.8% vs. 11%.
- CD19 immunotherapy: 4.9% vs. 6.6%.
- CD20-CD3 bispecific antibody: 1.1% vs. 16.5%.
- Immunotherapy (other): 7.1% vs. 9.9%.
- Other (systemic): 1.6% vs. 6.6%.
- PD-1 inhibitor: 2.2% vs. 4.4%.
- Stem cell transplant: both 1.1%.

The proportion of patients receiving at least one NALT [redacted] (Table 19). While median time to NALT or death in the [redacted] ([redacted] months vs. [redacted] months, respectively), median time to NALT or death [redacted] ([redacted] months vs. [redacted] months in the whole population). This difference can be attributed to the [redacted] (Section 2.6, Figure 4 and Figure 6), thus indicating that Glofit-GemOx effectively addresses the unmet need in the 2L population.

Table 19: Overview of NALT (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
Patients with ≥1 NALT, n (%)	52 (57.1)	46 (25.1)
Patients who received NALT prior to IRC-assessed PD (censored for IRC-assessed PFS)	19 (20.9)	9 (4.9)
Time to NALT or death	3.7 (3.3, 7.1)	13.8 (10.2, 23.6)

Median (95% CI) months		
Total patients (n [%]) with ≥ of:		
CAR T-cell therapy	12 (13.2)	8 (4.4)
CD19 immunotherapy	6 (6.6)	9 (4.9)
CD20-CD3 bispecific antibody	15 (16.5)	2 (1.1)
Chemotherapy (non-intensive)	15 (16.5)	16 (8.7)
Chemotherapy (intensive)	10 (11.0)	7 (3.8)
Immunotherapy (other)	9 (9.9)	13 (7.1)
Other (procedure)*	14 (15.4)	6 (3.3)
Other (systemic)	6 (6.6)	3 (1.6)
PD-1 inhibitor	4 (4.4)	4 (2.2)
Stem cell transplant	1 (1.1)	2 (1.1)
2L subpopulation	**n=57**	**n=115**
Patients with ≥1 NALT, n (%)	[redacted]	[redacted]
Patients who received NALT prior to IRC-assessed PD (censored for IRC-assessed PFS)	[redacted]	[redacted]
Time to NALT or death Median (95% CI) months	[redacted]	[redacted]
Total patients (n [%]) with ≥ of:		
CAR T-cell therapy	[redacted]	[redacted]
CD19 immunotherapy	[redacted]	[redacted]
CD20-CD3 bispecific antibody	[redacted]	[redacted]
Chemotherapy (non-intensive)	[redacted]	[redacted]
Chemotherapy (intensive)	[redacted]	[redacted]
Immunotherapy (other)	[redacted]	[redacted]
Other (procedure)	[redacted]	[redacted]
Other (systemic)	[redacted]	[redacted]
PD-1 inhibitor	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]

*R-GemOx arm: radiotherapy (n=13), excision of tumour (n=1); Glofit-GemOx arm: radiotherapy (n=5), excision of tumour (n=1); lysis of intestinal adhesions (n=1)
Source: STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

2.8 Subgroup analysis

At the primary analysis, an unstratified exploratory analysis of subgroups was conducted. There was a [redacted], and the 95% CIs for the unstratified HR in the [redacted], i.e., the estimated unstratified HR in the ITT population.

The subgroup analysis demonstrated [redacted] of Glofit-GemOx across high-risk and other key patient populations:

- Previous lines of systemic therapy for DLBCL
    - 1 line (n=172): OS HR=[redacted] (95% CI: [redacted])

    - ≥ 2 lines (n=102): OS HR=[redacted] (95% CI: [redacted])
- Response to last line of therapy
    - Refractory (n=166): OS HR=[redacted] (95% CI: [redacted])
    - Relapsed (n=108): OS HR=[redacted] (95% CI: [redacted])
- Refractory to first line of therapy
    - Yes (n=152): OS HR=[redacted] (95% CI: [redacted])
    - No (n=122): OS HR=[redacted] (95% CI: [redacted])

At the updated analysis, the treatment effect of Glofit-GemOx in the above subgroups was maintained:

- Previous lines of systemic therapy for DLBCL
    - 1 line (n=172): OS HR=0.68 (95% CI: 0.42, 1.09)
    - ≥ 2 lines (n=102): OS HR=0.55 (95% CI: 0.33, 0.93)
- Response to last line of therapy
    - Refractory (n=166): OS HR=0.65 (95% CI: 0.43, 0.99)
    - Relapsed (n=108): OS HR=0.51 (95% CI: 0.26, 0.98)
- Refractory to first line of therapy
    - Yes (n=153): OS HR=0.60 (95% CI: 0.40, 0.92)
    - No (n=121): OS HR=0.54 (95% CI: 0.29, 1.01)

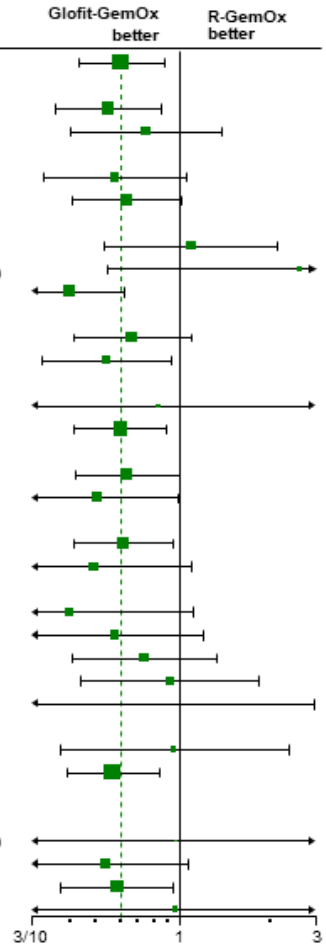
Forest plots of the HR for OS with 95% CIs within each subgroup are shown for the updated analysis in Figure 10. Given the known limitations of exploratory subgroup analyses (100, 101), especially those with small sample size, the results should be interpreted with caution.

While potential inconsistencies in the unstratified OS HR were observed in the subgroups by race (Asian: HR=0.40 [95% CI: 0.25, 0.65] vs. White: HR=1.24 [95% CI: 0.66, 2.33]) and by geographic region (Europe: HR=1.09 [95% CI: 0.54, 2.18]; North America: HR=2.62 [95% CI: 0.56, 12.34]; Rest of World: HR=0.41 [95% CI: 0.27, 0.64]) compared to the overall ITT population, these variations should be interpreted with caution. UK clinical experts at a recent advisory board agreed that the regional analysis is challenging to interpret due to the subgroups being underpowered, with wide confidence intervals and small patient numbers (80).

As part of the EMA submission, the latest CHMP assessment has concluded that the results from the ITT analysis can be extrapolated to the European population.

Figure 10: Pre-specified subgroup analysis of OS (ITT population; STARGLO)

Baseline Risk Factors	Total n	R-GemOx (n=91) n	Events	Median (Months)	Glofit-GemOx (n=183) n	Events	Median (Months)	HR	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Sex									
Male	158	53	36	10.3	105	51	20.4	0.56	(0.37, 0.86)
Female	116	38	16	20.2	78	29	NE	0.76	(0.41, 1.40)
Age group									
<65	102	35	19	9.0	67	29	NE	0.59	(0.33, 1.06)
≥65	172	56	33	14.3	116	51	22.9	0.65	(0.42, 1.01)
Enrollment by geographic region									
Europe	88	26	11	13.8	62	29	21.2	1.09	(0.54, 2.18)
North America	25	10	2	NE	15	8	13.3	2.62	(0.56, 12.34)
Rest of the World	161	55	39	8.3	106	43	NE	0.41	(0.27, 0.64)
No. of previous lines of systemic therapy for DLBCL									
1	172	57	28	15.7	115	44	NE	0.68	(0.42, 1.09)
≥2	102	34	24	6.7	68	36	18.3	0.55	(0.33, 0.93)
Prior CAR T-cell therapy									
Yes	21	8	4	27.8	13	6	13.7	0.84	(0.23, 3.01)
No	253	83	48	12.9	170	74	NE	0.62	(0.43, 0.89)
Relapse or refractory to last line of therapy									
Refractory	166	54	36	7.5	112	61	11.9	0.65	(0.43, 0.99)
Relapsed	108	37	16	27.8	71	19	NE	0.51	(0.26, 0.98)
Refractory to first line of therapy									
Yes	153	47	34	7.3	106	59	10.2	0.60	(0.40, 0.92)
No	121	44	18	27.8	77	21	NE	0.54	(0.29, 1.01)
Total number of risk factors for IPI (Derived)									
Low (0–1)	61	13	6	NE	48	12	NE	0.41	(0.15, 1.10)
Low–intermediate (2)	70	28	14	18.5	42	16	NE	0.59	(0.28, 1.20)
High–intermediate (3)	79	30	20	14.3	49	26	21.2	0.75	(0.42, 1.35)
High (4–5)	55	17	11	8.3	38	24	8.5	0.92	(0.45, 1.88)
Unknown	9	3	1	0.6	6	2	NE	0.18	(0.01, 2.93)
Bulky disease ≥10cm									
Yes	37	14	7	11.1	23	13	12.0	0.95	(0.38, 2.40)
No	236	76	45	13.5	160	67	NE	0.58	(0.40, 0.85)
Unknown	1	1	0	NE	-	-	-	NE	NE
Cell of origin									
ABC	6	2	1	NE	4	2	NE	0.97	(0.09, 10.98)
GCB	89	29	15	11.1	60	25	NE	0.55	(0.29, 1.06)
Non-GCB (by IHC + non-GCB unclassified)	147	48	32	10.9	99	45	25.5	0.60	(0.38, 0.94)
Unknown	32	12	4	20.2	20	8	NE	0.96	(0.28, 3.21)



Source: STARGLO_updated_CSR

2.9 Meta-analysis

At the time of submission, clinical evidence supporting the use of Glofit-GemOx for the treatment of 2L R/R DLBCL was available solely from the pivotal STARGLO study, so no meta-analysis was performed. As described in Section 1.3.2.1.2, while Pola-BR is recommended by NICE for R/R DLBCL and is listed as a comparator in the scope, this regimen is no longer considered a relevant comparator for 2L R/R DLBCL following the approval in March 2023 of Pola-R-CHP in the 1L setting. This view is supported by UK clinical experts who confirm that Pola-BR is very rarely used in the 2L setting and market share data, which demonstrates an increase in Pola-R-CHP and a decrease in Pola-BR use in the first- and second-line settings over 2024, respectively (80). As such, R-GemOx is the sole comparator for this appraisal.

2.10 Indirect and mixed treatment comparisons

A systematic literature review (SLR) and matching-adjusted indirect comparison (MAIC) feasibility assessment was conducted to assess the clinical evidence available for the treatment of patients with R/R DLBCL, to provide a comparison of Glofit-GemOx with comparators of interest (see appendix E).

As highlighted in section 1.1, the feasibility assessment concluded that it is not possible to conduct robust ITCs in the 3L+ setting to the following comparators: axicabtagene ciloleucel, loncastuximab tesirine and epcoritamab. Further details for the outcomes from the feasibility assessment for the ITC are provided below:

Axicabtagene ciloleucel

A total of 96 studies included in the SLR investigated axicabtagene ciloleucel. Sixty-four were excluded as they were retrospective, 21 were excluded as they included <40 patients, two were excluded based on histology, and a single study was excluded (conducted in the 2L only) as enrolled patients were eligible for ASCT (ZUMA-7).

Of the eight remaining prospective studies, data from ZUMA-1 could be considered for inclusion in a MAIC in the 2L+ population (102). ZUMA-1 reports a prospective, open-label, single-arm study of axicabtagene ciloleucel for the treatment of refractory large B cell lymphoma in the US and Israel. There are key differences between the inclusion/exclusion criteria of ZUMA-1 and STARGLO; ZUMA-1 enrolled patients after two prior systemic lines of therapy (including an anti-CD20 and an anthracycline containing regimen), with an ECOG

PS of 0 or 1. Notably ZUMA-1 only allowed enrolment of patients who were “chemotherapy-refractory”, defined as refractoriness to 1L, 2L+ or transplant. Therefore, to permit a robust comparison with ZUMA-1, a sub-selection of patients from STARGLO more closely aligned with ZUMA-1 were considered. The sub-selection generated included the following patients from STARGLO for comparison (n=58):

- ≥ 2 prior lines of therapy
- ECOG 0 or 1
- Refractory patients defined according to ZUMA-1 (progressive or stable disease as best response to the most recent chemotherapy regimen, or disease progression or relapse within 12 months of ASCT)
- No prior CAR-T therapy

A comparison of the STARGLO patient subgroup that is most closely aligned with the ZUMA-1 cohort indicated large imbalances regarding prior treatment lines and the proportion of patients with primary refractory disease (Table 20). These prognostic factors/effect modifiers would need to be adjusted for by the MAIC and doing so would result in a low effective sample size (ESS) and measures of treatment effect that would be associated with large levels of uncertainty. The feasibility assessment therefore concluded that a comparison would not be considered robust enough to provide meaningful results, therefore the ITC vs axicabtagene ciloleucel cannot be conducted.

Table 20: Summary of baseline characteristics across STARGLO and axicabtagene ciloleucel

Covariate	STARGLO 3L+, ECOG PS 0/1, refract pts defined as per ZUMA-1, no prior CAR-T; N=58	Comparator sources Axicabtagene ciloleucel ZUMA-1 (n=101)
High priority		
IPI, n (%)	[redacted]	0-2: 55 (54.5%) 3-4: 46 (45.5%)
Mean (SD) age, years	[redacted]	56.3 (12.0)
ECOG PS, n (%)	[redacted]	0: 42 (41.6%) 1: 59 (58.4%)
Ann Arbor Stage, n (%)	[redacted]	I–II: 15 (14.9%) III–IV: 86 (85.2%)
High LDH, n (%) [>ULN]	[redacted]	Elevated LDH: 62 (61.4%) LDH > ULN per local laboratory reference range

Extranodal disease, n (%) [yes, or number of sites]	[redacted]	70 (69.3%)
Refractory to 1st line, n (%)	[redacted] Best response of progressive or stable disease, or progression within 6 months of completion of first-line	26 (25.7%) ['primary refractory'] Definition of primary refractory in the refractory subgroup according to the ZUMA-1 protocol: experienced disease progression as best response to first line therapy or had stable disease after at least 4 cycles of first line therapy
Refractory to last line, n (%)	[redacted] Best response of progressive or stable disease, or progression within 6 months of completion of last line therapy	67 (66.3%) [best response as PD to last previous therapy; Locke 2019] 77 (76.2%) ['refractory to second-line or later'; a subject is considered to be refractory to 2nd or greater line therapy if the patient experienced PD as best response to the most recent therapy regimen; Locke 2019] 79.2% refractory to last line of treatment; Maloney 2021
Refractory to any line, n (%)	[redacted]	NR
Histological subtype: HGBCL, PMBCL, DLBCL NOS, tFL, n (%)	DLBCL NOS	PMBCL: 8 (7.9%) HGBCL: 6 (5.9%) [defined as double-hit or triple-hit or NOS]
Double/triple hit lymphoma, n (%)	[redacted]	5 (5.0%) [among patients with HGBCL-assumed]
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	[redacted] Relapse or refractory within 12 months after last ASCT	21 (20.8%) relapse after prior ASCT (not specified as early)
Number of prior treatment lines, n (%)	[redacted]	1: 3 (3.0%) 2: 28 (27.7%) ≥3: 70 (69.3%)
Medium priority		
Bulky disease, n (%)	[redacted]	≥10 cm: 16 (15.8%)
Refractory to chemotherapy, n (%)	[redacted]	NR
Refractory to rituximab and anthracycline, n (%)	[redacted] Refractory to Any Prior Anthracycline Therapy	NR

Refractory to rituximab (anti-CD20), n (%)	53 (88.3%)	NR
Time since last therapy, mean (SD)	2.8 (2.8)	NR
Low/unclear priority		
Cell type of origin, n (%)	[redacted]	ABC: 17 (16.8%) GCB: 49 (48.5%) Unknown: 35 (34.7%)
Bone marrow involvement, n (%)	[redacted]	Positive: 11 (10.9%) Negative: 82 (82.2%) Not assessed: 7 (6.9%)
Prior SCT, n (%)	[redacted]	25 (24.8%)
Prior CART, n (%)	[redacted]	NR
Male, n (%)	[redacted]	68 (67.3%)

3L+, third-line and beyond; ABC, activated B cell-like; ASCT, autologous stem cell transplant; GCB, germinal centre B cell; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B cell lymphoma; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B cell lymphoma; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma.

Loncastuximab tesirine

Of the seven studies examining loncastuximab tesirine, four were excluded as they were retrospective studies. Of the remaining three studies, LOTIS-2 (103) was deemed the most relevant for inclusion into the MAIC as the remaining two studies either reported limited outcome data (Lin 2023) or enrolled fewer patients (LOTIS-1).

However, only 68% of the LOTIS-2 population had an overlapping histology with STARGLO (DLBCL) (Table 21). It is not possible to conduct the ITC in DLBCL patients only as no baseline characteristics and/or outcome data are reported for the DLBCL subpopulation in LOTIS-2. Furthermore, imbalances are observed in prior treatment lines, prior ASCT, and prior CART use. These factors would need to be adjusted for by the MAIC and would result in a low ESS and measures of treatment effect that would be associated with large levels of uncertainty. The feasibility assessment therefore concluded that a comparison would not be considered robust enough to provide meaningful results, therefore the ITC vs loncastuximab tesirine cannot be conducted.

Table 21: Summary of baseline characteristics across the STARGLO and loncastuximab tesirine cohorts.

Covariate	STARGLO 3L+ (N=102)	Loncastuximab tesirine LOTIS-2 (n=145)
High priority		
	[redacted]	NR

IPI, n (%)	[redacted]	
Mean (SD) age, years	[redacted]	Median: 66 (IQR: 56-71)
ECOG PS, n (%)	[redacted]	NR (data provided in 12, 24 months follow-up study)
Ann Arbor Stage, n (%)	[redacted]	I-II: 33 (23%) III-IV: 112 (77%)
High LDH, n (%) [>ULN]	[redacted]	NR
Extranodal disease, n (%) [yes, or number of sites]	[redacted]	NR
Refractory to 1st line, n (%)	[redacted] Best response of progressive or stable disease, or progression within 6 months of completion of first-line	Response to first-line systemic therapy: Relapse: 99 (68%) Refractory: 29 (20%) Unknown: 17 (12%) Refractory disease defined as no response to therapy Relapse within 6 months of first-line therapy: 57 (39%)
Refractory to last line, n (%)	[redacted] Best response of progressive or stable disease, or progression within 6 months of completion of last line therapy	Response to most recent line of systemic therapy: Relapse: 43 (30%) Refractory: 84 (58) Unknown: 18 (12%)
Refractory to any line, n (%)	[redacted]	NR
Histological subtype: HGBCL, PMBCL,	DLBCL NOS	HGBCL : 11 (8%) PMBCL: 7 (5%)

DLBCL NOS, tFL, n (%)		Transformed DLBCL: 29 (20%) DLBCL NOS: 98 (68%) tFL: NR
Double/triple hit lymphoma, n (%)	NA	Double or triple hit DLBCL: 15 (10%)
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	[redacted] Relapse or refractory within 12 months after last ASCT	NR
Number of prior treatment lines, n (%) and median (range)	≥2: 102 (100%)	Median: 3 (IQR: 2-4) Prior lines 2: 63 (43%) 3: 35 (24%) 4: 47 (32%)
Medium priority		
Bulky disease, n (%)	[redacted]	8 (6%)
Refractory to chemotherapy, n (%)	[redacted]	NR
Refractory to rituximab and anthracycline, n (%)	[redacted] Refractory to any prior anthracycline therapy	NR
Refractory to rituximab (anti-CD20), n (%)	[redacted]	NR
Time since last treatment, mean (SD)	[redacted]	NR
Low/unclear priority		
Cell type of origin, n (%)	[redacted]	Cell type origin in DLBCL: GCB: 48 (33%) ABC: 23 (16%) Unknown: 74 (51%)
Bone marrow involvement, n (%)	[redacted]	NR
Prior SCT, n (%)	[redacted]	24 (17%)
Prior CAR-T, n (%)	[redacted]	13 (9%)
Male, n (%)	[redacted]	85 (59%)

ABC, activated B cell-like; ASCT, autologous stem cell transplant; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal centre B cell; HGBCL, high-grade B cell lymphoma; IHC, immunohistochemistry; NOS, not otherwise specified; NR, not reported; NA, Not applicable; PMBCL, primary mediastinal large B cell lymphoma; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma; IPI, International Prognostic Index; IQR, Inter quartile range, LDH, lactate dehydrogenase, ULN, upper limit of normal

Epcoritamab

Two studies included in the SLR investigated epcoritamab. EPCORE NHL-3 was a phase I/II trial evaluating epcoritamab monotherapy in Japanese patients in the 3L+ setting, but data were only available for 36 patients and therefore the study was excluded on sample size.

EPCORE NHL-1, investigated epcoritamab. However, EPCORE NHL-1 will permit a MAIC in the 3L+ population as the study included patients with a median of 3 (range 2–11) prior therapies.

EPCORE NHL-1 reports a prospective, open-label, single-arm Phase I/II dose escalation and dose expansion study of epcoritamab for the treatment of relapsed or refractory non-Hodgkin lymphoma (NHL) in Denmark, the Netherlands, UK and Spain (104). The study inclusion/exclusion criteria of the dose expansion cohort of EPCORE NHL-1 are aligned broadly with those of STARGLO, enrolling patients with relapsed, progressive or refractory CD20+ mature B cell NHL, an ECOG PS 0-2, and with prior CAR-T therapy cell eligible. Further, ASCT eligible patients were excluded from the study. However, EPCORE NHL-1 enrolled patients with at least 1 prior lines of systemic therapy and at least 1 previous treatment with an anti-CD20 monoclonal antibody-containing regimen. Therefore, to permit a more robust comparison with EPCORE NHL-1, a sub-selection of patients from STARGLO more closely aligned with EPCORE NHL-1 were considered. The sub-selection was generated including 3L+ patients from STARGLO only for comparison (**Table *22***).

Only 62% of the EPCORE-NHL-1 population had an overlapping histology with STARGLO (DLBCL). It is not possible to conduct the ITC in DLBCL patients only as no baseline characteristics and/or outcome data are reported for the DLBCL subpopulation in EPCORE-NHL-1. Furthermore, imbalances are observed in prior treatment lines, prior ASCT and prior CART use. These factors would need to be adjusted for by the MAIC and would result in a low ESS and measures of treatment effect that would be associated with large levels of uncertainty. The feasibility assessment therefore concluded that the ITC vs epcoritamab cannot be conducted.

Table 22: Summary of baseline characteristics across the STARGLO and epcoritamab cohorts

Covariate	STARGLO 3L+ (N=102)	Epcoritamab EPCORE-NHL-1 (N=157)
High priority		
IPI, n (%)	[redacted]	0–1: 55 (35.0%) ≥3: 82 (52.2%)
Mean (SD) age, years	[redacted]	Median: 64 (range: 20–83)
ECOG PS, n (%)	[redacted]	0: 74 (47.1%) 1: 78 (49.7%) 2: 5 (3.2%)

Ann Arbor Stage, n (%)	[redacted]	I–II: 39 (24.8%) III: 21 (13.4%) IV: 97 (61.8%)
High LDH, n (%) [>ULN]	[redacted]	NR
Extranodal disease, n (%) [yes, or number of sites]	[redacted]	Dose escalation phase: 29/46 (63.0%)
Refractory to 1st line, n (%)	[redacted] Best response of progressive or stable disease, or progression within 6 months of completion of first-line	Primary refractory-disease progression or SD as best response to therapy or disease progression within 6 months after completion of therapy: 96 (61.1%)
Refractory to last line, n (%)	[redacted] Best response of progressive or stable disease, or progression within 6 months of completion of last line therapy	Patients refractory to last line of systemic therapy 130 (82.8%)
Refractory to any line, n (%)	[redacted]	NR
Histological subtype: HGBCL, PMBCL, DLBCL NOS, tFL, n (%)	DLBCL NOS	HGBCL: 9 (5.7%) tFL: 40/139 (28.8%) DLBCL NOS: 139 (88.5%) PMBCL: 4 (2.5%)
Double/triple hit lymphoma, n (%)	NA	NR
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	[redacted] Relapse or refractory within 12 months after last ASCT	NR
Number of prior treatment lines, n (%) and median (range)	≥2: 102 (100%)	2: 46 (29.3%) 3: 50 (31.8%) ≥4: 61 (38.9%) Median: 3 (range: 2–11)

Medium priority		
Bulky disease, n (%)	[redacted]	NR
Refractory to chemotherapy, n (%)	[redacted]	NR
Refractory to rituximab and anthracycline, n (%)	[redacted] Refractory to Any Prior Anthracycline Therapy	NR
Refractory to rituximab (anti-CD20), n (%)	[redacted]	Dose escalation phase: 41/46 (89.1%)
Time since last treatment, mean (SD)	[redacted]	Median: 2.4 (range: 0.0-5.0)
Low/unclear priority		
Cell type of origin, n (%)	[redacted]	ABC/nonGCB: 56 (35.7%) GCB: 65 (41.4%) Unknown: 18 (11.5%) Not applicable: 18 (11.5%)
Bone marrow involvement, n (%)	[redacted]	NR
Prior SCT, n (%)	[redacted]	31 (19.7%)
Prior CAR-T, n (%)	[redacted]	61 (38.9%)
Male, n (%)	[redacted]	94 (59.9%)

Abbreviations: ABC, activated B cell; ASCT, autologous stem cell transplant; CRF, case report form; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal centre B cell; HGBCL, high-grade B cell lymphoma; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NA, not applicable; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B cell lymphoma; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma.

Glofitamab monotherapy

A propensity score analysis vs glofitamab monotherapy is possible due to the availability of individual patient data from the pivotal cohort of NP30179 (105). However, to achieve homogeneity in patient cohorts before making comparisons, Glofit-mono and Glofit-GemOx groups were subsetted to align with trial enrolment criteria (i.e. matching patients with two or more prior lines of therapy and without ECOG PS 2 patients), reducing the patient population to 100 patients (from 154) in the Glofit-mono group and 61 (from 68) in the Glofit-GemOx group. After adjusting for high, medium and low priority variables, the Glofit-GemOx arm had a very small ESS (<30), therefore only high and medium priority variables can be corrected for. Furthermore, after adjusting for imbalances in covariates including age, ECOG PS, Ann Arbor stage and refractoriness to first treatment and prior line of treatment, the ESS for Glofit-GemOx and Glofit-mono reduced to 46.98 and 91.3 respectively, indicating that the results from the analysis would be associated with considerable uncertainty.

As a consequence of the lack of robust evidence to conduct MAICs to the majority of comparators in the 3L+ setting, together with considerable uncertainty in the analysis vs glofitamab monotherapy, the relevant population for the economic evaluation presented in Section 3 is restricted to transplant ineligible R/R DLBCL patients in the 2L setting only. In doing so, the current submission is informed by the strongest available evidence, thereby reducing uncertainties in the analysis to allow for the most robust case for the cost-effectiveness of Glofit-GemOx to be considered. Furthermore, UK clinical experts confirmed that the greatest unmet need in R/R DLBCL is in the 2L setting, where treatment for patients who are transplant-ineligible is limited to R-GemOx, and that, if reimbursed, Glofit-GemOx would be prescribed in this setting regardless of its broad license indication.

2.11 Adverse reactions

The safety-evaluable population consisted of patients who received any amount of any study treatment, whether prematurely withdrawn from the study or not. All safety data are provided from the updated analysis with a CCOD of 16 February 2024. In the Glofit-GemOx arm, 8 patients discontinued after receiving obinutuzumab pre-treatment and did not receive glofitamab; 3 patients experienced Grade 5 AEs (COVID-19 associated AEs in 2 patients, 1 patient experience septic shock), 2 patients discontinued study treatment due to AEs (1 due to COVID-19, 1 due to myocardial infarction), 2 patients discontinued study treatment due to progressive disease or symptomatic deterioration and one patient withdrew their consent. Therefore, treatment exposure and safety data in patients on this arm are reported both for patients exposed to any study treatment (‘any treatment exposed’) (n=180) and patients exposed to glofitamab (n=172). In addition, efficacy data is provided for both the whole population (1 or ≥ 2 prior lines of therapy) and the subpopulation with only 1 prior line of therapy (2L subpopulation).

2.11.1 Exposure to study treatments

In the Glofit-GemOx arm (glofitamab-exposed), the median number of glofitamab infusions was 12.0 (range: [redacted]) with patients receiving a median of 11.0 cycles of glofitamab (range: [redacted]), the median treatment duration was 7.2 months ([redacted] days [range: [redacted]]), and the median total cumulative dose was 303.75 mg (range: [redacted]). The median dose intensity was 100% (range: [redacted]). In the R-GemOx arm, patients received a median of 4.0 infusions of rituximab (range: [redacted]), the median treatment duration was 2.1 months ([redacted] days [range: [redacted]]), and the median total cumulative dose was 1488.2 mg (range:

[redacted]). The median dose intensity was 100% (range: [redacted]). [redacted] on the trial received ≥90% of the planned dose of glofitamab or rituximab.

The median number of cycles of gemcitabine was 8.0 (range: [redacted]) in the Glofit-GemOx (glofitamab-exposed) population and 4.0 (range: [redacted]) in the R-GemOx population. The median treatment duration was 4.8 months ([redacted] days [range: [redacted]]) and 2.1 months ([redacted] days [range: [redacted]]) in the Glofit-GemOx (glofitamab-exposed) and R-GemOx populations, respectively. The median total cumulative dose of gemcitabine was 7882.75 mg (range: [redacted]) and 3997.74 mg (range: [redacted]), respectively, and the median dose intensity was 100% (range: [redacted]) and 100.0% (range: [redacted]), respectively. In the Glofit-GemOx (glofitamab-exposed) population, [redacted] of patients ([redacted]/172) received ≥ 90% of the planned dose of gemcitabine, and [redacted] in the R-GemOx population received ≥ 90% of the planned dose.

The median number of cycles of oxaliplatin was 8.0 (range: [redacted]) in the Glofit-GemOx (glofitamab-exposed) population and 4.0 (range: [redacted]) in the R-GemOx population. The median treatment duration was 4.8 months ([redacted] days [range: [redacted]]) and 2.1 months ([redacted] days [range: [redacted]]) in the Glofit-GemOx (glofitamab-exposed) and R-GemOx populations, respectively. The median total cumulative dose of oxaliplatin was 788.53 mg (range: [redacted]) and 396.20 mg (range: [redacted]), respectively, and the median dose intensity was 100% (range: [redacted]) and 100.0% (range: [redacted]), respectively. In the Glofit-GemOx (glofitamab-exposed) population, [redacted] of patients ([redacted]/172) received ≥ 90% of the planned dose of oxaliplatin, and [redacted] of patients ([redacted]/88) in the R-GemOx population received ≥ 90% of the planned dose.

Exposure to study treatments data for patients in the Glofit-GemOx (any treatment exposed) population were similar to that in the Glofit-GemOx (glofitamab-exposed) population and support Glofit-GemOx as a tolerable regimen (Table 23). In addition, exposure to study treatments [redacted] (Table 24).

Table 23: Summary of exposure to treatments (safety evaluable population; STARGLO)

	R-GemOx n=88	Glofit-GemOx (any treatment exposed) n=180	Glofit-GemOx (glofitamab-exposed) n=172
Obinutuzumab (pre-treatment)			
Number of infusions, median (range)	-	[redacted]	[redacted]

Dose intensity* [%], median (range)	-	[redacted]	[redacted]
Dose intensity* ≥90%	-	[redacted]	[redacted]
Glofitamab			
Number of cycles, median (range)	-	11.0 ([redacted])	11.0 ([redacted])
Categorised number of cycles, n (%)† Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	-	[redacted]	[redacted]
Number of infusions, median (range)	-	12.0 ([redacted])	12.0 ([redacted])
Dose intensity* [%], median (range)	-	100% ([redacted])	100% ([redacted])
Dose intensity* ≥90%	-	[redacted]	[redacted]
Total duration [days], median (range)	-	218.0 ([redacted])	218.0 ([redacted])
Rituximab			
Number of cycles, median (range)	4.0 ([redacted])	-	-
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	[redacted]	-	-
Number of infusions, median (range)	4.0 ([redacted])	-	-
Dose intensity* [%], median (range)	100.0% ([redacted])	-	-
Dose intensity* ≥90%	[redacted]	-	-
Total duration [days], median (range)	64.0 ([redacted])	-	-
Gemcitabine			
Number of cycles, median (range)	4.0 ([redacted])	8.0 ([redacted])	8.0 ([redacted])
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	[redacted]	[redacted]	[redacted]
Number of infusions, median (range)	4.0 ([redacted])	8.0 ([redacted])	8.0 ([redacted])
Dose intensity* [%], median (range)	100.0% ([redacted])	100.0% ([redacted])	100.0% ([redacted])
Dose intensity* ≥90%	[redacted]	[redacted]	[redacted]
Total duration [days], median (range)	63.0 ([redacted])	147.0 ([redacted])	147.0 ([redacted])
Oxaliplatin			
Number of cycles, median (range)	4.0 ([redacted])	8.0 ([redacted])	8.0 ([redacted])
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles	[redacted]	[redacted]	[redacted]

>12 cycles	[redacted]	[redacted]	[redacted]
Number of infusions, median (range)	4.0 ([redacted])	8.0 ([redacted])	8.0 ([redacted])
Dose intensity* [%], median (range)	100.0% ([redacted])	100.0% ([redacted])	100.0% ([redacted])
Dose intensity* ≥90%	[redacted]	[redacted]	[redacted]
Total duration [days], median (range)	63.0 ([redacted])	147.0 ([redacted])	147.0 ([redacted])

†In the glofitamab arm n=172 for any treatment exposed and glofitamab exposed; *Dose intensity is the number of doses actually received divided by the expected number of doses.
CCOD: 16th February 2024
Source: STARGLO_updated_CSR

Table 24: Summary of exposure to treatments (2L subpopulation; STARGLO)

	R-GemOx n=55	Glofit-GemOx (any treatment exposed) n=112	Glofit-GemOx (glofitamab-exposed) n=108
Obinutuzumab (pre-treatment)			
Number of infusions, median (range)	-	[redacted]	[redacted]
Dose intensity* [%], median (range)	-	[redacted]	[redacted]
Dose intensity* ≥90%	-	[redacted]	[redacted]
Glofitamab			
Number of cycles, median (range)	-	[redacted]	[redacted]
Categorised number of cycles, n (%)† Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	-	[redacted]	[redacted]
Number of infusions, median (range)	-	[redacted]	[redacted]
Dose intensity* [%], median (range)	-	[redacted]	[redacted]
Dose intensity* ≥90%	-	[redacted]	[redacted]
Total duration [days], median (range)	-	[redacted]	[redacted]
Rituximab			
Number of cycles, median (range)	[redacted]	-	-
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	[redacted]	-	-
Number of infusions, median (range)	[redacted]	-	-
Dose intensity* [%], median (range)	[redacted]	-	-
Dose intensity* ≥90%	[redacted]	-	-
Total duration [days], median (range)	[redacted]	-	-
Gemcitabine			

Number of cycles, median (range)	[redacted]	[redacted]	[redacted]
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	[redacted]	[redacted]	[redacted]
Number of infusions, median (range)	[redacted]	[redacted]	[redacted]
Dose intensity* [%], median (range)	[redacted]	[redacted]	[redacted]
Dose intensity* ≥90%	[redacted]	[redacted]	[redacted]
Total duration [days], median (range)	[redacted]	[redacted]	[redacted]
Oxaliplatin			
Number of cycles, median (range)	[redacted]	[redacted]	[redacted]
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	[redacted]	[redacted]	[redacted]
Number of infusions, median (range)	[redacted]	[redacted]	[redacted]
Dose intensity* [%], median (range)	[redacted]	[redacted]	[redacted]
Dose intensity* ≥90%	[redacted]	[redacted]	[redacted]
Total duration [days], median (range)	[redacted]	[redacted]	[redacted]

†In the glofitamab arm n=108 for any treatment exposed and glofitamab exposed; *Dose intensity is the number of doses actually received divided by the expected number of doses.
CCOD: 16th February 2024
Source: post-hoc outputs for the 2L subpopulation

2.11.2 Overview of safety

Overall, the safety analysis in the Glofit-GemOx (any treatment exposed; n=180) population is comparable to that in the Glofit-GemOx (Glofitamab-exposed; n=172) population. The safety profile of Glofit-GemOx was tolerable and consistent with the known risks of individual study drugs. Comparison of safety data for Glofit-GemOx and R-GemOx should be considered in the context of substantially different treatment exposure, as described above in Section 2.11.1; in the Glofit-GemOx arm, the median number of cycles of glofitamab and GemOx was 11 and 8, respectively and in the R-GemOx arm, the median number of cycles for all treatments was 4.

All patients in the Glofit-GemOx (glofitamab-exposed) (172/172 100.0%) population and almost all of the patients in the R-GemOx (84/88: 95.5%) population experienced at least one AE. Common AEs are described in Section 2.11.3 and AEs occurring in ≥ 1% of patients on either arm are detailed in Appendix D.

The proportion of patients that experienced grade ≥ 3 AEs was higher in the Glofit-GemOx arm (132/172 patients; 76.7%) compared with the R-GemOx arm (36/88 patients; 40.9%), and grade ≥ 3 AEs related to glofitamab/rituximab affected a higher proportion of patients in the Glofit-GemOx arm (85/172 patients: 49.4%) compared with the R-GemOx arm (20/88 patients: 22.7%) (Table 25). The majority of grade ≥ 3 events reported were haematological abnormalities including thrombocytopenia, neutropenia, anemia, and lymphopenia, consistent with the known safety profiles of glofitamab and GemOx.

Grade 5 (fatal) AEs were reported in a greater proportion of patients in the Glofit-GemOx arm (12/172 patients; 7.0%) compared with the R-GemOx arm (4/88 patients; 4.5%). The majority of fatal events were primarily due to infections on both arms, with a higher proportion of fatal COVID-19 and COVID-19 associated events reported on the Glofit-GemOx arm (5 out of the 12 fatal events reported).

A greater proportion of patients in the Glofit-GemOx arm (90/172 patients; 52.3%) suffered SAEs compared with the R-GemOx arm (15/88 patients; 17.0%). The most common SAE was [redacted], which only affected patients treated with Glofit-GemOx ([redacted]/172 patients; [redacted]). Other SAEs were driven by [redacted] (Glofit-GemOx with [redacted] and R-GemOx with [redacted]), which were predominantly [redacted] on the Glofit-GemOx arm and [redacted] on the R-GemOx arm. SAEs leading to withdrawal from glofitamab/rituximab were reported in a greater proportion of patients in the Glofit-GemOx arm (21/172 patients; 12.2%) compared with the R-GemOx arm (6/88 patients; 6.8%). The majority of SAEs leading to withdrawal of glofitamab/rituximab were due to [redacted]. SAEs related to glofitamab/rituximab were reported in a greater proportion of patients in the Glofit-GemOx arm (62/172 patients; 36.0%) compared with the R-GemOx arm (7/88 patients; 8.0%). The most common SAE related to glofitamab was [redacted] (Glofit-GemOx arm ([redacted]/172 patients; [redacted]) and to rituximab was [redacted] (both in [redacted]/88 patients; [redacted]).

AEs leading to any treatment withdrawal were reported in a greater proportion of patients in the Glofit-GemOx arm (43/172 patients; 25.0%) compared with the R-GemOx arm (11/88 patients; 12.5%). AEs related to glofitamab/rituximab leading to discontinuation of glofitamab/rituximab were reported in a greater proportion of patients in the Glofit-GemOx arm (13/172 patients; 7.6%) compared with the R-GemOx arm (3/88 patients; 3.4%). Considering the impacts of the COVID-19 pandemic and the cumulative exposure to chemotherapy on the Glofit-GemOx arm, from a higher proportion of patients remaining on study treatment for longer, the AEs leading to any treatment discontinuation were consistent

with the expected risks of glofitamab in combination with gemcitabine and oxaliplatin. An overview of AEs in each arm of the study is provided in Table 25.

[redacted] The frequency of patients with fatal AEs in the R-GemOx arm [redacted] ([redacted]) compared with the whole population ([redacted]) (Table 26).

Table 25: Overview of adverse events (safety evaluable population; STARGLO)

	R-GemOx n=88	Glofit-GemOx (any treatment exposed) n=180	Glofit-GemOx (glofitamab-exposed) n=172
Any AE, n (%)	84 (95.5%)	180 (100%)	[redacted]
related to rituximab/glofitamab	58 (65.9%)	149 (82.8%)	
related to obinutuzumab	[redacted]	[redacted]	
related to gemcitabine			
related to oxaliplatin			
SAE, n (%)	15 (17.0%)	98 (54.4%)	[redacted]
related to rituximab/glofitamab	7 (8.0%)	62 (34.4%)	
related to obinutuzumab	[redacted]	[redacted]	
related to gemcitabine			
related to oxaliplatin			
Grade 3+ AEs, n (%)	36 (40.9%)	140 (77.8%)	[redacted]
related to rituximab/glofitamab	20 (22.7%)	85 (47.2%)	
related to obinutuzumab	[redacted]	[redacted]	
related to gemcitabine			
related to oxaliplatin			
Grade 5 AEs, n (%)	4 (4.5%)	15 (8.3%)	[redacted]
AE leading to treatment withdrawal, n (%)	11 (12.5%)	48 (26.7%)	[redacted]
AE related to rituximab/glofitamab leading to withdrawal from rituximab/glofitamab	3 (3.4%)	13 (7.2%)	[redacted]
AE related to rituximab/glofitamab leading to dose interruption of rituximab/glofitamab	9 (10.2%)	43 (23.9%)	[redacted]

Source: STARGLO_updated_CSR

Table 26: Overview of adverse events (2L subpopulation; STARGLO)

	R-GemOx n=55	Glofit-GemOx (any treatment exposed) n=112	Glofit-GemOx (glofitamab-exposed) n=108
Any AE, n (%)	54 (98.2%)	112 (100%)	[redacted]
related to rituximab/glofitamab	[redacted]	[redacted]	
related to obinutuzumab			
related to gemcitabine			
related to oxaliplatin			
SAE, n (%)	[redacted]	[redacted]	[redacted]
related to rituximab/glofitamab			
related to obinutuzumab			
related to gemcitabine			
related to oxaliplatin			
Grade 3+ AEs, n (%)	23 (41.8%)	85 (75.9%)	[redacted]
related to rituximab/glofitamab	[redacted]	[redacted]	
related to obinutuzumab			
related to gemcitabine			
related to oxaliplatin			
Grade 5 AEs, n (%)	1 (1.8%)	9 (8.0%)	[redacted]
AE leading to treatment withdrawal, n (%)	[redacted]	[redacted]	[redacted]

AE related to rituximab/glofitamab leading to withdrawal from rituximab/glofitamab	[redacted]	[redacted]	[redacted]
AE related to rituximab/glofitamab leading to dose interruption of rituximab/glofitamab	[redacted]	[redacted]	[redacted]

Source: post-hoc outputs for the 2L subpopulation

2.11.3 Common adverse events

AEs that occurred in ≥ 10% of patients in both arms of the study are summarised for the whole population Table 27.

Common AEs (≥ 10%) in the Glofit-GemOx arm (glofitamab-exposed) with a difference of ≥ 10% incidence compared to the R-GemOx arm, excluding CRS, were as follows:

- [redacted] ([redacted] vs. [redacted])
- [redacted] ([redacted] vs. [redacted])
- [redacted] ([redacted] vs. [redacted])
- [redacted] ([redacted] vs. [redacted])
- [redacted] ([redacted] vs. [redacted])

Note that CRS was reported in 44.2% of patients in the Glofit-GemOx (glofitamab-exposed) population, and, as they are not at risk of a CRS event, in none of the patients in the R-GemOx population.

Table 27: Overview of adverse events with an incidence rate ≥ 10% (safety evaluable population; STARGLO)

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx n=88	Glofit-GemOx (any treatment exposed) n=180	Glofit-GemOx (glofitamab-exposed) n=172
Gastrointestinal disorders: Nausea Diarrhoea Vomiting Constipation	[redacted]	[redacted]	[redacted]
Investigations: Platelet count decreased Aspartate aminotransferase increased Alanine aminotransferase increased Neutrophil count decreased Lymphocyte count decreased White blood cell count decreased Blood alkaline phosphatase increased Serum ferritin increased Gamma-glutamyltransferase increased Blood lactate dehydrogenase increased C-reactive protein increased	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders: Anaemia Thrombocytopenia Neutropenia	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders: Decreased appetite Hypokalaemia	[redacted]	[redacted]	[redacted]

Hyponatraemia Hypomagnesaemia	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions: Fatigue Pyrexia Asthenia	[redacted]	[redacted]	[redacted]
Immune system disorders: Cytokine release syndrome	0 (0%)	[redacted]	76 (44.2%)
Infections and infestations:* COVID-19 Pneumonia	[redacted]	[redacted]	[redacted]
Nervous system disorders: Peripheral sensory neuropathy Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications: Infusion related reaction	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders: Rash	[redacted]	[redacted]	[redacted]
Psychiatric disorders: Insomnia	[redacted]	[redacted]	[redacted]

*In addition, there were 3 patients with COVID-19 pneumonia in the Glofit-GemOx any treatment exposed population, including 2 patients in the Glofit-GemOx glofitamab-exposed population. There were no cases of COVID-19 pneumonia reported in the R-GemOx arm.
CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR

2.11.4 Adverse events of special interest

The key clinically significant AEs of special interest (AESIs) related to glofitamab treatment, which may have implications for prescribing decisions and patient management, include Grade ≥ 2 CRS, Grade ≥ 2 neurologic AEs, tumour lysis syndrome (TLS), febrile neutropenia, Grade ≥ 2 AST, ALT or total bilirubin elevation, Grade ≥ 2 tumour flare, pneumonitis or interstitial lung disease (ILD) and colitis. The frequency of these AESIs in the glofitamab-exposed population at the CCOD of 16 February 2024 [redacted]

28 [redacted] **29**. The incidence of these events is consistent with the known existing safety profile of glofitamab.

Table 28: Overview of AESIs in glofitamab-exposed patients (safety evaluable population; STARGLO)

Patients experienced at least one AE	R-GemOx n=88	Glofit-GemOx (any treatment exposed) n=180	Glofit-GemOx (glofitamab-exposed) n=172
Grade ≥ 2 CRS (ASTCT grade)	[redacted]	[redacted]	[redacted]
Grade ≥ 2 neurologic	11 (12.5%)	52 (30.2%)	[redacted]
Grade ≥ 2 tumour flare	1 (1.1%)	1 (0.6%)	[redacted]
Grade ≥ 2 AST, ALT, or total bilirubin elevation	[redacted]	[redacted]	[redacted]
Tumour lysis syndrome	[redacted]	[redacted]	[redacted]

Febrile neutropenia	1 (1.1%)	6 (3.3%)	[redacted]
Pneumonitis or interstitial lung disease	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR

Table 29: Overview of AESIs in glofitamab-exposed patients (2L subpopulation; STARGLO)

Patients experienced at least one AE	R-GemOx n=55	Glofit-GemOx (any treatment exposed) n=112	Glofit-GemOx (glofitamab-exposed) n=108
Grade ≥ 2 CRS (ASTCT grade)	[redacted]	[redacted]	[redacted]
Grade ≥ 2 neurologic	[redacted]	[redacted]	[redacted]
Grade ≥ 2 tumour flare	[redacted]	[redacted]	[redacted]
Grade ≥ 2 AST, ALT, or total bilirubin elevation	[redacted]	[redacted]	[redacted]
Tumour lysis syndrome	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Pneumonitis or interstitial lung disease	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: post-hoc outputs for the 2L subpopulation

2.11.4.1 Cytokine release syndrome

CRS was the most common AE in patients treated with GemOx, mostly low grade and mostly occurring in Cycle 1 (Table 30). The rate and severity of these CRS events was similar to those observed with glofitamab monotherapy (106).

In the Glofit-GemOx arm, 76 of the 172 glofitamab-exposed patients (44.2%) reported at least one CRS AE (by ASTCT). The majority of patients with CRS had events with a maximum severity of grade 1 or 2 (grade 1: 54/172 patients, 31.4%; grade 2: 18/172 patients, 10.5%). A total of 4 patients (2.3%) reported grade 3 CRS AEs. There were no grade 4 or fatal CRS events. One patient had a grade 3 CRS confounded by a concurrent grade 5 septic shock that required multiple pressors. Serious CRS AEs were reported in [redacted] patients ([redacted]) (Table 31).

CRS AEs occurred most frequently following the first dose of glofitamab (2.5 mg) in Cycle 1 (60 patients; 34.9%), but also occurred in 24/167 patients (14.4%) following administration of glofitamab 10 mg (Cycle 1, Day 15) and in 15/161 patients (9.3%) following the first target dose of 30 mg (Cycle 2, Day 1), 10/149 patients (6.7%) following the 30 mg Cycle 3 dose and in 16/145 patients (11.0%) on or after the 30 mg Cycle 4+ doses. Grade ≥ 3 CRS events were only reported in Cycle 1. Grade ≥2 CRS AEs led to interruption of glofitamab

treatment in [redacted] ([redacted]) and discontinuation of glofitamab treatment in [redacted] ([redacted]).

Rates of CRS AEs and SAEs

[redacted] (Table 32 and Table 33).

Table 30: CRS AEs after each dose of glofitamab (glofitamab-exposed; STARGLO)

	Cycle 1		Cycle 2	Cycle 3	Cycle 4+	Overall across all cycles, highest grade
	After 2.5mg dose [C1D8] (n=172)	After 10mg dose [C1D15] (n=167)	After 30mg dose [C2D1] (n=161)	After 30mg dose [C3D1] (n=149)	After 30mg dose [C4D1] (n=145)	
Any grade, n (%)	60 (34.9%)	24 (14.4%)	15 (9.3%)	10 (6.7%)	16 (11.0%)	76 (44.2%)
1	42 (24.4%)	21 (12.6%)	15 (9.3%)	9 (6.0%)	14 (9.7%)	[redacted]
2	15 (8.7%)	2 (1.2%)	0	1 (0.7%)	2 (1.4%)	[redacted]
3	3 (1.7%)	1 (0.6%)	0	0	0	[redacted]

CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR

Table 31: Serious CRS AEs after each dose of glofitamab (glofitamab-exposed; STARGLO)

	Cycle 1		Cycle 2	Cycle 3	Cycle 4+	Overall across all cycles, highest grade
	After 2.5mg dose [C1D8] (n=172)	After 10mg dose [C1D15] (n=167)	After 30mg dose [C2D1] (n=161)	After 30mg dose [C3D1] (n=149)	After 30mg dose [C4D1] (n=145)	
Any grade, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR

Table 32: CRS AEs after each dose of glofitamab (2L subpopulation; glofitamab-exposed; STARGLO)

	Cycle 1		Cycle 2	Cycle 3	Cycle 4+	Overall across all cycles, highest grade
	After 2.5mg dose [C1D8] (n=[redacted])	After 10mg dose [C1D15] (n=[redacted])	After 30mg dose [C2D1] (n=[redacted])	After 30mg dose [C3D1] (n=[redacted])	After 30mg dose [C4D1] (n=[redacted])	
Any grade, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: post-hoc outputs for the 2L subpopulation

Table 33: Serious CRS AEs after each dose of glofitamab (2L subpopulation; glofitamab-exposed; STARGLO)

	Cycle 1		Cycle 2	Cycle 3	Cycle 4+	Overall across all cycles, highest grade
	After 2.5mg dose [C1D8] (n=[redacted])	After 10mg dose [C1D15] (n=[redacted])	After 30mg dose [C2D1] (n=[redacted])	After 30mg dose [C3D1] (n=[redacted])	After 30mg dose [C4D1] (n=[redacted])	
Any grade, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: post-hoc outputs for the 2L subpopulation

CRS was manageable with low rates of ICU admission (4/76 patients [5.3%] and no use of multiple pressors. Of those patients with a CRS AE, 28/76 patients (36.8%) received tocilizumab, 39/76 patients (51.3%) corticosteroids, and 18/76 patients (23.7%) both tocilizumab and a corticosteroid to manage their CRS AE. Low flow oxygen was used by 9/76 patients (11.8%), 2/76 patients (2.6%) required high flow oxygen, and fluids were required by 10/76 patients (13.2%) (Table 34).

The use of tocilizumab and management of CRS

[redacted]

[redacted] (Table 34).

Table 34: Summary of tocilizumab use and management of CRS (STARGLO)

Management in patients with CRS	Glofit-GemOx (glofitamab-exposed)
ITT population	**(n=76)**
Tocilizumab	28 (36.8%)
Corticosteroids	39 (51.3%)
Tocilizumab + corticosteroids	18 (23.7%)
ICU	4 (5.3%)
Fluids	10 (13.2%)
Single pressor	4 (5.3%)
Multiple pressors	0
Oxygen low flow	9 (11.8%)
Oxygen high flow	2 (2.6%)
Positive pressure	0
2L subpopulation	**(n=[redacted])**
Tocilizumab	[redacted]
Corticosteroids	[redacted]
Tocilizumab + corticosteroids	[redacted]
ICU	[redacted]
Fluids	[redacted]
Single pressor	[redacted]
Multiple pressors	[redacted]
Oxygen low flow	[redacted]
Oxygen high flow	[redacted]
Positive pressure	[redacted]

CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

2.11.4.2 Neurologic adverse events

Neurological AEs (NAEs) included preferred terms (PTs) reported from the Nervous System Disorders and Psychiatric Disorders system organ classes. NAEs (of any grade) were reported in [redacted] of patients in the Glofit-GemOx (glofitamab-exposed) arm and in [redacted] of patients in the R-GemOx arm. The most commonly reported PTs of any grade (≥ 3% of patients) are listed in Table 35.

There was a [redacted] of serious neurological AEs in the Glofit-GemOx (glofitamab-exposed) arm ([redacted]), and [redacted] were reported in the R-GemOx arm. Nevertheless, NAEs are considered a potential risk for glofitamab that will be followed up by routine pharmacovigilance.

Table 35: Neurologic adverse events (safety-evaluable population; STARGLO)

	R-GemOx n=88	Glofit-GemOx (glofitamab-exposed) n=172
Any grade AE, n (%)	[redacted]	[redacted]
Grade 1–2	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]
Individual AE terms in ≥3% patients, n (%)		
Peripheral sensory neuropathy	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Polyneuropathy	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR

2.11.5 Deaths

At the CCOD of 16 February 2024, [redacted] of the 260 patients ([redacted]) in the safety-evaluable population had died. Deaths were [redacted] in the R-GemOx arm ([redacted]/88; [redacted]) compared with the Glofit-GemOx arm ([redacted]/172; [redacted]).

The most frequent cause of death was [redacted], which accounted for [redacted] in the Glofit-GemOx arm ([redacted]; [redacted]) compared with the R-GemOx arm ([redacted]; [redacted]).

Deaths due to AEs occurred in a [redacted] in the Glofit-GemOx arm ([redacted]; [redacted]) population compared with the R-GemOx arm ([redacted]; [redacted]). Of the deaths within 30 days from last study drug, AEs accounted for [redacted] ([redacted]) deaths in the Glofit-GemOx population and [redacted] ([redacted]) deaths in the R-GemOx population. Of the deaths occurring > 30 days from last study drug administration, [redacted] ([redacted]) deaths in the Glofit-GemOx population and [redacted] ([redacted]) deaths in the R-GemOx population were due to AEs.

Fatal AEs were the cause of [redacted] in the Glofit-GemOx population ([redacted]; [redacted] of deaths) compared with the R-GemOx population ([redacted]; [redacted] of deaths). The most common fatal AE was [redacted], which caused [redacted] of deaths ([redacted]) in

the Glofit-GemOx population. There were [redacted] COVID-19 fatal AE in the R-GemOx population (Table 33).

The proportion of deaths in the 2L subpopulation [redacted], respectively, in the R-GemOx arm and [redacted] in the Glofit-GemOx arm. The timing of deaths with respect to end of treatment (≥ 30 / <30 days from last study drug administration) [redacted] compared with the whole study population. COVID-19 caused [redacted] in the Glofit-GemOx population and [redacted] in the R-GemOx population (Table 33).

Table 36: Deaths (safety-evaluable population; STARGLO)

	R-GemOx	Glofit-GemOx (glofitamab-exposed)
Whole population	**n=88**	**n=172**
Total deaths	[redacted]	[redacted]
Primary cause: progressive disease AE	[redacted]	[redacted]
Days from last study drug administration: ≤ 30 days > 30 days	[redacted]	[redacted]
Deaths ≤ 30 days from last study drug administration with AE as primary cause	[redacted]	[redacted]
Deaths > 30 days from last study drug administration with AE as primary cause	[redacted]	[redacted]
Fatal AEs: Total COVID-19	[redacted]	[redacted]
2L subpopulation	**n=55**	**n=108**
Total deaths	[redacted]	[redacted]
Primary cause: progressive disease AE	[redacted]	[redacted]
Days from last study drug administration: ≤ 30 days > 30 days	[redacted]	[redacted]
Deaths ≤ 30 days from last study drug administration with AE as primary cause	[redacted]	[redacted]
Deaths > 30 days from last study drug administration with AE as primary cause	[redacted]	[redacted]
Fatal AEs: Total	[redacted]	[redacted]

COVID-19	[redacted]	[redacted]

CCOD: 16 Feb 2024
Source: STARGLO_updated_CSR and post-hoc outputs for the 2L subpopulation

2.12 Ongoing studies

Patient follow-up for the STARGLO study (GO41944) is ongoing, with the next clinical cut-off date planned for [redacted] when analyses will be conducted for publication of longer follow-up. [redacted] will follow until [redacted] of follow-up data are published.

2.13 Interpretation of clinical effectiveness and safety evidence

High-dose chemotherapy with ASCT is a potentially curative option for R/R DLBCL but is only suitable for younger, fit patients who demonstrate chemosensitive disease and have access to a transplant centre (Tilly et al. 2015). There is a high unmet need for effective off-the-shelf therapies for patients with R/R DLBCL who are ineligible for ASCT. In the UK, R-GemOx is the most commonly used systemic therapy for these patients in the 2L; however, patients often discontinue treatment after a few cycles due to disease relapse or a refractory response, and five-year survival is only 13.9% (83). At recent advisory boards, UK clinical experts described 2L treatments for ASCT-ineligible patients as a ‘stepping stone’ to 3L treatments, such as CAR T-cell therapy and bispecific antibodies (80, 90). As such, patients may be exposed to 2L therapy that is ineffective whilst associated with significant toxicity and may not be able to access 3L treatments due to failing health, rapidly progressing disease or death. There is therefore a significant unmet need for effective therapies to treat DLBCL after first relapse in patients who are ineligible for ASCT.

The Glofit-GemOx regimen evaluated in the pivotal STARGLO study was designed to intentionally leverage key synergies in the respective mechanisms of action for each agent, with the aim to develop a new treatment regimen with enhanced efficacy while maintaining a similar level of overall tolerability. In the study, the safety and efficacy of Glofit-GemOx was evaluated in comparison with R-GemOx. At recent advisory boards, a panel of UK lymphoma experts agreed that the demographics and baseline characteristics of the STARGLO population was broadly generalisable to the UK treatable 2L, transplant-ineligible DLBCL population (80, 90). At the primary analysis, the primary endpoint of OS was met, with a 41% reduction in the risk of death in patients treated with Glofit-GemOx compared to patients treated with R-GemOx. Median IRC-assessed PFS was 12.1 and 3.3 months, respectively (HR=0.37), and the IRC-assessed CR rate was 50.3% and 22%, respectively. Results of the updated analysis of STARGLO, representing up to an additional 10.5 months

of follow-up data, support the conclusions from the primary analysis, and further confirm the durability of responses achieved with Glofit-GemOx combination therapy. The data for OS and the key secondary efficacy endpoints [redacted].

Based on the analyses of cumulative safety data collected until the later CCOD, the safety profile of the Glofit-GemOx combination was tolerable and consistent with the known risks of the individual study drugs:

- CRS was experienced in 44.2% of patients in the Glofit-GemOx arm; most CRS events were grade ≤2, occurred in Cycle 1 and resolved without treatment. [redacted] Grade ≥ 2 CRS was reported in [redacted] of Glofit-GemOx patients, which is [redacted] observed with glofitamab monotherapy (16%) in phase I/II study NCT03075696
- Due to its mode of action resulting in B-cell depletion, serious infections are anticipated with glofitamab administration. SAEs relating to infection occurred in 22.7% of patients on Glofit-GemOx and 12.5% of patients on R-GemOx, [redacted].
- Most neurological AEs were grade [redacted], and these were reported in [redacted] of patients on the Glofit-GemOx arm and [redacted] of patients on the R-GemOx arm.

The safety profile of Glofit-GemOx was [redacted].

In conclusion, glofitamab in combination with gemcitabine/oxaliplatin has demonstrated a significant benefit based on improved OS, PFS and CR rate over R-GemOx, along with a manageable safety profile. This regimen represents an innovative off-the-shelf, fixed-duration treatment that addresses the unmet need for patients with R/R DLBCL NOS who are ineligible for ASCT who have progressed during or after one prior treatment.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

In line with the NICE health technology evaluations: the manual (2022) (107), a systematic literature review (SLR) was conducted to identify published health economic evaluations for DLBCL in the second-line and beyond (2L+) setting. An SLR was previously conducted in May 2016 to identify published economic evaluations in patients with first-line DLBCL; however, this search strategy was not restricted by line of therapy and therefore the previous search strategy could be updated to identify economic evaluations in R/R DLBCL. The search was subsequently updated in August 2021, September 2022 and August 2024. It should be noted that the review of the studies excluded at full publication review for the original SLR did not identify any relevant R/R DLBCL economic evaluations and therefore the current updated SLR fully reflects the available evidence base for this indication.

In brief, electronic database searches (Embase, MEDLINE, EconLit and Evidence Based Medicine [EBM] Reviews) were conducted. Supplementary sources were also hand searched for completeness, including reference lists of included studies, conference proceedings, relevant additional databases and websites, and global health technology assessment (HTA) body websites.

A total of 54 relevant published economic evaluations were identified (108-159), of which 35 were full publications (108-133, 142-147, 150, 160, 161) (Table 37) and 19 were previously published HTA submissions (134-141, 148, 149, 151-159) (Table 38). Details of the SLR can be found in Appendix E.

Fifteen of the included studies were cost-effectiveness analyses (CEAs) and cost-utility analyses (CUAs), having reported incremental cost-effectiveness ratios (ICERs) as cost per quality-adjusted life years (QALYs) and cost per life years gained (LYGs) (109, 113, 122, 123, 127, 129, 133, 142-147, 150, 160). Nineteen studies were cost-utility analyses as they reported cost per QALY only (108, 110-112, 114-121, 124-126, 128, 130, 132, 161). Only one study was a cost-effectiveness analysis; however, this was not explicitly stated and inferred from the outcomes (mean costs and mean life days/survival time) (131).

The following patient populations were modelled across the 35 included economic evaluations (note that the economic evaluation by Wu et al. (108) included both 3L+ and 2L only patients):

- Patients with R/R DLBCL in the 3L+ setting (N=17) (108, 111, 113, 114, 121, 123, 125-129, 132, 145-147, 150, 161)
- Patients with R/R DLBCL reported to be specifically in the 2L+ setting (N=2) (122, 131)
- Patients with R/R DLBCL reported to be specifically in the 2L setting (N=11) (108, 110, 112, 115-120, 160, 161)
- Patients with R/R DLBCL (lines of treatment not specified) (N=6) (124, 130, 133, 142-144)

Of the 35 economic evaluations identified, a range of models were used to model costs and outcomes: partitioned survival models (PSMs) or models with a PSM component (N=25) (109-113, 115, 119-123, 126, 127, 129, 130, 132, 133, 142, 143, 145-147, 150, 160, 161), (including a hybrid decision tree and PSM (N=3) (119, 121, 123), a hybrid decision tree and semi-Markov PSM (N=2) (116, 146), a partitioned survival mixture cure model (N=1) (126), a semi-Markov PSM (N=1) (133)), a Markov model (N=5) (108, 117, 124, 125, 128), a decision tree (N=1) (144), a state-transition, microsimulation (N=1) (118), and a discrete event simulation (N=2) (114, 131).

Figure 11: PRISMA flow diagram for SLR of economic evaluations

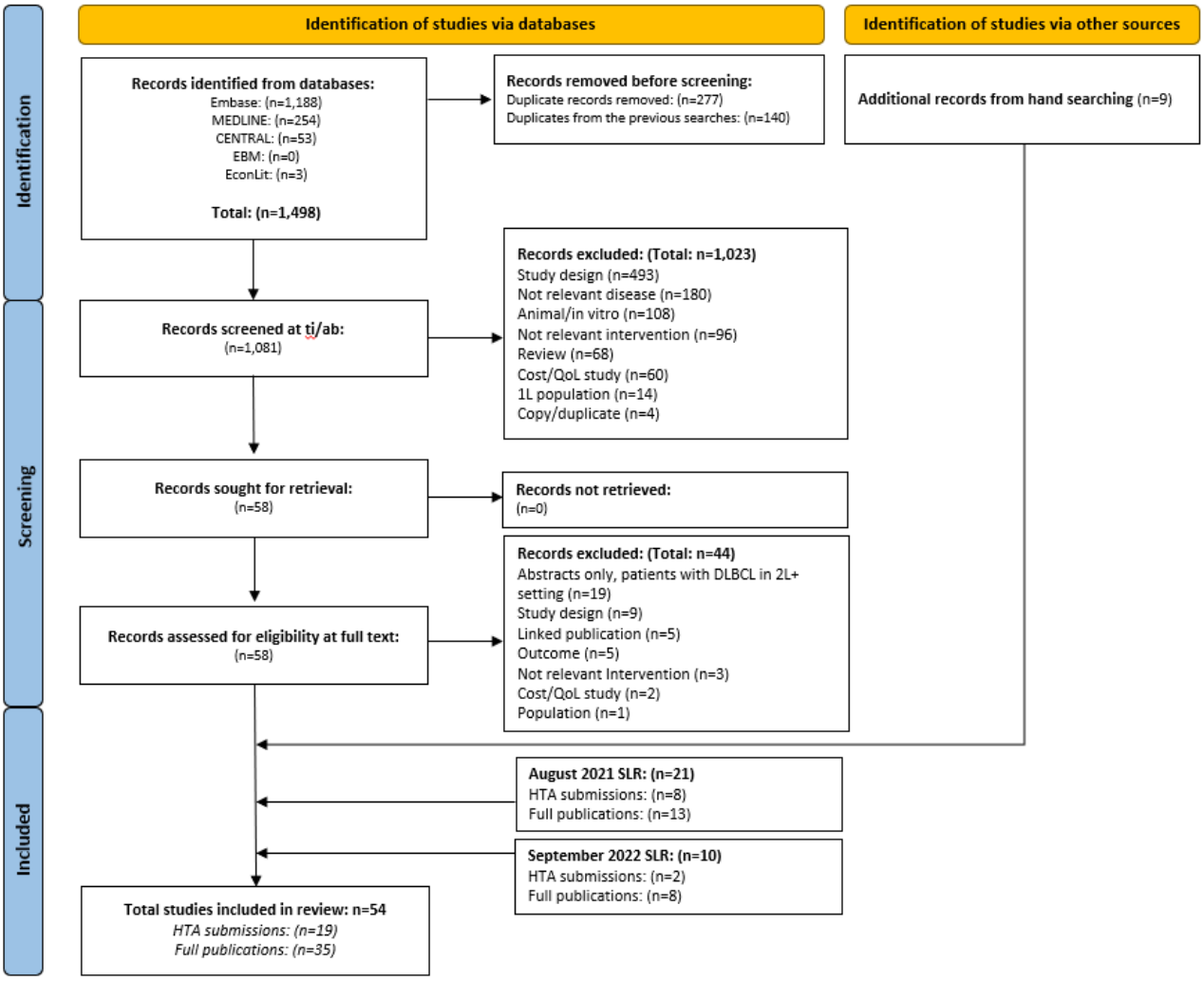


Table 37: Summary list of published cost-effectiveness studies (N=35)

Study	Type of study	Country	Population	Intervention(s)	Comparator(s)
Bastos-Oreiro, 2022 (142)	CEA/CUA	Spain	Patients with R/R DLBCL (mean age 58 years)	Axi-cel	Tisagenlecleucel
Betts, 2020 (122)	CEA/CUA	US	Patients with R/R DLBCL after ≥1 line of chemotherapy, aged ≥18 years old, who were ineligible for HSCT based on the GO29365 trial	Polatuzumab vedotin + bendamustine + rituximab	Bendamustine + rituximab
Calamia, 2021 (143)	CEA/CUA	US	Patients with R/R DLBCL who were ineligible for ASCT	Polatuzumab vedotin + bendamustine + rituximab	Tafasitamab + lenalidomide
Carey, 2023 (121)	CUA	Ireland	Patients with R/R DLBCL (starting age 56 years; 61% male)	Tisagenlecleucel	Salvage chemotherapy
Cher, 2020 (123)	CEA/CUA	Singapore	Patients (median age 56 years) who have failed two or more lines of systemic therapies, consistent with the trial population reported in the JULIET study	Tisagenlecleucel	Salvage chemotherapy
Choe, 2022 (119)	CUA	US	Patients with R/R DLBCL	Axi-cel (2L) Tisagenlecleucel (2L and 3L+)	SOC
Choe, 2024 (120)	CUA	US	Patients with R/R DLBCL in the 2L setting (aged 60 years; 57% male)	Liso-cel (2L)	SOC
Cummings-Joyner, 2022 (144)	CEA/CUA	US	Patients with R/R DLBCL treated with CAR-T cell therapies	1) Axi-cel 2) Liso-cel	Tisagenlecleucel
Garcia-Sancho, 2024 (160)	CEA/CUA	Spain	Patients with R/R LBCL meeting ZUMA-7 inclusion criteria	Axi-cel (2L)	SOC
Hillis, 2022 (145)	CEA/CUA	Canada	Patients with R/R DLBCL, aged ≥18 years, after ≥2 lines of treatment	Axi-cel	BSC (cyclophosphamide, etoposide, and gemcitabine)
Kambhampati 2022 (117)	CUA	US	Patients with R/R-DLBCL (mean age 65 years), with primary refractory disease or early relapse; <12 months from initial therapy	Axi-cel (2L)	SOC
Kelkar, 2023 (118)	CUA	US	Patients with DLBCL refractory to initial therapies or relapsing within 12 months after initial therapy	Axi-cel (2L) Liso-cel (2L)	SOC

Kymes, 2012 (124)	CUA	US	Patients with relapsed DLBCL, undergoing HSCT	G-CSF + plerixafor	G-CSF alone
Li, 2022 (146)	CEA/CUA	China	Patients with R/R DLBCL, aged ≥18 years, after ≥2 lines of systemic therapy	Axi-cel	Salvage chemotherapy (R-DHAP)
Li, 2023 (116)	CUA	China; US	Patients with R/R LBCL in 2L setting, meeting ZUMA-7 inclusion criteria	Axi-cel (2L)	SOC
Lin, 2019 (125)	CUA	US	Patients (mean age 58 years) with R/R DLBCL after ≥2 lines of therapy or relapsed ≤12 months after SCT	Axi-cel	Tisagenlecleucel
Liu, 2021 (126)	CUA	US	Patients with R/R LBCL after ≥2 lines of systemic therapy	Axi-cel	Tisagenlecleucel
Loftager, 2023 (115)	CUA	Sweden	Transplant-intended DLBCL patients with early R/R after completing 1L chemoimmunotherapy	Axi-cel (2L)	SOC
Masucci, 2024 (114)	CUA	Canada	Adult patients with R/R DLBCL after ≥2 lines of systemic therapy	Tisagenlecleucel	Salvage chemotherapy
Moradi-Lakeh, 2021 (127)	CEA/CUA	Switzerland	Patients (paediatric and young adult patients up to 25 years) with B-cell precursor R/R ALL and adult patients with R/R DLBCL who have received ≥2 lines of chemotherapy, including rituximab and anthracycline, and either have failed ASCT or were ineligible for or did not consent to ASCT	Tisagenlecleucel	Salvage chemotherapy
Oluwole, 2022 (147)	CEA/CUA	US	Patients with R/R DLBCL, aged ≥18 years, after ≥2 lines of systemic therapy	Axi-cel	Liso-cel
Oluwole, 2024a (113) [Update of the CUA reported by Liu 2021 (126); including longer-term follow-up data from ZUMA-1 and JULIET]	CEA/CUA	US	Adult patients with R/R LBCL after ≥2 lines of systemic therapy	Axi-cel	Tisagenlecleucel

Oluwole, 2024b (112) [Update of the CUA reported by Perales, 2022(110); including longer-term follow-up data from ZUMA-7]	CUA	US	Patients with R/R LBCL meeting ZUMA-7 inclusion criteria	Axi-cel (2L)	SOC
Parker, 2023 (111)	CUA	US	Adults with R/R LBCL after at least two prior therapies per the TRANSCEND NHL 001 trial	Liso-cel	1) Axi-cel 2) Tisagenlecleucel
Patel, 2020 (128)	CUA	US	Patients (median age 69 years, 66% male) with R/R DLBCL and median 2 lines of prior therapy who were ineligible for HSCT due to age, comorbidity, performance status, insufficient response to salvage therapy, failed prior transplantation, or patient refusal	Polatuzumab vedotin + bendamustine + rituximab	Bendamustine + rituximab
Perales, 2022 (110)	CUA	US	Patients with R/R LBCL meeting ZUMA-7 inclusion criteria	Axi-cel (2L)	SOC
Qi, 2021 (129)	CEA/CUA	US	Patients with R/R LBCL after ≥2 lines of systemic therapy	Tisagenlecleucel	Salvage chemotherapy
Roth, 2018 (150)	CEA/CUA	US	Patients with R/R LBCL meeting the ZUMA-1 inclusion criteria	Axi-cel	Salvage chemotherapy
Tsutsue, 2024a (109)	CEA/CUA	Japan	Patients with R/R LBCL who received ≥2 prior lines of therapy	Axi-cel	1) Liso-cel 2) Tisagenlecleucel
Tsutsue, 2024b (161)	CUA	Japan	Patients with R/R LBCL meeting ZUMA-7 inclusion criteria	Axi-cel (2L)	SOC
Wakase, 2021 (130)	CEA/CUA	Japan	Patients with R/R DLBCL who were ineligible for, or relapsed after, ASCT	Tisagenlecleucel	Salvage chemotherapy
Wang, 2017 (131)	CEA	UK	Patients with newly diagnosed DLBCL	Initial decision to administer 1L chemotherapy for curative intent	Manage supportively with a palliative approach

Wang, 2021 (132)	CUA	Singapore	Patients with R/R DLBCL after ≥2 lines of systemic therapies	Tisagenlecleucel	Salvage chemotherapy with or without HSCT
Whittington, 2019 (133)	CEA/CUA	US	Patients with R/R B-cell lymphoma	Axi-cel	Chemotherapy
Wu, 2023 (108)	CUA	China	Patients with DLBCL treated in different lines of therapy (untreated and primary refractory patients)	1) Liso-cel 2) Tisagenlecleucel 3) Axi-cel	SOC (with or without ASCT)

1L, first-line; 2L, second-line; ALL, acute lymphoblastic leukaemia; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T cell; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DLBCL, diffuse large B cell lymphoma; G-CSF, granulocyte colony stimulating factor; HSCT, haematopoietic stem cell transplantation; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; R-DHAP, rituximab – dexamethasone, high dose cytarabine, and cisplatin; RR, relapsed/refractory; SCT, stem cell transplant; SOC, standard of care UK, United Kingdom; US, United States.

Table 38: HTA submissions including R/R DLBCL populations

Submission **Study design** **Currency (year)**	**Population summary** **Intervention/comparator**	**Modelling methods**	**Model inputs**
CADTH, 2019 (134) CUA CAD (2017)	**Population:** Adult patients with R/R DLBCL who are ineligible for or relapsed after ASCT (2L+) **Intervention:** tisagenlecleucel **Comparator:** salvage chemotherapy (consisting of rituximab, gemcitabine, cisplatin, and dexamethasone)	• **Model type:** PSM • **Disease pathways:** ○ PFS ○ PD ○ Death • **Time horizon:** 20 years • **Perspective:** payer • **Discount rate:** 1.5%, costs and health outcomes • **Cycle length:** 1 month • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** JULIET, UPenn trial, SCHOLAR-1 **Cost:** NR **HRQoL:** published literature, JULIET
CADTH, 2022a (148) CEA/CUA	**Population:** Adult patients with R/R DLBCL who failed at least 2 prior lines of treatment (3L+)	• **Model type:** decision tree + PSM • **Disease pathways:** ○ Pre-treatment stratification:	**Clinical:** TRANSCEND, JULIET, ZUMA-1, SCHOLAR-1

CAD (NR)	**Intervention:** liso-cel **Comparator:** axi-cel, tisagenlecleucel	(a) CAR-T: (b) Survived and received CAR-T (c) Survived but did not receive CAR-T (d) Died prior to CAR-T infusion (e) Salvage chemotherapy ○ PSM (partitioned survival analysis): (a) PFS (b) PD (c) Dead • **Time horizon:** lifetime (50 years) • **Perspective:** payer • **Discount rate:** 1.5%, costs and health outcomes • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** ○ Cost per QALY ○ Cost per LYG	**Cost:** Canadian Institute for Health Information, Ontario Drug Benefit Formulary, IQVIA Delta PA database, prior CADTH reports, Ontario Ministry of Health and Ontario Ministry of Long-Term Care, INESSS **HRQoL:** TRANSCEND
CADTH, 2022b (149) CUA CAD (NR)	**Population:** Patients with R/R DLBCL who are not eligible for ASCT **Intervention:** tafasitamab + lenalidomide **Comparator:** R-GemOx, R-GDP, GDP	• **Model type:** PSM • **Disease pathways:** NR • **Time horizon:** 20 years • **Perspective:** payer • **Discount rate:** NR • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** L-MIND, RE-MIND2, sponsor-submitted MAIC **Cost:** NR **HRQoL:** NICE TA567

CADTH 2023 (157) CUA CAD (NR)	**Population:** Adult patients with DLBCL or high-grade B-cell lymphoma that is refractory to 1L chemoimmunotherapy or that relapses within 12 months of chemoimmunotherapy **Intervention:** Axicabtagene ciloleucel **Comparator:** SOC (Salvage chemotherapy regimens including R-GDP, R-ICE, R-DHAP, followed by HDT and ASCT in responders	• **Model type:** PSM • **Perspective:** payer • **Disease pathway:** ○ Event-free a) On treatment b) Off treatment ○ Post-event/PD a) On next therapy b) Off treatment ○ Death • **Time horizon:** Lifetime (50 years) • **Discount rate:** 1.5%, costs and health outcomes • **Cycle length:** 1 month • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** ZUMA-7 study (March 2021 data cut) **Cost:** CADTH report, Cancer Care Ontario, Pharmacoeconomic evaluation [internal sponsor's report], CIHI, Ontario Ministry of Health, Ontario Schedule of Benefits and Physician services, ZUMA-7 trial, published literature **HRQoL:** ZUMA-7, JULIET
CADTH 2024a (158) CUA CAD (NR)	**Population:** Patients with R/R DLBCL after ≥2 prior lines of therapy who are ineligible for or unable to access CAR-T cell therapy **Intervention:** Glofitamab **Comparator:** ○ Salvage chemotherapy (rituximab-based regimens represented by R-GDP) ○ Polatuzumab vedotin + bendamustine + rituximab	• **Model type:** PSM • **Perspective:** payer • **Disease pathway:** ○ PFS on treatment ○ PFS off treatment ○ PD ○ Death • **Time horizon:** 20 years • **Discount rate:** 1.5%, costs and health outcomes • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** NP30179, SCHOLAR-1, GO29365 **Cost:** NR **HRQoL:** NP30179
CADTH 2024b (159)	**Population:** Adult patients with R/R DLBCL not otherwise specified, DLBCL transformed	• **Model type:** PSM • **Perspective:** payer	**Clinical:** EPCORE NHL-1 **Cost:** NR

CUA CAD (NR)	from indolent lymphoma, high-grade B-cell lymphoma, PMBCL or FL Grade 3B after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T cell therapy **Intervention:** Epcoritamab **Comparator:** Polatuzumab vedotin + bendamustine + rituximab	• **Disease pathway:** NR • **Time horizon:** Lifetime (30 years) • **Discount rate:** NR • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**HRQoL:** NR
NICE TA306 (138) CUA GBP (NR)	**Population:** Adult patients with multiply R/R aggressive non-Hodgkin's B-cell lymphoma (2L+) **Intervention:** pixantrone **Comparator:** physician's choice	• **Model type:** Semi-Markov model • **Disease pathways:** ○ No progression (a) Patients on initial 3L or 4L treatment (b) Patients who discontinued 3L or 4L treatment but had not experienced progression ○ Progressive ○ Relapse • **Time horizon:** 23 years • **Perspective:** payer • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 week • **Half cycle correction:** yes • **Outcomes:** Cost per QALY	**Clinical:** PIX301 (aggressive B-cell population) **Cost:** NHS reference costs, NHS Commercial Medicines Unit's eMIT database **HRQoL:** published literature
NICE TA559 (135) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL, PMBCL, and transformed FL who are ineligible for ASCT (2L+) **Intervention:** axi-cel	• **Model type:** PSM • **Disease pathways:** ○ Pre-progression ○ Post-progression ○ Death	**Clinical:** ZUMA-1 study (August 2017 data cut), SCHOLAR-1 **Cost:** PSSRU, National Audit Office, NHS National Schedule of Reference Costs, published literature

	Comparator: BSC (blended comparator of different treatment regimens [GEM, GEM-P, R-GCVP, RVP])	• **Time horizon:** 44 years • **Perspective:** payer (assumed) • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 month • **Half cycle correction:** yes • **Outcomes:** Cost per QALY [Lee, 2023 reported the impact of using a dynamic general population mortality modeling approach versus a conventional static approach using OS curves from TA559 (162)]	**HRQoL:** ZUMA-1, NICE TA306, NICE TA169, published literature
NICE TA567 (136) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL after two or more lines of systemic therapy (3L+) **Intervention:** tisagenlecleucel **Comparator:** salvage chemotherapy or pixantrone monotherapy	• **Model type:** decision tree + PSM • **Disease pathways:** ○ Decision tree: (a) Successfully receive infusion with tisagenlecleucel (and then proceed to PSM for tisagenlecleucel) (b) Do not receive tisagenlecleucel due to manufacturing failure or AEs (therefore discontinue treatment and revert to comparator therapies) (c) Death before tisagenlecleucel infusion ○ PSM: (a) PFS (b) PD (c) Death • **Time horizon:** 46 years • **Perspective:** payer • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 month	**Clinical:** JULIET, published literature **Cost:** JULIET (December 2017 data cut) **HRQoL:** JULIET, published literature

		• **Half cycle correction:** NR • **Outcomes:** Cost per QALY	
NICE TA649 (137) CEA/CUA GBP (NR)	**Population:** Adults patients with R/R DLBCL who are ineligible for HSCT (2L+) **Intervention:** polatuzumab vedotin + bendamustine + rituximab **Comparator:** bendamustine + rituximab	• **Model type:** PSM • **Disease pathways:** ○ PFS ○ PD ○ Death • **Time horizon:** lifetime (45 years) • **Perspective:** payer • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 week • **Half cycle correction:** yes • **Outcomes:** ○ Cost per QALY ○ Cost per LYG	**Clinical:** GO29365 study (October 2018 data cut) **Cost:** NHS reference costs 2017/18, BNF online, National Audit Office, GO29365, published literature **HRQoL:** ZUMA-1, NICE TA306, published literature
NICE TA895 (154) CEA/CUA GBP (2021)	**Population:** Adult patients with primary refractory or early relapse (≤ 12 months) DLBCL after 1 systemic therapy who are intended for transplant (1L+) **Intervention:** Axicabtagene ciloleucel **Comparator:** SOC (R-ICE, R-DHAP, R-ESHAP or R-GDP) followed by HDT/ASCT	• **Model type:** PSM • **Perspective:** payer and societal • **Disease pathway:** ○ Event-free a) On treatment b) Off treatment ○ Post-event a) On next therapy b) Off treatment ○ Death • **Time horizon:** Lifetime (50 years) • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 month (30.44 days) • **Half cycle correction:** Yes • **Outcomes:**	**Clinical:** ZUMA-7 (March 18, 2021 data cut) **Cost:** NHS Reference Costs 2019/20, eMIT 2020, eMIT 2021, MIMS 2021, BNF 2021, BNF 2022, NICE NG52, NICE TA559, NICE TA567, Assumption, published literature **HRQoL:** ZUMA-7, JULIET, assumption, published literature

		○ Cost per QALY ○ Cost per LYG	
NICE TA927 (155) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL who have received at least two prior systemic therapies **Intervention:** Glofitamab **Comparator:** ○ Polatuzumab vedotin + bendamustine + rituximab ○ Axicabtagene ciloleucel ○ Bendamustine + rituximab	• **Model type:** PSM • **Perspective:** payer and societal • **Disease pathway:** ○ PFS ○ PD ○ Death • **Time horizon:** 60 years • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 month • **Half cycle correction:** Yes • **Outcomes:** Cost per QALY	**Clinical:** NP30179 study (June 2022 data cut) **Cost:** NHS reference costs for 2020/21, NHS Business Services Authority, Calculation from NP30179 trial, NICE TA649, NICE TA306 **HRQoL:** NP30179 trial, NICE TA559, NICE TA306
NICE TA947 (156) CEA/CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL and high-grade B-cell lymphoma, after two or more lines of systemic therapy **Intervention:** Loncastuximab tesirine **Comparator:** ○ Polatuzumab vedotin + bendamustine + rituximab ○ Chemotherapy (DHAP, cisplatin + gemcitabine + dexamethasone, ifosfamide + carboplatin + etoposide, ifosfamide + epirubicin + etoposide, rituximab + GemOx, bendamustine + rituximab)	• **Model type:** PSM • **Perspective:** payer and societal • **Disease pathway:** ○ PFS ○ PD ○ Death • **Time horizon:** Lifetime (40 years) • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** 1 week • **Half cycle correction:** Yes • **Outcomes:** ○ Cost per QALY ○ Cost per LYG	**Clinical:** LOTIS-2, GO29365, CORAL extension **Cost:** eMIT/BNF, NHS Reference Costs 2020/21, NHS Reference Costs 2017/18, National Audit Office, NICE TA576, NICE TA567, NICE TA649, NICE GID-TA10645, assumption, published literature **HRQoL:** LOTIS-2

SMC 2189 (139) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL and PMBCL after two or more lines of therapy (3L+) **Intervention:** axi-cel **Comparator:** BSC (blended comparator of different treatment regimens [GEM, GEM-P, R-GCVP, RVP])	• **Model type:** PSM • **Disease pathways:** ○ Pre-progression ○ Post-progression ○ Death • **Time horizon:** 44 years • **Perspective:** NR • **Discount rate:** NR • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** ZUMA-1, SCHOLAR-1 **Cost:** NR **HRQoL:** ZUMA-1, published literature
SMC 2200 (140) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL after two or more lines of systemic therapy (3L+) **Intervention:** tisagenlecleucel **Comparator:** salvage chemotherapy (GemOx and GDP)	• **Model type:** Decision tree + PSM • **Disease pathways:** ○ Decision tree: (a) Successfully receive infusion with tisagenlecleucel (and then proceed to PSM for tisagenlecleucel) (b) Do not receive tisagenlecleucel due to manufacturing failure or AEs (therefore discontinue treatment and revert to comparator therapies) (c) Death before tisagenlecleucel infusion ○ PSM: (a) PFS (b) PD (c) Death • **Time horizon:** 46 years • **Perspective:** NR • **Discount rate:** NR • **Cycle length:** NR	**Clinical:** JULIET, HMRN, CORAL study **Cost:** NR **HRQoL:** JULIET

		• **Half cycle correction:** NR • **Outcomes:** Cost per QALY	
SMC 2282 (141) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL who are ineligible for HSCT (2L+) **Intervention:** polatuzumab vedotin + bendamustine + rituximab **Comparator:** bendamustine + rituximab	• **Model type:** PSM • **Disease pathways:** ○ PFS ○ PD ○ Death • **Time horizon:** 45 years • **Perspective:** payer • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** GO29365 March 2019 data cut **Cost:** NR **HRQoL:** ZUMA-1, previous NICE appraisals for R/R LBCL and R/R DLBCL
SMC 2524 (151) CUA GBP (NR)	**Population:** Adult patients with R/R DLBCL who are not candidates for HSCT (2L+) **Intervention:** polatuzumab vedotin + bendamustine + rituximab **Comparator:** ○ Bendamustine + rituximab ○ R-GemOx	• **Model type:** PSM • **Disease pathways:** ○ PFS (subdivided by whether patients were on/off treatment) ○ PD ○ Death • **Time horizon:** 45 years • **Perspective:** payer • **Discount rate:** NR • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** GO29365 October 2021 data cut **Cost:** NR **HRQoL:** ZUMA-1
SMC 2609 (152) CUA	**Population:** Adult patients with R/R DLBCL and HGBL, after two or more lines of systemic therapy (3L+)	• **Model type:** PSM • **Disease pathways:** ○ PFS	**Clinical:** GO29365 extension study (polatuzumab with bendamustine plus rituximab); LOTIS-2 (**I**oncastuximab tesirine) September 2022 data cut

GBP (NR)	**Intervention:** loncastuximab tesirine **Comparator:** polatuzumab with bendamustine plus rituximab	○ PD ○ Death • **Time horizon:** 40 years • **Perspective:** payer • **Discount rate:** 3.5%, costs and health outcomes • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Cost:** NR **HRQoL:** LOTIS-2
SMC 2628 (153) CUA GBP (NR)	**Population:** Adult patients with DLBCL and HGBL that relapsed within 12 months from completion of, or is refractory to, first-line chemo-immunotherapy (2L) **Intervention:** Axicabtagene ciloleucel **Comparator: s**alvage chemotherapy followed by HDT-auto-SCT in responders	• **Model type:** PSM • **Disease pathways:** ○ Event-free (subdivided into 'on treatment' and 'on next treatment' substates) ○ Post-event (subdivided into 'on next treatment' and 'off treatment' substates) ○ Death • **Time horizon:** 50 years • **Perspective:** payer • **Discount rate:** NR • **Cycle length:** NR • **Half cycle correction:** NR • **Outcomes:** Cost per QALY	**Clinical:** ZUMA-7 March 2021 data cut, EFS; January 2023 data cut, OS **Cost:** NR **HRQoL:** ZUMA-7 (event-free health state); ZUMA-1 (post-event health state)

2L/3L/4L+, second-line/third-line/fourth-line and later lines; ASCT, autologous stem cell transplant; BNF, British National Formulary; BSC, best supportive care; CAD, Canadian Dollars; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DHAP, Dexamethasone, high dose cytarabine, and cisplatin; DLBCL, diffuse large B-cell lymphoma; eMIT, Drugs and pharmaceutical electronic market information tool; FL, follicular lymphoma; GBP, Great British Pounds; GDP, gemcitabine, dexamethasone, and cisplatin; GEM, gemcitabine and methylprednisolone; GEM-P, gemcitabine, methylprednisolone, and cisplatin; GemOx, gemcitabine and oxaliplatin; HDT, High-dose therapy; HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplant; INESSS, Institut national d'excellence en santé et services sociaux; LBCL, large B-cell lymphoma; LYG, life year gained; MAIC, matching adjusted indirect comparison; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PD, progressed disease; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; PSM, partitioned survival model; QALY, quality adjusted life years; R-DHAP, Rituximab – dexamethasone, high dose cytarabine, and cisplatin; R-ESHAP, Rituximab – etoposide, methylprednisolone, cytarabine, and cisplatin; R-GCVP, rituximab, gemcitabine,

cyclophosphamide, vincristine, prednisolone; R-GDP, Rituximab – ifosfamide, carboplatin, and etoposide; R-ICE, Rituximab – ifosfamide, carboplatin, and etoposide; RVP, rituximab, vincristine, and prednisolone; RR, relapsed/refractory; SMC, Scottish Medicines Consortium

3.2 Economic analysis

The economic case presented in this submission is based on a cost-utility analysis assessing the use of Glofit-GemOx versus R-GemOx for the treatment of adult patients with R/R DLBCL after first-line systemic therapy who are ineligible for ASCT. The analysis takes into account a patient access scheme (PAS) discount for glofitamab.

The cost-effectiveness studies identified in Section 3.1 were examined to inform the economic analysis presented in this submission. Previously published modelling approaches were mostly PSMs or Markov models, with the majority of models adhering to the common oncology three-state framework (pre-progression, progressed disease, and death), regardless of modelling type, as this represents the most important clinical outcomes for patients.

PSMs are commonly used in oncology, as detailed in NICE TSD 19 (163), and lend themselves to situations where transitions between all states cannot be explicitly identified and modelled, for example, where post-progression survival cannot be estimated from reported data as only PFS and OS are reported, and comparator data may not be available. It has been demonstrated that there is little difference in estimated outcomes between partitioned survival and Markov models, and that the assumptions underpinning analysis are more relevant than the choice of the modelling approach (164, 165). The largest consideration is whether time to progression or death is expected to be inherently different between arms and whether the model is able to capture these endpoints appropriately (164, 165). PSMs can reflect these relevant clinical endpoints well and are appropriate where data is not available to inform alternative approaches that require more granularity (164, 165). A PSM can therefore capture long-term impact of oncology interventions in terms of both OS and PFS, which were the primary and secondary endpoints in the STARGLO study, respectively.

Importantly, PSMs do not require any PFS to OS surrogacy assumptions and do not translate any PFS benefit into an OS benefit. Therefore, PFS and OS data, being taken directly from the STARGLO trial, better reflect the impact of Glofit-GemOx on the clinical course of R/R DLBCL.

Taking into account the above considerations, a *de novo* three-state PSM was built to inform decision making. This modelling approach is in line with previous TAs in the same indication (135, 137, 155, 156).

3.2.1 Clinical evidence used in the model

The proposed license indication for Glofit-GemOx is for the treatment of adult patients with R/R DLBCL NOS who are ineligible for transplant and have received at least one prior treatment). However the submission focuses specifically on transplant-ineligible patients who have progressed during or after one prior treatment only (i.e. for patients in the 2L setting).

The NICE scope identifies rituximab-based chemotherapy (of which, R-GemOx is considered standard of care for 2L transplant-ineligible DLBCL patients) and Pola-BR as relevant comparators in the 2L setting. Although Pola-BR is recommended by NICE for R/R DLBCL, this regimen is no longer considered a relevant comparator in the R/R DLBCL setting today (see Section 1.3.2.1.2). This is due to the declining use of Pola-BR following the approval of first-line polatuzumab plus R-CHP (the current estimated 2L market share of Pola-BR is [redacted]), together with clinician reluctance to treat R/R patients with bendamustine-containing regimens since this may prohibit future treatment with CAR-T and bispecific monoclonal antibodies (94-96). As such, R-GemOx is the primary comparator for this appraisal.

The STARGLO study is a randomised phase III clinical trial comparing Glofit-GemOx with R-GemOx in transplant-ineligible R/R DLBCL patients, and therefore this study provides comparative evidence for patients who received Glofit-GemOx and R-GemOx in the 2L setting. In the model, data from the STARGLO study have been used to inform the clinical efficacy, safety and time on treatment of Glofit-GemOx and R-GemOx for the treatment of adult patients with R/R DLBCL who are ineligible for ASCT and received one prior line of systemic therapy only. The updated analysis from STARGLO was used in the model to benefit from the longer follow-up time, thereby improving the maturity and reliability of the data.

The STARGLO study is the only study available to provide clinical evidence for Glofit-GemOx in the intended population and can therefore be considered the best available evidence to inform the modelling. All analyses in this submission have been conducted from a National Health Service (NHS)/Personal Social Services (PSS) perspective.

3.2.2 Patient population

Glofit-GemOx is proposed for use within the NHS in England for adult patients with R/R DLBCL who are ineligible for ASCT and have received at least one prior systemic therapy; however, as discussed in Section 1.1, this submission focusses on patients in the 2L setting

only. The rationale for restricting the reimbursement population to these patients only is based on:

- **The available evidence for Glofit-GemOx**: Robust ITCs vs. comparators in the 3L+ setting cannot be conducted or are highly uncertain (see Section 2.10) due to either an absence of aggregated data to enable matching or significant imbalances remaining in matched populations, resulting in a very small effective sample size. Restricting the reimbursement population to the 2L setting is supported by the strength of the available evidence base as approximately two-thirds of patients enrolled in the STARGLO study received Glofit-GemOx or R-GemOx as a 2L treatment and is therefore not limited by small patient numbers.

- **Relevance to NHS clinical practice**: UK clinical experts have confirmed that the greatest unmet need in R/R DLBCL is in the 2L setting, where treatment for transplant-ineligible patients is limited to R-GemOx, therefore the use of Glofit-GemOx would primarily be in the 2L given the lack of effective treatments and availability of glofitamab monotherapy for 3L+ patients (80).

- **Optimising cost-effectiveness**: Given the limitations and challenges in conducting robust ITCs in the 3L+ setting, restricting the population to 2L only where the evidence is strongest reduces uncertainties in the analysis and allows for the most robust case for the cost-effectiveness of Glofit-GemOx to be considered.

The cost-effectiveness model therefore makes use of efficacy data for Glofit-GemOx and R-GemOx from the 2L subpopulation of patients with R/R DLBCL enrolled in STARGLO.

In the base case analysis, baseline patient parameters were derived from the baseline characteristics of the 2L subpopulation from STARGLO, as detailed in Table 39. Clinical experts consulted by Roche concurred that the characteristics were broadly representative of those treated in the UK (80).

Table 39: Baseline parameters in base case – 2L subpopulation only

Parameter	Mean	Source
Age (years)	[redacted]	STARGLO trial
Baseline body weight (kg)	[redacted]	STARGLO trial
Baseline height (cm)	[redacted]	STARGLO trial
Baseline BSA (m^2)	[redacted]	STARGLO trial
Proportion of cohort male	[redacted]	STARGLO trial

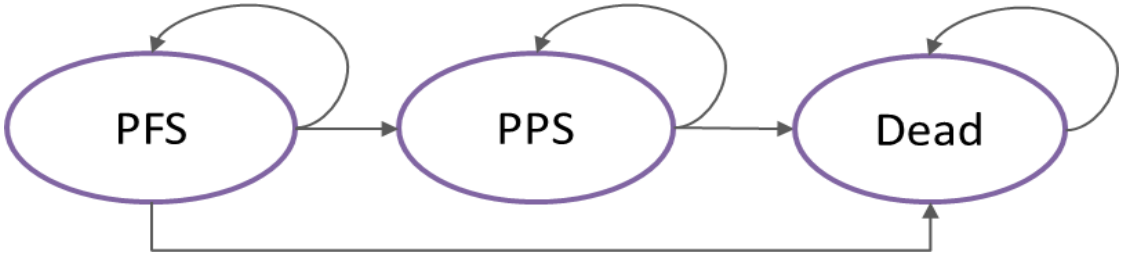
BSA, body surface area

3.2.3 Model structure

A *de novo* partitioned survival (area under the curve [AUC]) model structure was developed, representing PFS, progressive disease (PD), and death. These health states reflect the disease severity and clinical landmarks, as well as key distinctions in mortality, HRQoL, and the use of healthcare resources.

The economic modelling of Glofit-GemOx and R-GemOx in this indication required that comparative efficacy be pieced together from the STARGLO trial. Within the AUC model, health state occupancy was determined by partitioning the proportion of patients alive into PFS and PD at discrete time points based on the OS and PFS curves from the STARGLO trial. The model structure is shown in Figure 12.

Figure 12: Model schematic



PFS, progression-free survival; PPS, post-progression survival

All patients entered the model in the PFS health state and remained in this health state until their disease progressed, or they died. Once in the progressed health state, patients could either remain in the progressed health state or move to the death state. Patients in the model could not transition to an improved health state, i.e., from PPS to PFS.

The economic model uses a 60-year time horizon, which was expected to be sufficiently long to capture all important differences in costs or clinical outcomes between arms as all patients in the model were expected to be in the death state by the end of 60 years. In the base case scenario, background mortality is modelled as a function of the age distribution rather than the mean age of the cohort; this requires a relatively longer time model horizon. As such, the 60-year time horizon can be essentially considered equivalent of a lifetime horizon. Furthermore, at an advisory board meeting, clinical experts commented on the wide age range in the study, providing further rational for modelling background mortality as a function of the age distribution rather than the mean age of the cohort.

The model uses weekly cycles with the proportion of patients in each health state calculated after each cycle. A cycle duration of one week was considered appropriate for this evaluation because it enables the model to reflect differing timings of drug administrations between

arms and the time scale over which patients may experience changes in their symptoms. In addition, transitions between health states can occur at any time within the cycle. In order to account for the over- or underestimation of transitions occurring at the beginning or end of the cycle, half-cycle correction was applied, in line with previous NICE technology appraisals in this disease area (135-137, 155, 156, 166).

3.2.3.1 Derivation of health state occupancy estimates

The decrease in the proportion of patients residing in the progression-free state over time (starting from 100%) was determined by parametric models fit to the PFS curves from the STARGLO data. The PFS curves indicate, for each time point, the proportion of patients who have not progressed or died.

The progressed disease state accommodates all patients who have experienced disease progression but have not yet died. The proportion of patients in this state was calculated as the difference between the proportion of living patients and the proportion of patients who were both living and pre-progression. The transitions into and out from the progression health state were thus not modelled explicitly, a defining feature of PSMs.

Death was modelled as an absorbing state, meaning that all patients eventually enter this state and cannot leave it. The transition rate of patients from the progression-free and progressed disease heath states into the death state was determined by parametric models fit to the OS curves derived from the STARGLO trial. A correction to ensure the hazard of death estimated from the OS curves could not be lower than that from the background mortality of an age- and sex-adjusted cohort from the general population was applied at every model cycle. OS curves indicate the proportion of patients who are alive at a given point in time or, equivalently, the proportion of patients who die during a model cycle dependent on the time since treatment initiation.

In line with the NICE Technology Evaluations Manual, model results are reported in terms of costs, QALYs gained, life-years (LYs) gained, net-health benefit (NHB), net-monetary benefit (NMB), and ICERs (107).

Costs and health-related utilities were allocated by health state to calculate the weighted cost and QALYs per cycle. Cost and health outcomes were discounted at a 3.5% discount rate and, according to the NICE reference case, an NHS and PSS perspective was assumed (107).

3.2.3.2 Derivation of treatment line occupancy

Time to off treatment (TTOT) data from STARGLO was used to model the actual duration on treatment. While patients remained progression-free, they could be on or off treatment. Once in the PD health state, it was assumed that patients would move to a further line of treatment. The proportions of patients on subsequent therapies, and the duration for which they receive them, was informed by UK clinical experts and the STARGLO trial respectively (80). The distribution of subsequent therapies varies by arm in the model as UK clinical experts confirmed that treatment decisions beyond the 2L setting will be informed by prior treatment decisions, i.e. re-treatment with glofitamab monotherapy or treatment with epcoritamab would not be permitted in patients who received Glofit-GemOx.

In previous TAs where treatment stopping rules have been applied (167-169), treatment effect waning has also been applied; this is a common approach in modelling immunotherapies. However, relative treatment effect for PFS is assumed not to wane over time in the current model base-case. This was selected as most of the patients have been off-treatment long enough that substantial changes in the observed hazards for PFS (steeply declining with no signal of increase over time) are not expected to occur beyond the end of the observed data.

3.2.3.3 Outcome measures

The primary model output is the ICER expressed as incremental costs per QALY gained. The model provides an overview of other health economic outcomes such as total QALYs, costs, NMB, NHB, and life-years associated with each treatment in total and in a disaggregated form.

3.2.4 Intervention technology and comparators

The health economic model was developed to compare the cost-effectiveness of Glofit-GemOx vs. R-GemOx for 2L R/R DLBCL. Although the final scope includes regimens for use in the 3L and beyond setting (axicabtagene ciloleucel, loncastuximab tesirine, epcoritamab and glofitamab monotherapy), a feasibility assessment has concluded that robust indirect treatment comparisons cannot be conducted against these treatments; therefore, the reimbursement application has been restricted to 2L use only.

Relapsing or being refractory to 1L treatment remains a major cause of morbidity and mortality for patients with DLBCL. Most relapses occur within 24 months of starting treatment (60, 64) and the majority of patients with R/R disease have poor outcomes (65-67). Patients

who require 2L and subsequent lines of therapy have a particularly poor prognosis and experience disease progression with an increased risk of side effects of treatments (68). Salvage therapy for R/R DLBCL is limited by a patient's ability to tolerate the therapy and the limited efficacy of treatment.

Treatment options for transplant-ineligible R/R DLBCL are limited to immunochemotherapy and Pola-BR. Although axicabtagene ciloleucel is also available in the 2L setting via the CDF (154), patients may only receive this if a clinician considers the patient to be a suitable candidate for transplant, and therefore this regimen is not in scope for the appraisal as patients must be ineligible for transplant in order to receive Glofit-GemOx.

At a recent advisory board, nine UK clinicians confirmed that the majority of patients in the 2L setting would receive rituximab-based chemotherapy, with R-GemOx being the primary regimen used (80). Clinicians also confirmed that R-GemOx is representative of other R-chemo based regimens in the 2L setting in that the efficacy and safety observed is reflective of other chemotherapy regimens in combination with rituximab in this setting (80). Although R-GemOx is well tolerated, survival outcomes with this regimen are poor, with five-year survival rates of just 13.9% (83). Therefore, there remains a significant unmet need for treatment options that offer a survival benefit for 2L R/R DLBCL patients.

While Pola-BR is a NICE approved option for 2L DLBCL, polatuzumab is now available in combination with R-CHP as a first-line treatment for DLBCL (170). Since this NICE recommendation (March 2023), Pola-R-CHP is increasingly becoming the standard of care for front-line DLBCL treatment; market research among UK healthcare professionals conducted by Roche between September to November 2024 indicates that the estimated 1L market share of Pola-R-CHP is [redacted]. This is corroborated by actual IPSOS market share data, which has demonstrated an increased use of this regimen over 2024 - from [redacted] of patients between January and March 2024 to [redacted] between August and October 2024.

As current BlueTeq criteria does not permit retreatment with polatuzumab vedotin, the use and relevance of Pola-BR as an option for R/R DLBCL has been decreasing ever since the approval of Pola-R-CHP. UK clinical experts confirmed to Roche at the advisory board meeting that Pola-BR is now rarely used in the 2L setting (80). This is partly due to the increasing use of front-line Pola-R-CHP but also due to a tendency among clinicians to avoid bendamustine-containing regimens in 2L patients since this can cause severe and prolonged T-cell depletion, thereby precluding the use of CAR-T therapy or bispecific antibodies (glofitamab monotherapy and epcoritamab) in the 3L and beyond setting (94-96). This view

is also corroborated by market share data obtained by the company, which has seen a decrease in Pola-BR use as a 2L regimen from [redacted] in January-March 2024, to just [redacted] in the August-October 2024 data read out (which is similar to shares seen in June to August and July to September, which was [redacted] in both read outs).

Interestingly, the decline in Pola-BR use seen during this time appears to be replaced by an increase in R-chemo, with market share for this increasing from [redacted] to [redacted] over the same period. Based on clinical opinion that states that R-GemOx is the standard of care for 2L patients not eligible for transplant, it is assumed that this is the most commonly prescribed R-chemo regimen within this market share data.

Given the opinion of UK clinicians, the trend shown in the market share data, the rationale to avoid bendamustine-containing regimens in the 2L setting and BlueTeq restrictions around re-exposure to polatuzumab, Roche considers Pola-BR to no longer be a relevant comparator for R/R DLBCL. Therefore, R-GemOx remains the sole comparator for the current appraisal.

3.3 Clinical parameters and variables

3.3.1 Evidence synthesis

Evidence to describe the characteristics of the patient population and the effectiveness of Glofit-GemOx compared with R-GemOx was derived from STARGLO. The patient baseline characteristics that are used as inputs in the CEM are provided in Table 39 and are based on the baseline characteristics for the 2L subpopulation enrolled in STARGLO.

3.3.2 Survival analysis

The follow-up period for PFS and OS in the STARGLO trial was shorter than the model lifetime horizon; therefore, extrapolations were required from PFS and OS data.

For the base case, parameters for each arm were selected in line with recommendations in TSD 14 (150). The base case parametric extrapolation for each treatment was selected on the basis of goodness of fit to the data using the Akaike Information Criterion and Bayesian Information Criterion (AIC and BIC), as well as by graphical assessment of each parametric function. The AIC ranking was followed by graphical assessment of the visual fit of the distribution to the data compared with the KM curve and assessment of the empirical hazard data to see if it was suggestive of specific distributions (such as a constant hazard suggesting an exponential). Distributions that were poor visual fits or produced clearly

implausible projections were discarded, with the remaining distribution with the lowest AIC statistic considered for use in the base case. The chosen distributions were validated for long-term plausibility by clinical experts at the advisory board (80).

3.3.3 Progression-free survival

PFS was a secondary endpoint in the STARGLO trial. The median PFS was statistically significantly greater in the Glofit-GemOx arm (20.4 months) compared with R-GemOx (5.6 months) in the 2L subpopulation (stratified HR=0.41, p=0.0003).

Table 40: STARGLO PFS results – 2L subpopulation

	R-GemOx n=57	Glofit-GemOx n=115
Patients with event, n (%)	51 (44.3)	27 (47.4)
Median PFS (months), 95% CI	5.6 (3.0, 13.1)	20.4 (9.2, NE)
HR (stratified), 95% CI; p value	0.41 (0.25, 0.67; p<0.0003)	

CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

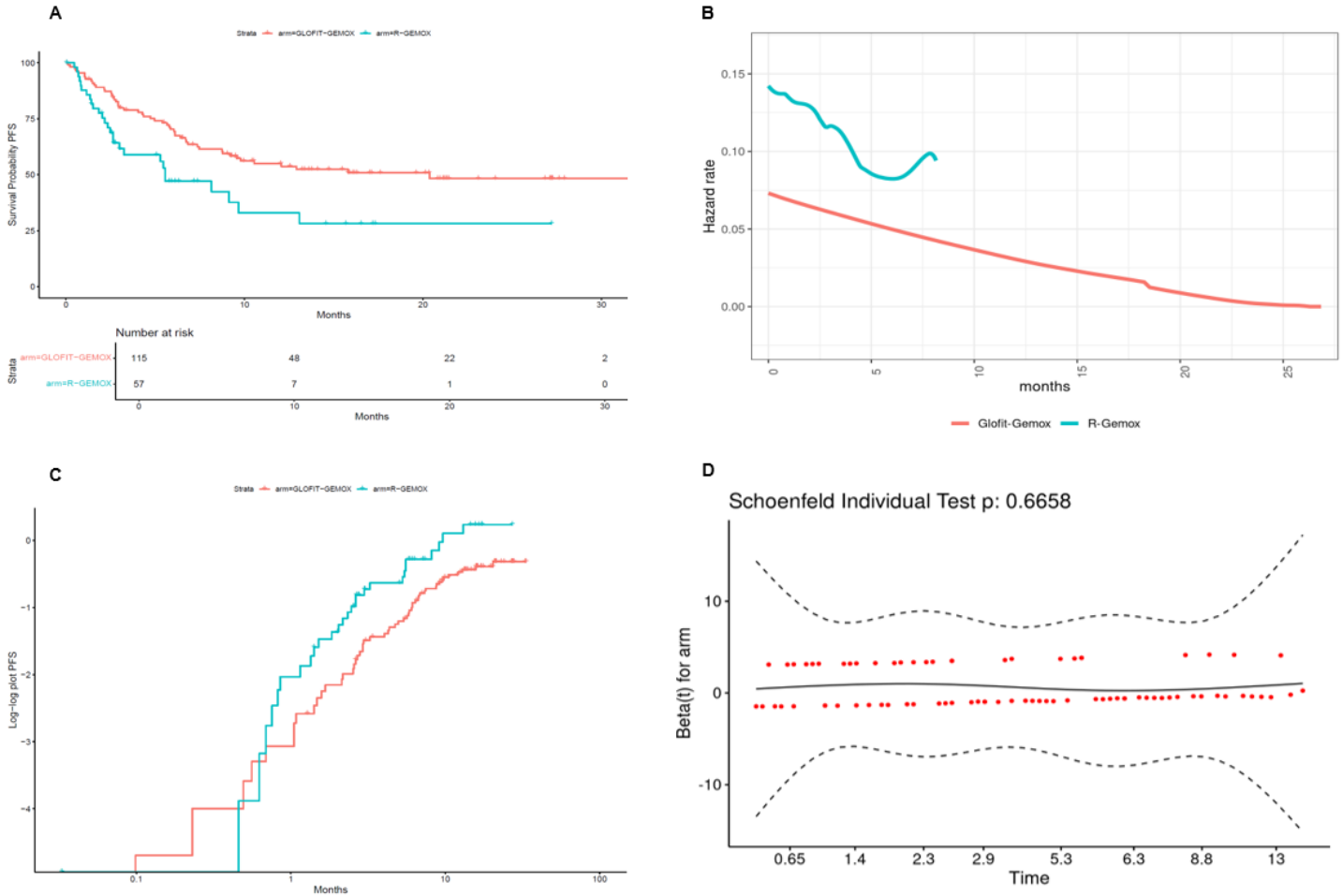
The PFS KM curves for Glofit-GemOx and R-GemOx (Figure 13, panel A) clearly demonstrate a reduced mortality risk for patients treated with Glofit-GemOx compared to R-GemOx. The Schoenfeld test (p=0.6658) (Figure 13, panel D) would allow acceptance of the proportional hazards assumption, but as the log-log plot shows convergence at the earlier time points (Figure 13, panel C), the proportional hazards assumption was rejected and the PFS curves were fitted independently.

In the base case, standard parametric distributions were used to extrapolate PFS from STARGLO over the time horizon of the model for the Glofit-GemOx arm independently. The Glofit-GemOx base case distribution was based on the overall goodness of fit and clinical plausibility of the extrapolations.

Analysis of survival and hazard plots suggest a monotonic hazard rate for Glofit-GemOx (with a continuous decline in hazard rate), whereas the hazard rate for R-GemOx is non-monotonic (Figure 13, panel B). Although the shape of the hazard for Glofit-GemOx is compatible with the exponential and Weibull distributions, clinical experts at the UK advisory board considered that these distributions underestimated the long-term PFS for Glofit-GemOx (80). Furthermore, visual inspection of the curves demonstrates that the exponential distribution overestimates PFS at early stages of the model (Figure 14), which is supported by this distribution having the worst AIC/BIC ranking. Moreover, NICE DSU TSD 14 recommends to fit the same distribution to both treatment arms when fitting individual

parametric models to each arm, as different distributions allow very different shapes and would require greater justification (171).

Figure 13: PFS KM, hazard plot, log-log plot and Schoenfeld test for Glofit-GemOx vs. R-GemOx



Panel A: PFS KM curves for Glofit-GemOx vs. R-GemOx, 2L only; B: hazard plot for PFS, Glofit-GemOx vs. R-GemOx; C: log-log plot; D: Schoenfeld test

Figure 14. PFS Hazard rate and survival plots considered for Glofit-GemOx and R-GemOx

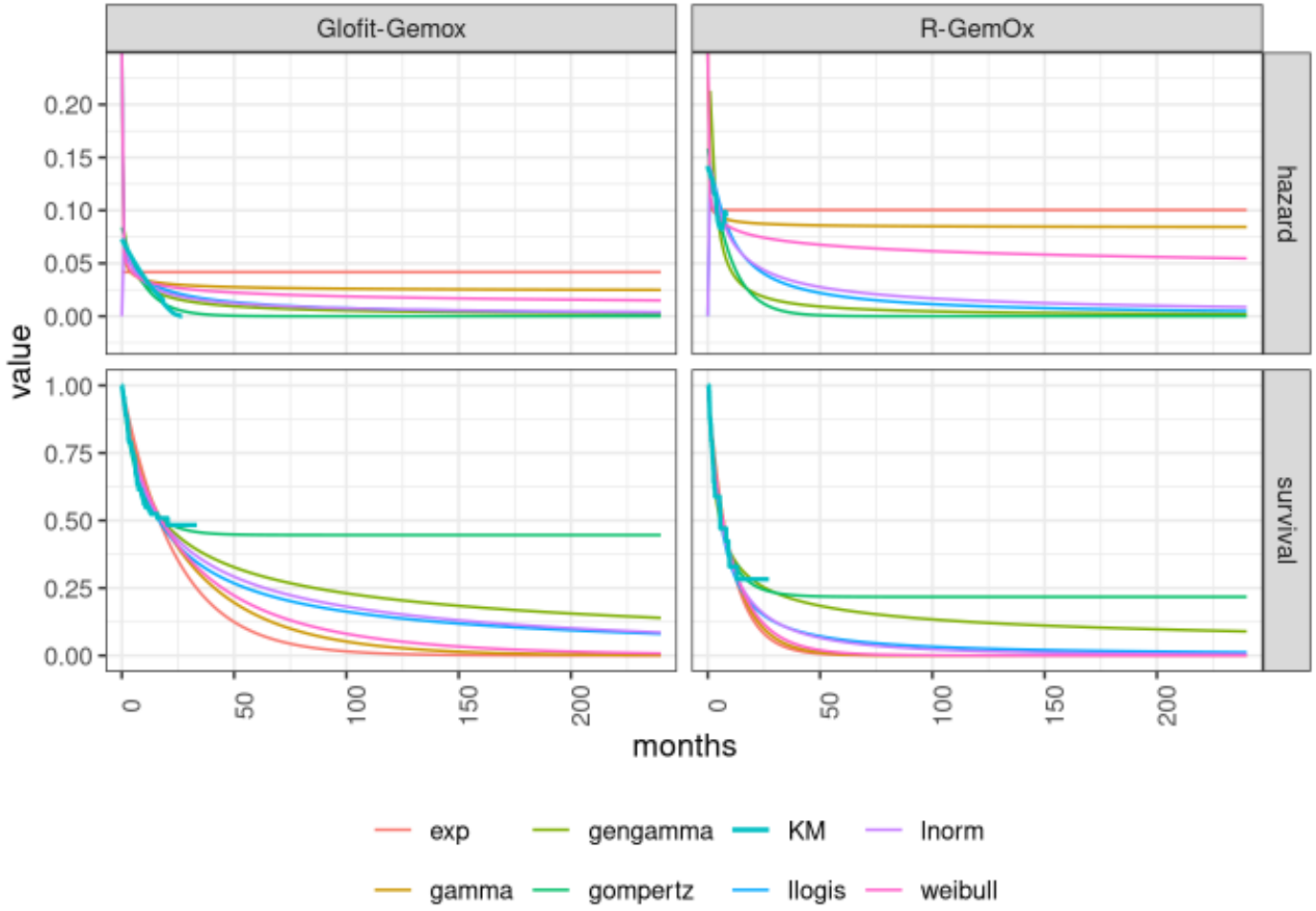


Table 41 summarises the AIC and BIC values for each extrapolation, with a lower AIC or BIC value indicating a better fitting model. Based on these values, the Gompertz distribution is shown to be the best fit for Glofit-GemOx; however, when visually evaluating the curves (Figure 14), this distribution yields clinically implausible estimates of long-term PFS. Log-normal was the second-highest ranked distribution, with the log-logistic and generalised gamma distributions being within five points of the log-normal distribution, indicating that there is not a strong rationale for these distributions to be selected over log-normal on the basis of statistical fit (172). For R-GemOx, the generalised gamma and log-normal distributions are the highest ranked AIC and BIC ranked distributions respectively; however, when evaluating the curves the generalised gamma overestimates the proportion of patients progression-free at 5 (and 10) years in the model (21%) compared to published estimates of 13% at 5 years in the literature (83).The Gompertz distribution is also a reasonable fit based on AIC/BIC statistics. However, as with the generalised gamma, this distribution also overestimates long-term PFS.

Table 41: Summary of goodness-of-fit data for PFS (standard parametric independent models)

	Exponential	Weibull	Log-normal	Gen gamma	Log-logistic	Gompertz	Gamma
Glofit-GemOx							
AIC	428.086	423.427	417.119	418.415	419.001	413.477	425.030
BIC	430.831	428.917	422.609	426.609	424.491	418.996	430.520
AIC Ranking	7	5	2	3	4	1	6
BIC Ranking	7	5	2	4	3	1	6
R-GemOx							
AIC	180.121	181.124	174.986	173.361	176.795	176.998	181.763
BIC	182.165	185.210	179.072	179.490	180.881	181.084	185.849
AIC Ranking	5	6	2	1	3	4	7
BIC Ranking	5	6	1	2	3	4	7

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Clinical experts at the advisory board considered that both the log-normal and log-logistic model produced the most plausible PFS estimates for Glofit-GemOx, while the log-normal and log-logistic models provided the best longer-term estimations of PFS for R-GemOx.

Taking the above factors into account the log-normal distribution was chosen for both Glofit-GemOx and R-GemOx base case. Alternative distributions have been explored in scenario analyses.

3.3.4 Overall survival

OS was the primary endpoint in the STARGLO trial. More patients experienced an event in the R-GemOx arm compared with the Glofit-GemOx arm (49.1% vs. 38.3%). The median OS was not reached in the Glofit-GemOx arm but was 15.7 months in the R-GemOx arm; stratified HR of 0.67 (95% CI: 0.41, 1.07; p=0.0916).

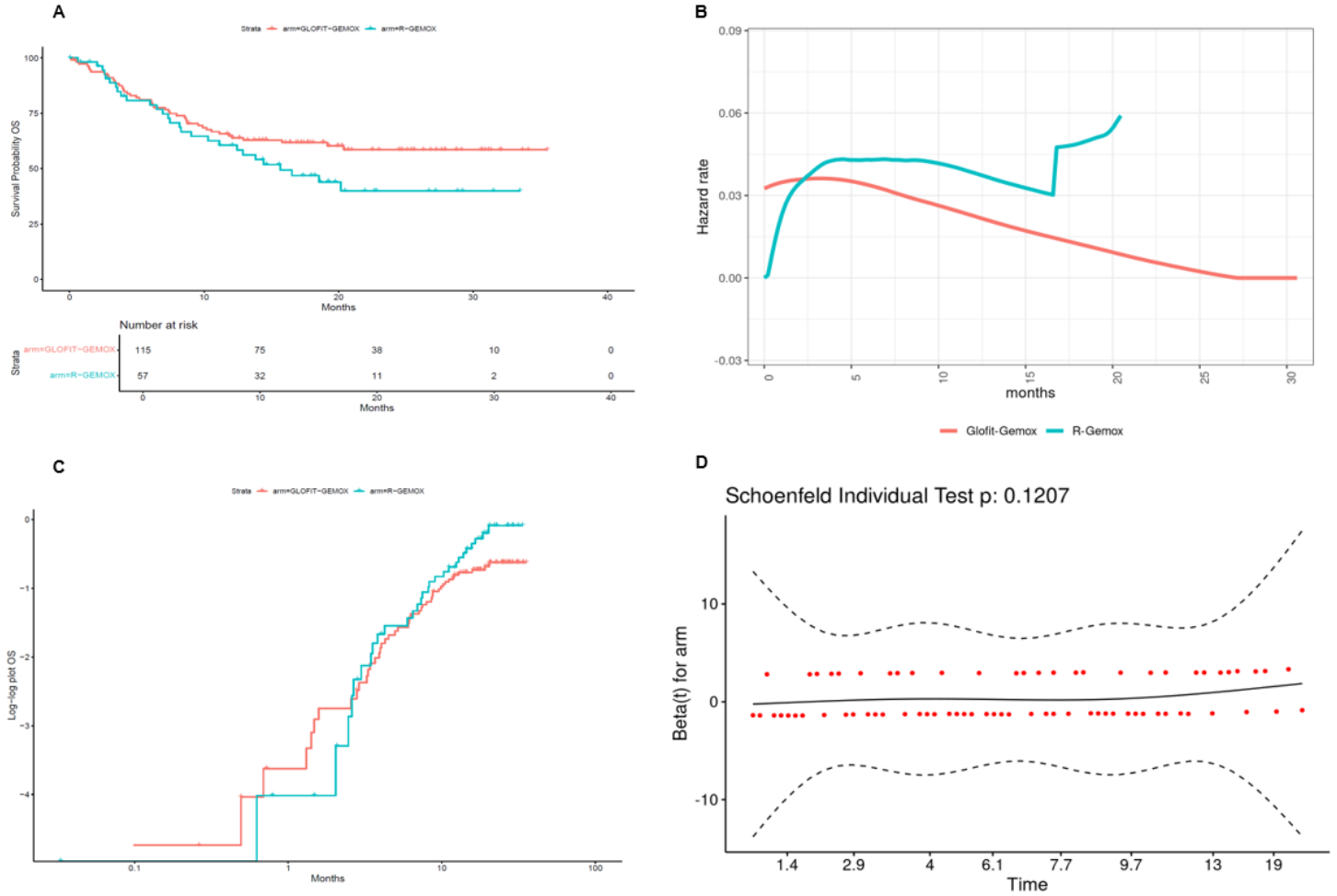
Table 42: STARGLO OS results – 2L only patients

	R-GemOx n=57	Glofit-GemOx n=115
Patients with event, n (%)	28 (49.1)	44 (38.3)
Median OS (months), 95% CI	15.7 (10.3, NE)	NE (20.4, NE)
HR (stratified), 95% CI; p value	0.67 (0.41, 1.07; p=0.0916)	

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival

The OS KM curves for Glofit-GemOx and R-GemOx (Figure 15, panel A) clearly demonstrate an increased survival benefit for patients treated with Glofit-GemOx compared to R-GemOx. The Schoenfeld test (p=0.1207) (Figure 15, panel D) would allow acceptance of the proportional hazards assumption, but as the log-log plot shows convergence at multiple time points (Figure 15, panel C), the proportional hazards assumption was rejected and the OS curves were fitted independently. Analysis of survival and hazard plots suggest non-monotonic hazard rates for both Glofit-GemOx and R-GemOx (Figure 15, panel B), indicating compatibility with log-normal, log-logistic and generalised gamma distributions.

Figure 15: OS KM, hazard plot, log-log plot and Schoenfeld test for Glofit-GemOx vs. R-GemOx



Panel A: OS KM curves for Glofit-GemOx vs. R-GemOx, 2L only; B: hazard plot for PFS, Glofit-GemOx vs. R-GemOx; C: log-log plot; D: Schoenfeld test

Figure 16: OS Hazard rate and survival plots considered for Glofit-GemOx and R-GemOx

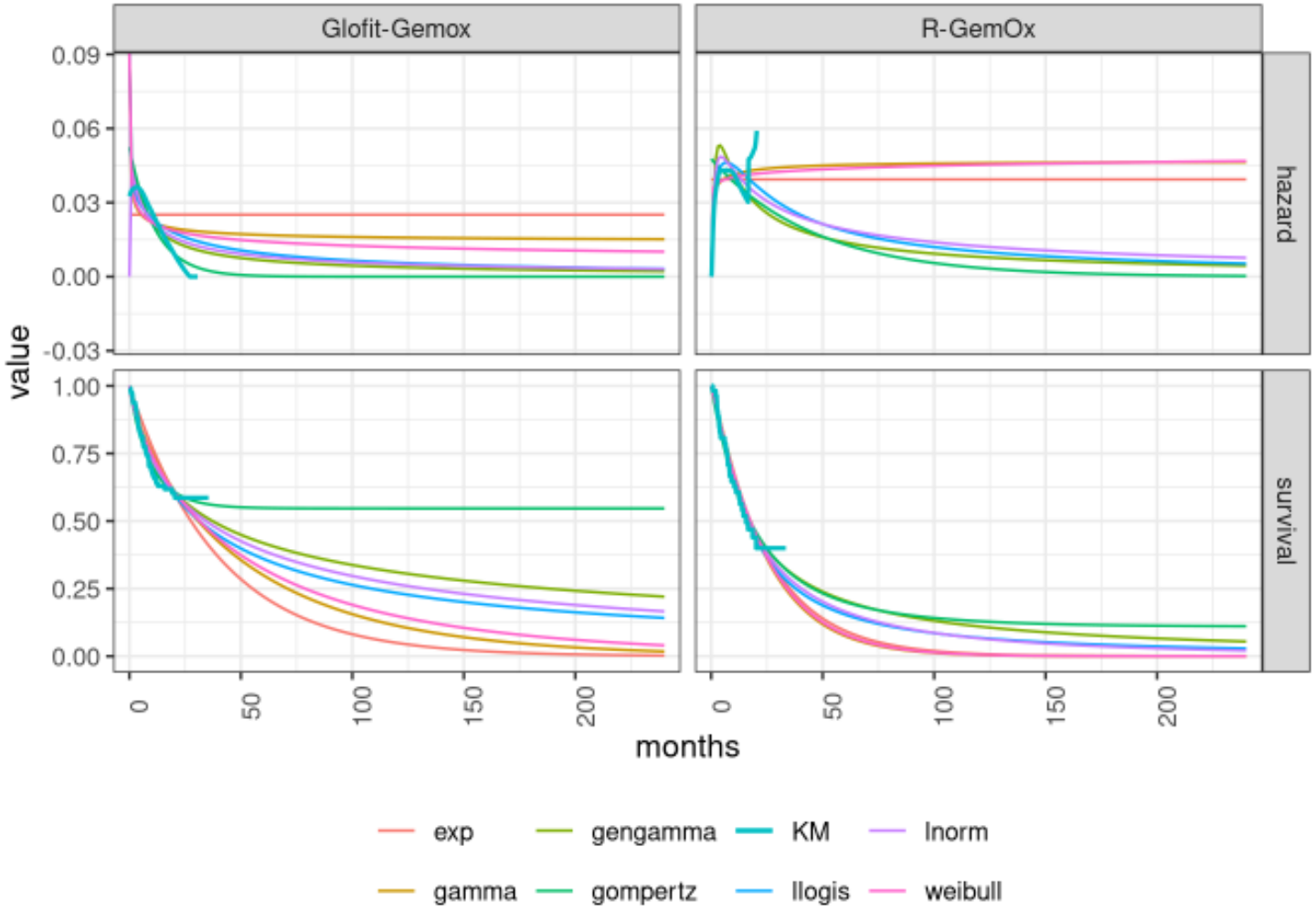


Table 43 summarises the AIC and BIC values for each extrapolation. Based on these values, the Gompertz distribution is shown to be the best fit for Glofit-GemOx; however when visually evaluating the curves (Figure 16), this distribution yields clinically implausible estimates of long-term survival. Log-normal was the second-highest ranked distribution, with the log-logistic and generalised gamma distributions being within five points of this. For R-GemOx, the log normal and exponential distributions were the highest AIC and BIC ranked distributions respectively, but all distributions were within five points of the highest ranked distribution.

Table 43: Summary of goodness-of-fit data for OS (standard parametric independent models)

	Exponential	Weibull	Log-normal	Gen gamma	Log-logistic	Gompertz	Gamma
Glofit-GemOx							
AIC	414.259	411.522	406.577	408.132	408.408	402.273	412.613
BIC	417.004	417.012	412.067	416.367	413.898	407.763	418.103
AIC Ranking	7	5	2	3	4	1	6
BIC Ranking	5	6	2	4	3	1	7
R-GemOx							
AIC	239.135	241.054	237.649	239.277	238.683	240.525	240.848
BIC	241.178	245.141	241.735	245.407	242.769	244.611	244.934
AIC Ranking	3	7	1	4	2	5	6
BIC Ranking	1	6	2	7	3	4	5

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Clinical experts at the advisory board concurred that both the log-normal and log-logistic models produced the most plausible OS estimates for both Glofit-GemOx and R-GemOx (80).

Taking the above factors into account the log-normal distribution was chosen for both Glofit-GemOx and R-GemOx base case. Alternative distributions have been explored in scenario analyses.

3.3.4.1 Long-term remission/survivorship

Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous R/R DLBCL NICE submissions, irrespective of the technology being assessed (154-156, 166). Furthermore, it was agreed in the glofitamab monotherapy appraisal (TA927) that people whose cancer had not progressed for 3 years after starting their third treatment (with

glofitamab or any of the comparators) would remain progression-free and their cancer would not progress at a later date (155).

To account for the previously agreed cure rates in DLBCL, it is assumed that, as with the 3L glofitamab monotherapy appraisal, patients alive and progression-free at 3 years in the current model enter long-term remission. This is supported by the plateau observed in the KM PFS curve for the 2L subpopulation in STARGLO (Figure 13, panel A), together with the fact that just [redacted] of patients in the Glofit-GemOx arm went on to receive at least one subsequent treatment, compared to [redacted] patients in the R-GemOx arm.

This assumption is supported by UK lymphoma experts who concurred that 3 years is a clinically plausible time point for when transplant ineligible DLBCL patients treated in the 2L setting would enter long term remission if progression-free. Furthermore, one clinical expert noted that it is common practice for centres to discharge DLBCL patients who are relapse free 2 years after the end of treatment, irrespective of their line of treatment or what they have been treated with, therefore assuming long-term remission at the 3 year time point from the start of 2L treatment would align to this clinical practise

On entering long-term remission, patients do not continue to progress, revert to near general population utility values (assumed 10% lower vs. general population as per TA927), and do not accrue any further costs. In addition, after 3 years, when the majority of progressed patients in the model have died, mortality risk for the remaining patients reverts to a near general population level (9% excess vs. the general population [in line with value applied from TA559 and TA567, based on a standardised mortality rate (SMR) identified from Maurer 2014] (55)), adjusted to account for potential excess comorbidities (136, 137). Scenarios with alternative cure rates of 2 and 5 years were explored as scenario analyses, together with assuming no quality-of-life detriment and no excess mortality in long-term remission and an alternative source for mortality rate (Howlader et al. 2017 (173)) (see Section 3.12). To maintain consistency, long-term remission is assumed to be treatment independent, with the same assumptions applied to all treatment arms in the model.

3.3.5 All-cause mortality

Background mortality was calculated using age- and gender-specific all-cause mortality rates by year in the general UK population, obtained from the National Life Tables, England & Wales (period expectation of life based on data for the years 2021-2023) (174). Sex-adjusted 1-year mortality rates were calculated as a weighted average of sex-specific mortality rates from this source, adjusted by the relevant cohort sex distribution and an SMR

adjustment to account for increased mortality risk due to excess comorbidities. The CEM allows the use of different data sources for the applied SMR, as per previous NICE TAs (e.g., TA559/TA567).

Background mortality is modelled as a function of the age distribution. The cohort age distribution method was selected for the base case as it better reflects the heterogeneity in the actual background mortality of the patients in the cohort (175) (mean age of [redacted] years, range [redacted]). Furthermore, the use of observed empirical data is more likely to accurately estimate quality-adjusted life expectancy, which is appropriate for potentially curative treatments where survival for cured patients is calculated on the basis of general population mortality (176). This approach is consistent with other approaches that use distributions of patient demographic variables to accurately estimate model parameters in cohort-based economic evaluations (177), and was recently accepted in the appraisal of polatuzumab vedotin for untreated DLBCL (170). Nevertheless, the economic model provides an option to switch to a more traditional average cohort age method to estimate background mortality, and this has been included as a scenario analysis.

3.3.6 Treatment discontinuation

In the base case, TTOT data from STARGLO was used to model the actual duration on treatment, limited to not exceed PFS. As TTOT data was complete from STARGLO, there was no need to fit a distribution to the KM data and, as treatment for glofitamab in the Glofit-GemOx combination is limited to a maximum of 12 cycles, there was no need for curve fitting for extrapolation. Using the KM TTOT data directly removes adding an unnecessary level of uncertainty resulting from curve fitting. Base case TTOT model estimates are provided in Table 44.

Table 44: Base case estimates for TTOT

	Glofitamab	Gemcitabine (Glofit-GemOx)	Oxaliplatin (Glofit-GemOx)	Rituximab	Gemcitabine (R-GemOx)	Oxaliplatin (R-GemOx)
Model results, time on treatment						
Mean number (cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median number (cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean time (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion still on treatment						
0 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.7 Adverse events

AEs are an inevitable consequence of any intervention. To reflect this, AEs were applied in the model affecting costs and QALYs accrued with each intervention. Only treatment-related AEs with a severity grade of 3 or higher were considered in the model (see Table 45) to reflect those events that are most likely to impact cost-effectiveness. This is in line with the approach used in NICE TA559 and TA567. Furthermore, only AEs occurring in over 1% of patients were considered.

Table 45: Treatment-related adverse events considered in the model – 2L subpopulation

Grade 3–5 AEs	Total number of AEs	
	Glofit-GemOx	R-GemOx
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

AEs, adverse events

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life studies

An SLR was conducted to identify studies evaluating HRQoL in R/R DLBCL. Further details of the SLR can be found in the report provided as Appendix F.

Fourteen publications (reporting on twelve unique studies) were identified that reported results for patients with DLBCL in the 2L+ settings (178-191); of these, eight were presented as abstracts/posters only, and six were presented as full publications.

Three studies specifically reported results for the 2L setting (187, 188, 190):

- A full publication reporting utility values for patients with R/R DLBCL enrolled in the multicentre, phase 2 single-arm PILOT study conducted at 18 clinical sites in the US (190)

- A full publication reporting utility values for patients with R/R DLBCL enrolled in the international, multicentre phase 3, open-label RCT (ZUMA-7) (188)
- Poster reporting a health state elicitation study employing the UK general population (187)

Two studies reported results for patients with DLBCL in the 1L, 2L, or 3L+ settings (N=2):

- An abstract reporting a health state elicitation study in patients with DLBCL (182)
- A full publication detailing a retrospective review of data from the Adelphi DLBCL Disease Specific Programme (DSP)™ database (multinational, cross-sectional survey of physicians and adult patients conducted in the US and five European countries [France, Germany, Italy, Spain, and the UK] conducted between January 2021 and May 2021) (185)

3.4.2 Health-related quality-of-life data from clinical trials

Patient-reported outcomes were collected in STARGLO through use of the EORTC QLQ-C30, FACT-Lym LymS, and EQ-5D-5L instruments. Measurement and validation of HRQoL using the EQ-5D directly from patients is consistent with the NICE reference case, and therefore HRQoL from STARGLO is used in the base case analysis (based on the ITT population due to the increased sample size and the assumption that utilities will not differ between 2L and 2L+ patients, although this is explored in a scenario analysis). The data were mapped to the EQ-5D-3L using algorithm by Hernández Alava et al. (192) as per the NICE reference case.

The mapped EQ-5D-3L index values were used to estimate utilities for three health states: PFS on-treatment, PFS off-treatment and PPS. A distinction between PFS on- and off-treatment was made to account for the potential impact of treatment related factors (such as toxicities, burden of administration, etc.) on utility. This allows more granularity in the characterisation of the utility experienced by patients in PFS over time and to better distinguish between the utility for patients receiving treatment until progression and, for example, that of patients off-treatment but in remission, compared to an average PFS utility. This approach is also likely able to better capture the impact of treatment related toxicities on utility compared to estimating individual AEs disutilities, as utility measurements are typically rarely available for the same visits at which AEs take place.

Utility measurements were assigned to PFS or PPS health states by comparing the date of progression with the corresponding date of measurement for the predicted utility. If the date of measurement was later than the date of progression, the patient was set as PPS. If it was

not possible to assign a utility measurement to either PFS or PPS due to censoring, that measurement was classified as unknown, as the patient could have progressed between the date of censoring and the date of measurement. These visits were then excluded from the sample. A similar approach was used for on- and off-treatment states but using the date of treatment discontinuation as reference.

An age adjustment to health state utilities using the method from Ara and Brazier was also implemented (193). This age-adjustment is based on a linear estimation of how utility changes in the general population as a function of sex and age. In this model, the linear function is used to calculate a multiplier, corresponding to proportional utility loss as a function of age, which is used in the final calculation of QALYs for each model cycle.

In addition to utilities for STARGLO 2L only patients, the model also allows the application of utilities from a previous NICE appraisal (TA649) and to test scenarios where proximity to death utilities (on-/off-treatment) are applied (see scenario analyses).

3.4.3 Mapping

EQ-5D-5L data collected during STARGLO were mapped to the EQ-5D-3L using the algorithm by Hernández Alava et al. (192) as per the NICE reference case.

3.4.4 Adverse reactions

All grade ≥3 adverse events for Glofit-GemOx and R-GemOx with an incidence of ≥1% in at least one treatment arm were sourced from the STARGLO study.

Two approaches could be taken regarding the inclusion of the impact of AEs on HRQoL:

1. The assumption that any disutility has already been incorporated in the base case health state utilities through the trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;

2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied

The base case analysis takes the former assumption (disutility has already been incorporated) to avoid double-counting. The adverse events considered in the model are presented in Section 3.3.7.

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

Table 46: Base case utility values and scenario utility values

Scenario	State	Utility values	Standard error
Base case: STARGLO (ITT)	PFS – on treatment	0.758	0.011
	PFS – on treatment	0.751	0.012
	PPS	0.685	0.016
Scenario: STARGLO (2L only)	PFS – on treatment	0.757	0.012
	PFS – on treatment	0.757	0.013
	PPS	0.691	0.021
Scenario: TA649	PFS	0.72	0.03
	PPS	0.65	0.06
Scenario: Proximity to death utilities – on tx	≤ 10 weeks before death	0.729	0.029
	> 10 & ≤ 30 weeks before death	0.727	0.017
	> 30 & ≤ 60 weeks before death	0.764	0.015
	> 60 weeks before death	0.768	0.013
Scenario: Proximity to death utilities – off tx	≤ 10 weeks before death	0.695	0.019
	> 10 & ≤ 30 weeks before death	0.733	0.015
	> 30 & ≤ 60 weeks before death	0.751	0.015
	> 60 weeks before death	0.765	0.017

PFS, progression-free survival; PPS, post progression survival

A brazier age-adjusted health state utility value coefficient was also applied (Table 47). This age-adjustment is a linear estimation of how utility changes in the general population as a function of sex and age. In this model, the linear function was used to calculate a multiplier, corresponding to proportional utility loss as a function of age, which was used in the final calculation of QALYs for each cycle in each treatment model.

Table 47: Brazier age-adjusted coefficients

Parameter	Estimate (SE)
(Intercept)	0.95086
sexM	0.02121
age	-0.00026
age2	-0.00003

SE, standard error.

3.5 Cost and healthcare resource use identification, measurement and valuation

3.5.1 Published costs and resources studies

An SLR was conducted to identify studies describing the costs and resource use associated with the management of patients with R/R DLBCL. Electronic databases were searched via Ovid in August 2021, September 2022, and August 2024 and further supplemented by hand searching of the grey literature. Databases included Embase, MEDLINE, Evidence Based Medicine Reviews, and EconLit. Potentially relevant articles published post-2014 for the NHS Economic Evaluation Database (NHS EED) and the Databases of Abstracts and Reviews of Effects (DARE), and post-2016 for the HTA database were identified via the University of York Centres for Reviews and Dissemination (CRD) website. Supplementary sources searched included conference proceedings, HTA body websites, additional relevant websites such as the National Institute for Health Research (NIHR) HTA, and reference lists of eligible studies and relevant reviews.

A total of 85 studies were identified reporting cost and resource use data for patients with DLBCL in the R/R setting (full publications, N=38; conference abstracts, N=47) (105, 194-277). The majority of studies had a retrospective study design (N=70) (105, 194-209, 211, 212, 214, 215, 217, 218, 220, 221, 223-225, 227, 230-235, 237, 238, 240-250, 252-254, 256-264, 266, 268-276). The remaining studies consisted of cost analyses (N=6) (213, 216, 219, 228, 265, 267), longitudinal studies (N=2) (210, 277), claims database analyses (N=2) (239, 251), a cross-sectional study (N=1) (226), a real-world evidence study (N=1) (236), an economic model (N=1) (255), an economic framework for therapy valuation (N=1) (229), and an analysis of Phase 1 pivotal trial results (N=1) (222). Nine studies analysed data from the clinical studies, TRANSCEND NHL 001 [NCT02631044] (208, 222, 223), TRANSFORM [NCT03575351] (256, 268, 269), NP30179 [NCT03075696] (267), EPCORE NHL-1 [NCT03625037] (267), PILOT [NCT03483103] (268, 269), and JULIET [NCT02445248] (234, 235).

A wide range of patients with R/R DLBCL were reported to have been considered across the 85 included studies. Four studies provided cost and resource use data for the 2L setting only (255, 256, 268, 269). Please refer to appendix G for full details.

3.5.2 Intervention and comparators' costs and resource use

3.5.2.1 Glofitamab costs

The costs of glofitamab, including drug procurement (Table 48), administration (Table 50), and monitoring (Table 51) were applied in the CEM, at specific cycles, based on acquisition, administration and monitoring costs. Unit costs are costed per resource as reported in the NHS reference costs for 2023-2024 (278).

The administration of glofitamab is assumed to take place under supervision at hospital and has been costed as a prolonged infusion, with the first attendance for all appointments taking place in line with the dosing schedule. Subsequent administration is assumed to take place in an outpatient setting, costed as subsequent elements of the chemotherapy cycle.

Glofitamab is administered via intravenous infusion for a maximum of twelve 21-day cycles, according to a step-up dosing schedule in Cycle 1 (2.5 mg on D8, 10 mg on D15) and at a dose of 30 mg in Cycles 2−12. The glofitamab step-up dosing schedule also includes pre-treatment with a single dose of obinutuzumab (1000 mg) 7 days prior to the first dose of glofitamab to mitigate the risk of CRS. As such, vial sharing was not assumed as the step-up dosing regimen for glofitamab does not require the 2.5 mg or 10 mg vials to be split. Gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) were administered IV on Day 2 of Cycle 1 and Day 1 or 2 (per local practice) of subsequent cycles, up to Cycle 8.

As per the glofitamab SmPC (279), all patients must be monitored for at least 24 hours after completion of the first infusion. For subsequent doses, patients who experienced Grade ≥2 CRS (12.79%, average between rates according to ASTCT grading scales in the pooled efficacy population (97)) with the previous infusion should be monitored after completion of the infusion. Glofitamab additional monitoring costs can be seen in Table 51.

Table 48: Glofitamab dosing and acquisition

Dosing (mg)	2.5/10/30
Dose per cycle	As above
Cost (excluding PAS)	£687.00 (2.5 mg); £2748.00 (10 mg)
Pre-treatment – obinutuzumab (excluding PAS)	1000 mg: £3312.00 (Cycle 1: Day 1)
Cost per dose (excluding PAS)	2.5 mg: £687.00 (Cycle 1: Day 8) 10 mg: £2748.00 (Cycle 1: Day 15) 30 mg: £8244.00 (Cycle 2: Day 1)
Administration costs	See Table 50
Monitoring costs	See Table 51

PAS, patient access scheme.

Table 49: Gemcitabine and Oxaliplatin dosing and acquisition

Gemcitabine	
Dosing (mg)	1000 mg/m^2 (Day 2 every 21 days)
Dose per cycle	500 mg/m^2
Cost	£9.86
Cost per dose	1000 mg/m^2: £20.09
Administration costs	See Table 50
Oxaliplatin	
Dosing (mg)	100 mg/m^2 (Day 2 every 21 days)
Dose per cycle	50 mg/m^2
Cost	£17.47
Cost per dose	100 mg/m^2: £25.84
Administration costs	See Table 50

Table 50: Administration costs for Glofit-GemOx and R-GemOx

Component	National cost collection for the NHS	Cost	Inflated costs
Administration (first appointment)	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance (SB14Z)	£570.00	NHS Reference Costs 2023 to 2024 (278)
Administration (subsequent appointments)	Subsequent elements of chemotherapy cycle (SB15Z)	£426.00	NHS Reference Costs 2023 to 2024 (278)

Table 51: Monitoring costs for glofitamab

Component	% pts	Cycles applied for	National NHS cost collection	Cost	Inflated costs
Monitoring (24 hours after first glofitamab infusion)	100	1	Average of malignant lymphoma (currency codes SA31A-F): day case	£488.57	NHS Reference Costs 2023 to 2024 (278)
Monitoring (22 hours for patients experiencing Grade ≥2 CRS after first glofitamab infusion)	12.79	2	2 x average of malignant lymphoma (currency codes SA31A-F): day case	£977.14	NHS Reference Costs 2023 to 2024 (278)

CRS, cytokine release syndrome

3.5.2.2 Patient access scheme (PAS)

A PAS has been applied, comprising a simple discount of [redacted] from the glofitamab list price. In order to best replicate the true economic impact of a positive recommendation for glofitamab, the economic evaluation presented in this submission applies the PAS in the base case analysis (Table 52).

Table 52: Acquisition costs of glofitamab following application of PAS

Vial size	No PAS	PAS
2.5 mg	£687	[redacted]
10 mg	£2,748	[redacted]

PAS, patient access scheme.

Obinutuzumab is used as a pre-treatment ahead of glofitamab administration. As obinutuzumab is a Roche product, the confidential discount is known. Therefore, the PAS price for obinutuzumab ([redacted]) is applied to all of the results reported in Sections 3.10-11.

3.5.2.3 Comparator costs

Comparator dosing and schedule were estimated in accordance with BNF recommendations and assumed no vial sharing where applicable (Table 53). As the dosing for some treatments was weight or body surface area (BSA) dependent, wastage may occur and impacting the cost per treatment cycle. To account for this, an algorithm has been applied in the economic model which calculates the combination of small and large vials to minimise the overall treatment cost. Furthermore, for treatments that are BSA dependent, the base-case analysis assumes that drug dosing is estimated as the planned dosing according to treatment protocols, calculated using individual patient characteristics from the STARGLO trial.

In the R-GemOx regimen, rituximab was given at 375 mg/m^2 every 21 days; gemcitabine and oxaliplatin were as per the Glofit-GemOx arm. This regimen was given up to a maximum of 8 cycles.

Administration costs for the comparators were assumed to be the same as for glofitamab for the first cycle and then costed as subsequent elements of a chemotherapy cycle for all subsequent administrations (Table 50).

Table 53: Comparator dosing and acquisition

Comparator	Unit cost	Source
Rituximab (100 mg)	£314.33	BNF (5)
Rituximab (500 mg)	£785.84	BNF (5)
Gemcitabine (200 mg)	£3.51	eMIT (4)
Gemcitabine (1000 mg)	£9.86	eMIT (4)
Oxaliplatin (50 mg)	£6.47	eMIT (4)
Oxaliplatin (100 mg)	£17.47	eMIT (4)

Table 54: Comparator cost per cycle

Comparator	Cost per cycle
Rituximab	£1,098.23
Gemcitabine	£20.09
Oxaliplatin	£25.84

3.5.3 Treatment costs at subsequent lines of therapy

Cost of subsequent treatments post-progression were included to account for the costs of treatment sequencing in later lines of therapy. All post-discontinuation therapies included are approved in the UK and are reflective of clinical practice in the 3L+ setting. The post discontinuation therapy cost was applied to the proportion of patients who move from the PFS to PPS health state each cycle. This takes into account the mean duration of treatment, the proportion assumed to use each treatment option and the associated cost.

The mean duration on treatment and proportion of patients receiving different subsequent treatments upon progression on each induction treatment are listed in Table 55 and are informed by data from STARGLO and UK clinical expert opinion obtained at an advisory board meeting (80). The proportions of patients receiving different subsequent treatments varies between arms based on prior treatments received, since clinical experts agreed that a patient receiving Glofit-GemOx for instance would not go on to receive glofitamab or epcoritamab monotherapy in later lines in clinical practice. The costs associated with each subsequent treatment is listed in Table 56 and Table 57 shows total cost post discontinuation for glofitamab and all included comparators.

With respect to the costs of administering CAR T-cell therapies, the committee appraising lisocabtagene maraleucel (GID-TA10778) concluded that the tariff cost of £58,964 should be applied for CAR T-cell therapies following feedback from the NHS England Cancer Drugs Fund Lead that this value had been agreed and was applicable for the 2024/25 financial year (280). In the same appraisal, the EAG preferred to exclude the costs associated with

adverse events (estimated by the company as £10,611) from the CAR T-cell tariff cost when applying this for subsequent CAR T-cell therapy use since the costs associated with adverse event management were not applied to other subsequent treatment options. The current appraisal therefore follows this approach with a tariff cost of £48,353 applied in the model.

Administration costs were assumed to be the same as for glofitamab (Table ***50***) for the first cycle and costed as subsequent elements of a chemotherapy cycle for all subsequent administrations.

Subsequent treatment costs are assumed to not apply for patients in long-term remission (progression-free after 30 months – see Section 3.3.4.1). As different proportions of people are assumed to be in long-term remission in each treatment arm, post discontinuation costs are therefore estimated to be different for each modelled treatment (Table 57).

Table 55: Proportion assumed to take each subsequent therapy by arm following 2L therapy

Subsequent therapy	% on Glofit-GemOx	Mean duration in weeks	% on R-GemOx	Mean duration in weeks
BR	5.0	0.4	1.0	4.3
Average R-chemo	10.0	2.6	4.5	2.1
Other chemo regimens (non-R)	5.0	3.2	1.0	2.1
Pola-BR	5.0	10.6	5.0	2.2
Clinical trial/other	15.0	6.1	2.5	6.1
Radiotherapy	4.0	1.0	5.0	1
Allogenic SCT	1.0	1.0	1.0	1*
Axicabtagene ciloleucel	30.0	1.0	30.0	1*
Loncastuximab tesirine	25.0	4.8	5	40.9
Glofitamab	0	0	25	14.6
Epcoritamab	0	0	20	3.6

* One-off treatment

Table 56: Weekly treatment costs for post-discontinuation including administration (list price)

Treatment	Total cost (£)	Comments
BR	927.60	Average cost of BR
Average R-chemo	847.54	Average cost of R-chemo regimens

Other chemo regimens (non-R)	170.87	Average of the non-rituximab based regimens
Pola-BR	4,254.37	Average cost of pola-BR
Clinical trial/other	868.38	Mean of all therapies, excluding one-off, and BSC
Radiotherapy	3,884.93	One-off cost, following approach from Tafa-Len NICE submission (10*admins), costed with NHS reference cost 23/24 (SC21-28Z, SC30Z, SC31Z weighted average)
Allogenic stem cell transplant	82,417.81	One-off cost, estimated as per CAR-T NICE TA559/TA567
Axicabtagene ciloleucel	141,836.67	One off cost
Loncastuximab tesirine	5,566.21	Average cost of loncastuximab tesirine
Glofitamab	2,225.53	Average cost of glofitamab
Epcoritamab	3,155.24	Average cost of epcoritamab

Table 57: Total post-discontinuation costs

Treatment	Total cost
Glofit-GemOx	£52,700.07
R-GemOx	£66,066.37

3.5.4 Resource use costs

Resource use costs were applied to each model cycle a patient was alive. These costs were different between the PFS and post-progression health states and were independent of treatment arm (Table 58). They are therefore considered to represent health care resource use that is specific to disease status rather than treatment arm.

A microcosting approach to resource use costs was taken to determine the resources used in supportive care for each health state or event. Resource use for PFS (on- and off-treatment), PPS and one-off costs at progression were extracted from the appraisal of Pola-BR for R/R DLBCL (TA649), and discussed with clinicians who felt that the approach was reasonable but suggested amendments to the resource estimates based on current clinical experience (80). For instance, district nurse visits should be reduced, with specialist nurse visits increased; radiologist visits should align with the number of scans required; and bone marrow biopsy resource should be set to zero, as per TA954 (166). These resource estimates were then costed using NHS reference costs or applying an appropriate inflation

to 2023 costs, based on the NHS Cost Inflation Index (NHSCII) from the Personal Social Services Research Unit (PSSRU) (281).

No separate terminal care costs were applied in the model, as these costs are expected to be captured in the resource use costs.

The costs applied for resource use, including the costs associated with the PFS and PPS health state, are reported in Table 58. Table 59 shows the one-off costs associated with disease progression. This one-off cost was applied in the cycle that progression takes place.

Table 58: Weekly resource use costs

Unit	Unit cost	Resource use of PFS state on treatment	Resource use of PFS state off treatment	Resource use of progression state	Source
Professional and social services					
Residential care (day)	£190.00	0.75	0.19	0.00	TA649 (137)
Day care (day)	£78.00	0.28	0.07	0.47	
Home care (day)	£35.71	1.17	0.43	2.34	
Hospice (day)	£198.10	0.01	0.00	0.23	
Health care professionals and hospital resource use					
Oncologist (visit)	£204.00	0.33	0.11	0.08	TA649 (137)
Haematologist (visit)	£193.00	0.20	0.05	0.25	
Radiologist (visit)	£157.00	0.08	0.08	0.00	
Nurse (visit)	£57.00	0.38	0.10	0.00	
Specialist nurse (visit)	£57.00	0.58	0.19	0.63	
GP (visit)	£49.00	0.10	0.13	0.83	
District nurse (visit)	£57.00	0.38	0.10	1.00	
CT scan	£184.00	0.08	0.08	0.00	
Inpatient day	£319.00	0.10	0.04	0.05	
Palliative care team	£194.00	0.00	0.00	0.33	
Treatment follow-up					
Full blood counts	£7.00	0.83	0.83	0.25	TA649 (137)
LDH	£7.00	0.50	0.50	0.08	
Liver function	£7.00	0.83	0.83	0.25	
Renal function	£7.00	0.83	0.83	0.08	
Immunoglobulin	£7.00	0.17	0.17	0.08	
Calcium phosphate	£7.00	0.17	0.17	0.25	
Total weekly supportive costs used in model					
Model state			**Used cost**		
Progression-free state			**£475.89**		
Progression-free state off treatment			**£179.65**		
Progression state			**£452.96**		

CT, computed tomography; GP, general practitioner; PFS, progression-free survival

Table 59: One-off progression costs

Unit	Unit cost	Proportion of patients requiring resource	Source
ECG	£142.00	15.9%	NHSSRC 2023/24; EY51Z
MUGA	£378.00	7.9%	NHSSRC 2023/24; RN22Z
MRI	£246.00	20.0%	NHSSRC 2023/24; RD01A
PET-CT	£638.00	85.0%	NHSSRC 2023/24; RN01A
Total one-off progression costs		**% of patients**	**Used cost**
		100	**£643.94**

ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PET-CT, positron emission tomography – computed tomography

3.5.6 Adverse reaction unit costs and resource use

The costs of AEs during the time on treatment were calculated based on the average number of treatment-related AEs per patient per week in STARGLO and the unit cost of these AEs (Table 60). Costs were assumed based on relevant recent technology appraisals and costed using the most recent reference costs.

As noted in Section 3.4.4, only treatment-related AEs with a severity grade of 3 and higher were costed in the model.

Table 60. Costs of AEs included in the model

Grade 3–5 AEs	Mean cost	Source(s)
Alanine aminotransferase increased	£153.00	NHS ref costs 23/24: WF01A service code 306
Anaemia	£392.72	NHS ref costs 23/24: Weighted average of SA01G-K, SA03G-H, SA04G-L, SA05G-J; DC
CRS	£11,031.31	Assumed to consistent of tocilizumab and ICU hospitalisation (see submission section 3.5.6)
Diarrhoea	£511.30	NHS ref costs 23/24: Weighted average of FD10J-M; DC
Lymphocyte count decreased	£411.36	NHS ref costs 23/24; Weighted average of SA08G-J; Day Case
Neutrophil count decreased	£388.37	NHS ref costs 23/24: Weighted average of SA35A-E; DC
Neutropenia	£388.37	NHS ref costs 23/24: Weighted average of SA35A-E; DC
Pneumonia	£679.86	NHS ref costs 23/24: Weighted average of DZ11K-V; NES
Platelet count decreased	£346.70	NHS ref costs 23/24: Weighted average of SA12G-SA12K; DC

Thrombocytopenia	£346.70	NHS ref costs 23/24: Weighted average of SA12G-SA12K; DC
White blood cell count decreased	£388.37	NHS ref costs 23/24: Weighted average of SA35A-E; DC

CRS, cytokine release syndrome

The costing of CRS management was based on the approach used in NP30179, with the most significant cost components considered. It was assumed everyone experiencing CRS as a treatment-related AE with a severity grade of 3 or higher would require 2 doses of tocilizumab. Tocilizumab administration costs are assumed to consist of pharmacist time and rheumatologist time (see Table 61). In line with what was accepted in TA559, it is also assumed that these patients would require 4 days of intensive care unit (ICU) hospitalisation (see Table 61) (135). While corticosteroids (methylprednisolone and dexamethasone) are used in the management of CRS, given the relative cost of these compared to other cost components, including these costs in the calculation had a negligible impact, and were therefore excluded for simplicity.

Table 61: CRS AE management

Cost component	Cost per unit	Unit	Total cost	Source
Tocilizumab	£703.69	2	£1,407.39	[redacted] (average weight); £1.28/mg for the IV (BNF); Tocilizumab 8 mg/kg intravenously (not to exceed 800 mg), as administered in STARGLO
Pharmacist time	£31.20	2	£62.40	Cost of preparation taken from TA812; tocilizumab infusion time is 1 hour
Rheumatology	£227	2	£454.00	NHS ref cost 2023/24; WF02A; Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up
Intensive care unit (ICU) hospitalisation	£2,276.88	4	£9,107.52	NHS ref costs 2023/24;weighted average of HRGs for non-specific, general adult critical care
Total cost			**£11,031.31**	

BNF, British national formulary; HRGs, healthcare resource groups; IV, intravenous

The probability of events was combined with the cost of each AE in each treatment arm (see Table 45). These costs were then applied in the model to the proportion who remain on treatment in each cycle.

Table 62: Adverse event costs per cycle

Drug regimen	Cost per model cycle (weekly)
Glofit-GemOx	£180.41
R-GemOx	£113.78

3.5.7 Miscellaneous unit costs and resource use

No additional costs were considered in this analysis.

3.6 Severity

In line with the NICE Methods Manual, an adjustment to the value of a QALY can apply where there is a shortfall in QALYs for people living with a condition, compared with a person without the condition, over the remaining lifetime of the patients.

Baseline characteristics from the STARGLO trial were used to inform the expected total discounted QALYs for the general population (Table 63).

Expected QALYs for a person free from R/R DLBCL were then calculated using the QALY shortfall calculator from McNamara et al 2022, applying the reference case HRQoL norms based on EQ-5D data from the Health Survey for England (waves 2017-2018) (282).

Total QALYs for people living with 2L DLBCL were informed by the discounted QALYs from the cost-effectiveness model. To align with the previous glofitamab appraisal, the base case assumes no further progression for 2L patients remaining progression-free at 3 years, with utility reverting to near general population utility. Additionally, at 3 years, mortality risk reverts to a near general population level (see Section 3.3.4.1). The total QALYs for the current UK population of patients with R/R DLBCL in the 2L setting was set equal to the QALYs associated with R-GemOx.

This resulted in a proportional QALY shortfall in the comparison vs. R-GemOx of [redacted] and an absolute QALY shortfall of [redacted]. As such, no adjustment to the value of Glofit-GemOx QALYs applies for this comparison.

Table 63: Baseline characteristics informing general population QALYs

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion males	[redacted]	Section 3.2.2
Starting age	[redacted]	[redacted]

Table 64: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
PFS – on treatment / off treatment	[redacted]	[redacted]
PPS	[redacted]	[redacted]

PFS, progression-free survival; PPS, post-progression survival

Table 65: QALY shortfall analysis

Expected total QALYs for the general population	Assumed current treatment	Total QALYs expected for people living with the condition, under current treatment	Absolute QALY shortfall	Proportional QALY shortfall
9.86	R-GemOx	[redacted]	[redacted]	[redacted]

Note: QALYs discounted at 3.5%
QALY, quality adjusted life year

3.7 Uncertainty

The model presents the cost-effectiveness analysis of Glofit-GemOx for the treatment of patients with R/R DLBCL after one prior line of therapy. The economic evaluation is informed by the phase III randomised clinical trial comparing Glofit-GemOx vs. R-GemOx, and the model results are generally robust across scenario and sensitivity analyses (see Section 3.11). However, limitations of the analysis include a somewhat limited follow-up, with some uncertainty about the long-term evolution of OS (median follow-up durations of 20.5 months in the treatment arm and 19.3 months in the comparator arm for OS, along with event rates of 38.3% and 49.1% respectively in STARGLO trial). That being said, the STARGLO study is the only study available to provide clinical evidence for Glofit-GemOx in the intended population and can therefore be considered the best available evidence to inform the modelling.

UK clinical experts at the advisory board noted that the median age in STARGLO was slightly lower than in the UK treatable population (not untypical for a clinical trial), and they also recognised the wide age range in the study, providing further rational for modelling background mortality as a function of the age distribution rather than the mean age of the

cohort (80). However, overall they agreed that the baseline characteristics of the STARGLO population were broadly representative of UK clinical practice.

Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous R/R DLBCL NICE submissions, irrespective of the technology being assessed (154-156, 166). There remains uncertainty around what constitutes the threshold after which patients with durable remissions can be considered as long-term survivors. Given the impact of potential excess comorbidities in this population, the actual HRQoL and mortality risk in these patients compared to the general population is also uncertain. However, assuming long-term remission is supported by the plateau observed in the KM PFS curve for the 2L subpopulation in STARGLO (Figure 11, panel A) and UK lymphoma experts who concurred that 3 years is a clinically plausible time point for when transplant ineligible DLBCL patients treated in the 2L setting would enter long term remission if progression-free.

Scenario analyses have been conducted to assess the robustness of the base case assumptions; scenarios explored assumptions around the cure rate (2 and 5 years), choice of parametric distribution for PFS and OS, approach to modelling background utility and choice of utilities.

3.8 Managed access proposal

The company is committed to securing reimbursement for Glofit-GemOx for 2L patients with R/R DLBCL. If routine commissioning is not possible, Roche is open to consideration for a managed access agreement and a proposal for further data collection will be provided.

3.9 Summary of base-case analysis inputs and assumptions

A summary of all values, and their respective distributions applied, used in the base case analysis is presented in Table 66.

Table 66: 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
Baseline parameters			
Baseline parameters [redacted]	Table 39	None	[redacted]
Survival and progression functions			
PFS – Glofit-GemOx	Table 41	Distribution specific	3.3.3
OS – Glofit-GemOx	Table 43	Distribution specific	3.3.4
PFS – R-GemOx	Table 41	Distribution specific	3.3.3

OS – R-GemOx	Table 43	Distribution specific	3.3.4
All-cause mortality	None	None	3.3.5
TTOT	Table 44	Distribution specific	3.3.6
Clinical parameters			
Adverse event rates	Table 45	Normal	B.3.3.7
Utility values			
STARGLO utility values (base-case)	Table 46	Beta	3.4.5
Brazier age-adjusted coefficients	Table 47	None	3.4.5
Utility scenarios	Table 46	Beta	3.4.5
Cost and resource use			
Glofit-GemOx - dosing and acquisition	Table 48, Table 49	None	3.5.2
Glofit-GemOx - administration costs	Table 50	Generalised gamma	3.5.2
Glofitamab - monitoring costs	Table 51	None	3.5.2
Comparators - dosing and acquisition	Table 53	None	3.5.2
Comparators - costs per cycle	Table 54	None	3.5.2
Comparators - administration costs	Table 50	Generalised gamma	3.5.2
Proportion assumed to take subsequent therapy	Table 55	None	3.5.3
Post discontinuation - weekly treatment costs	Table 56	None	3.5.4
Post-discontinuation costs	Table 57	Generalised gamma	3.5.4
Resource use costs – weekly	Table 58	Generalised gamma	3.5.4
Resource use one-off costs	Table 59	None	3.5.4
Adverse event costs	Table 62	Log-normal	3.5.6

PFS, progression-free survival; OS, overall survival; TTOT, time-to-off treatment

3.9.1 Assumptions

During the construction of the economic model, it was necessary to make some assumptions, both structural and related to model inputs. The assumptions underlying the economic model presented in this submission (Table 67) were tested, where possible, in the sensitivity analyses described in Section 3.11.

Table 67: Summary of model assumptions

Topic	Assumption	Justification/reason
Treatment effect	No treatment waning applied after treatment cessation.	Treatment waning was not included as the majority of patients taking glofitamab had completed their regimen within the observed period.
Utilities	Same utility values applied to all treatment arms	No evidence was available to suggest that the HRQoL experienced by patients on Glofit-GemOx would differ when compared with those taking R-GemOx.
Dosing	Cheapest combination of vial sizes will be administered	This assumption is in line with the reference case though it is acknowledged that in practice, it may sometimes be necessary to use more expensive options.
Vial sharing	No vial sharing is considered	This assumption was validated by clinicians who were interviewed.
Long-term remission/survivorship	Patients alive and progression-free at 3 years are assumed to enter long-term remission with no further progression or costs, and revert to near general population utility. Also after 3 years, mortality risk reverts to near general population levels. Both HRQoL and mortality are adjusted to take account of expected comorbidities.	Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous 2L+ and 3L+ DLBCL NICE submissions (TA649, TA559, TA567), irrespective of the technology being assessed (135-137). Furthermore, it was agreed in the glofitamab monotherapy appraisal (TA927) that people whose cancer had not progressed for 3 years after starting their third treatment (with glofitamab or any of the comparators) would remain progression-free and their cancer would not progress at a later date. Assuming long-term remission is also supported by the plateau observed in the KM PFS curve and UK lymphoma experts who concurred that 3 years is a clinically plausible time point enter long term remission if progression-free after 2L treatment.

DLBCL, diffuse large B cell lymphoma; HRQoL, health-related quality of life; R/R relapsed/refractory

3.10 Base-case results

The base case cost-effectiveness results for Glofit-GemOx with the current approved PAS discount (see Section 3.5.2.2) are presented in Table 68. Glofit-GemOx is shown to be cost-effective at a £20,000 threshold versus R-GemOx.

Table 68: Deterministic base-case cost-effectiveness results (glofitamab PAS price, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at £20,000	NMB at £30,000
Glofit-GemOx	[redacted]	6.73	[redacted]						
R-GemOx	[redacted]	4.31	[redacted]	[redacted]	2.42	[redacted]	£3,672	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specific distributions, summarised in Table 66.

The median probabilistic incremental costs and QALYs gained from Glofit-GemOx vs. R-GemOx with the PAS discount considered for 1,000 iterations are given in Table 69. The pairwise cost-effectiveness acceptability curves are presented in Figure 17. Assuming a willingness-to-pay (WTP) threshold of £20,000 and £30,000 per QALY gained, the probability of Glofit-GemOx being the most cost-effective treatment vs. R-GemOx was [redacted] and [redacted], respectively. The incremental results of each iteration in the PSA are displayed in Figure 18. The results from the probabilistic analysis are in line with those of the deterministic analysis in terms of the estimated QALY and LY gains and the estimated incremental costs. This demonstrates that the deterministic base case results are robust as they are likely to represent the average experience per person treated with Glofit-GemOx.

Table 69: Probabilistic base-case cost-effectiveness results (glofitamab PAS price, comparator and subsequent treatment list price)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at £20,000
Glofit-GemOx	[redacted]	6.69	[redacted]					
R-GemOx	[redacted]	4.26	[redacted]	[redacted]	2.43	[redacted]	£3,381	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years

Figure 17: Cost-effectiveness acceptability curve (glofitamab PAS price, comparator and subsequent treatment list price)

Figure 18: Incremental cost-effectiveness plane (glofitamab PAS price, comparator subsequent treatment list price)

3.11.2 Deterministic sensitivity analysis

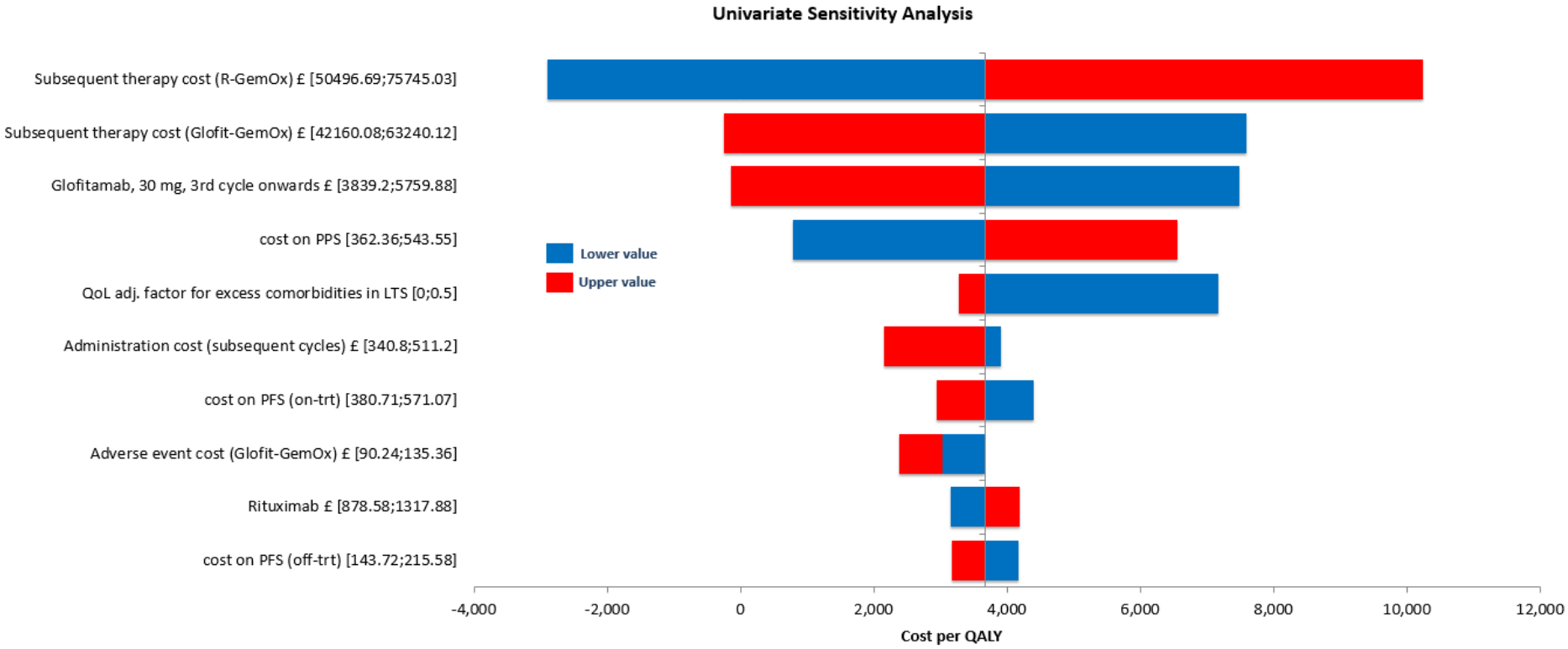
Figure 19 and Figure 20 presents the ten most influential parameters on cost-effectiveness with descending sensitivity when Glofit-GemOx is compared to R-GemOx.

The parameter that had the largest impact on the results was the cost of subsequent therapies following treatment with R-GemOx. This is not unexpected as the cost of the regimens received in the 3L+ setting in this arm has a large impact on the incremental costs. Similarly, adjusting general population utility values by a factor of 50% is shown to have a large impact on NMB, which again is an expected result given the impact on reducing incremental QALYs. For all parameters presented in the tornado plot, none were shown to an exert a significant impact compared to the deterministic base case with respect to NMB at a WTP of £20,000, thereby indicating a low level of uncertainty around the cost-effectiveness conclusion.

Figure 19: Tornado diagram showing OWSA results on NMB – Glofit-GemOx vs. R-GemOx (glofitamab PAS price, comparator and subsequent treatment list price)

[redacted]

Figure 20: Tornado diagram showing OWSA results on cost per QALY – Glofit-GemOx vs. R-GemOx (glofitamab PAS price, comparator and subsequent treatment list price)



3.11.3 Scenario analysis

Explored scenario analyses are described below, with the full results summarised in Table 70. In addition to ICERs, NMB applying a WTP threshold of 20K per QALY gained is also reported, with a positive percentage change in NMB compared to the base case indicating improved cost-effectiveness for that scenario.

Background mortality and time horizon

As discussed in Section 3.3.5, background mortality in the base case analysis was modelled as a function of the age distribution. Applying a more traditional average cohort age method to estimate background mortality (together with a time-horizon of 35 years) results in a marginal improvement in the ICER (£3,396). However, the cohort age distribution method is preferred for the base case as it better reflects the heterogeneity in the actual background mortality of the patients in the cohort and is more likely to accurately estimate quality-adjusted life expectancy. Scenario analyses on time horizon exerted no change on the base case ICER, and therefore the 60 year time horizon can be considered robust.

Survival modelling

The base case parametric models chosen to represent PFS and OS outcomes for each arm were developed and selected in line with NICE DSU guidelines. However, it is acknowledged that for the most part this is subject to each analyst's judgement, which can introduce structural uncertainty. As such, scenario analyses were conducted to assess the impact of these choices.

Table 70 shows that impact of applying the generalised gamma and log-logistic distributions, which are the next best fitting distributions by AIC/BIC statistics after the base case of log-normal, for PFS to the Glofit-GemOx curve. These distributions are applied to both the Glofit-GemOx and R-GemOx arms as per TSD14 recommendations, although it should be noted that the generalised gamma distribution overestimates the proportion of progression-free patients in the R-GemOx arm compared to published literature values (83). The impact of applying the generalised gamma and log-logistic distributions for PFS results in ICERs of £19,877 and £6,758, respectively.

Similarly, applying the generalised gamma and log-logistic distributions for the modelling of OS in both arms decreased the ICER to £1,669 and increased it to £4,243, respectively. In all scenarios of alternative parametric distributions that are considered good fits to the data by AIC/BIC statistics resulted in Glofit-GemOx being considered cost-effective vs. R-GemOx

at a WTP threshold of £20,000. It is important to acknowledge, however, that generalised gamma does not generate plausible estimates of proportions of patients who are progression-free on R-GemOx at later time points in the model. The base case analysis, which applies the log-normal distribution for both PFS and OS on the basis of visual fit, analysis of survival and hazard plots, AIC/BIC statistics and clinical opinion can therefore be considered a stable assumption.

Long-term remission

Cure rates in DLBCL have been agreed in multiple appraisals in DLBCL, and the base case analysis for this current appraisal of Glofit-GemOx aligns with the previously agreed cure rates in the 3L glofitamab monotherapy appraisal, where patients alive and progression-free at 3 years entered long-term remission. Other assumptions for patients entering long-term remission were that they did not continue to progress, reverted to near general population utility values (10% lower vs. general population), and accrued no further costs. Furthermore, after 3 years, mortality risk for the remaining patients reverts to a near general population level (9% excess vs. general population based on an SMR identified from Maurer 2014] (55)).

These assumptions were explored in multiple scenario analyses. Alternative cure rate assumptions were explored at 2 years and a more conservative five years, both of which still result in Glofit-GemOx being considered cost-effective vs. R-GemOx (specifically, Glofit-GemOx was dominant, and an increased ICER of £11,379, respectively).

Alternative assumptions that removed adjustment of general population utility values and excess mortality lowered the ICER compared to the base case to £3,273 and £3,141, respectively, while applying an alternative source for mortality rate from Howlader et al. had resulted in a marginal increase in the ICER to £5,549.

These analyses therefore demonstrate that aligning long-term remission assumptions in the current appraisal to those previously agreed for glofitamab monotherapy is robust as all alternative scenarios result in Glofit-GemOx being considered cost-effective vs. R-GemOx.

Utilities

Alternative sources for health state utility values were explored in scenario analyses, including values derived from STARGLO for 2L only patients, applying values from the previous Pola-BR appraisal (TA649) as well as switching from PFS/PD utilities to proximity to death values.

All scenarios explored exerted a negligible impact on the ICER compared to the base case value (Table 70), indicating a high level of certainty with respect to the utilities used in the current analysis, thereby supporting the use of the EQ-5D values from the ITT population of STARGLO.

Comparator and subsequent treatment discounts

Where it is known that confidential discounts are in place for comparators, the NICE user manual for the submission template recommends presenting scenarios with a range of potential discounts to aid decision making. ICER ranges have been presented in the comparison to R-GemOx with varying levels of discount applied to the assumed list price for the comparator regimen, but also subsequent treatments in the 3L+ setting. Please note that as polatuzumab vedotin is a Roche product, the precise discount is applied in these analyses therefore the scenarios in which a 25%, 50% and 75% discount applied is applicable to non-Roche products only.

In all scenarios, Glofit-GemOx is still considered cost-effective vs. R-GemOx at a WTP threshold of £20,000, with the highest ICER when a 75% comparator discount is assumed being £11,656.

Table 70: Scenario analysis results (glofitamab PAS price, comparator and subsequent treatment list price)

Parameter modifier	ICER vs. R-GemOx	% change from base-case	NMB at £20,000	% change from base-case
Base case	£3,672	-	[redacted]	[redacted]
Time horizon				
Time horizon, 30 years	£3,784	3.05	[redacted]	[redacted]
Time horizon, 40 years	£3,700	0.76	[redacted]	[redacted]
Time horizon, 50 years	£3,677	0.14	[redacted]	[redacted]
Approach to modelling background mortality				
Average cohort age (35 year time horizon)	£3,396	-7.52	[redacted]	[redacted]
Survival modelling and long-term remission				
PFS distribution – generalised gamma	£19,877	441.31	[redacted]	[redacted]
PFS distribution – log-logistic	£6,758	84.04	[redacted]	[redacted]
OS distribution – generalised gamma	£1,669	-54.55	[redacted]	[redacted]
OS distribution – log-logistic	£4,243	15.55	[redacted]	[redacted]

Cure point (PFS and OS) – 2 years	Dominant	-	[redacted]	[redacted]
Cure point (PFS and OS) – 5 years	£11,379	209.89	[redacted]	[redacted]
No QoL adjustment in long-term remission	£3,273	-10.87	[redacted]	[redacted]
No excess mortality in long-term remission	£3,141	-14.46	[redacted]	[redacted]
Standard mortality rate source (Howlader et al. 2017)	£5,449	48.39	[redacted]	[redacted]
Utilities				
STARGLO – EQ-5D-5L from 2L only	£3,680	0.22	[redacted]	[redacted]
Proximity to death utilities	£2,539	-30.86	[redacted]	[redacted]
TA649	£3,646	-0.71	[redacted]	[redacted]
Discounting				
1.5% discounting for costs and effects	£1,441	-60.76	[redacted]	[redacted]
Comparator and subsequent treatment PAS				
25%	£6,057	64.95	[redacted]	[redacted]
50%	£8,857	141.20	[redacted]	[redacted]
75%	£11,656	217.43	[redacted]	[redacted]

2L, second-line; EQ-5D-5L, EuroQol five-dimensional five-level; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QoL, quality of life

3.12 Subgroup analysis

No subgroup analysis has been conducted for this decision problem.

3.13 Benefits not captured in the QALY calculation

UK clinical experts report that there is an urgent need for effective treatments for patients in the 2L setting who are ineligible for transplant; standard of care for these patients is R-GemOx (as the preferred R-chemo regimen) even though it is widely acknowledged that this is only to allow patients to progress to the 3L setting where more effective treatment options are available (80). As such, there is an urgent need for novel 2L treatment options for transplant-ineligible patients that offer effective, durable remissions, extend duration of life and are readily available.

Glofitamab is a first-in-class ready to use CD20xCD3 T-cell engaging bispecific antibody, with a unique 2:1 binding format designed to deliver potent antitumour efficacy, in a fixed duration treatment regimen. Glofitamab offers the potential for strong surface antigen binding, rapid T-cell activation, effective tumour cell killing and the ability to combine with

another CD20-targeted agents in the therapy of B-cell malignancies. The pharmacokinetic properties of glofitamab allow dosing every 3 weeks and, together with the fixed duration (12 cycles over approximately 8.5 months), simplifies treatment administration compared with other available therapies, possibly improving patient adherence, which is critical to maximise clinical benefit (283). By combining glofitamab with gemcitabine and oxaliplatin, there is the potential to improve treatment outcomes for patients further owing to the enhanced anti-tumour effect compared with the single-agent outcomes.

In patients with 2L R/R DLBCL, treatment with Glofit-GemOx is associated with an increased CR rate compared with R-GemOx (63.5% vs. 28.1%). Moreover, the CR with Glofit-GemOx remains durable even after treatment is completed (median DOR currently not estimable at updated analysis). As a PSM was used for the economic analysis of Glofit-GemOx vs. R-GemOx, observed benefits linked to tumour response are not likely to be accounted for in the QALY calculation, as PFS and OS drive the results.

For patients who completed their second line of chemoimmunotherapy, there is the opportunity to experience treatment-free remission and, if they do not experience a second disease relapse, the chance of no further treatment for DLBCL. The PFS for patients with Glofit-GemOx is substantially improved compared with R-GemOx, with 55% and 33% of patients, respectively, alive and progression-free 12 months after 2L treatment initiation. At the latest analysis of STARGLO data, [redacted] of patients treated with 2L R-GemOx required further anti-lymphoma treatment compared with only [redacted] of patients treated with Glofit-GemOx. Enhancement to quality of life for patients who do not have to attend hospital for treatment visits and additional further lines of anti-lymphoma therapy, that in most cases involves additional treatment-related toxicity and prolonged hospital in-patient stays, is not captured in the health economic modelling. It should be noted that the positive impact on patients' lives through avoidance of further treatment is not captured in the QALY calculations.

When compared to R-GemOx for the treatment of transplant-ineligible patients with R/R DLBCL in the 2L setting, Glofit-GemOx demonstrated clinically meaningful benefits over R-GemOx, albeit with the OS and duration of complete response benefits not being statistically significant in this underpowered subgroup of the study. While all aforementioned benefits of Glofit-GemOx vs. R-GemOx may not be fully captured in the QALY calculations, from an economic perspective, Glofit-GemOx is cost-effective compared with the current standard of care for these patients.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

The model methodology was designed to align with NICE's preferred methods. As described in Section 3.2.3, an AUC (or partitioned survival analysis) structure was selected for the analysis based on guidance provided in TSD 19 (163) and the precedents of committee acceptance in recent technology appraisals in DLBCL (135, 137, 154-156, 166). The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to fully capture all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5% (107). Finally, health state utilities were based on those collected in STARGLO, a trial including patients representative of the decision problem, which when mapped to EQ-5D-3L following recommended methods, were shown to be consistent with previously accepted values.

The model was subject to an external quality assurance procedure, which included technical validation of key model inputs and calculations.

Clinical expert opinion was sought during model development to inform model assumptions, to ensure they were clinically valid and/or aligned with UK clinical practice for 2L R/R DLBCL. Specifically, an advisory board of nine UK clinicians was held in November 2024 to discuss the natural history of R/R DLBCL and standard clinical practice in the UK, in order to inform the model and assumptions underpinning the analysis for this submission (80).

3.15 Interpretation and conclusions of economic evidence

The model uses the available evidence in the most intuitive way and all data has been analysed in line with NICE DSU recommendations. While the submission focuses on a narrower population compared to the technology's marketing authorisation, this is supported by the fact that the analysis is informed by the most robust dataset available to demonstrate the cost-effectiveness of Glofit-GemOx in 2L transplant-ineligible DLBCL.

ITCs vs. comparators in the 3L+ setting were either not possible or highly uncertain due to an absence of aggregated data or very small effective sample sizes resulting from adjustments to address covariate imbalances. In contrast, evidence for Glofit-GemOx vs. R-GemOx, which UK clinicians consider to be the standard of care for the treatment of 2L transplant-ineligible DLBCL, is available from the phase III randomised clinical trial, STARGLO, where approximately two-thirds of patients enrolled in the study received these regimens after relapsing following or being refractory to 1L treatment. By restricting the

reimbursement population, the current submission focusses on the most robust evidence available and the population with the greatest unmet need, and therefore the target positioning for Glofit-GemOx has the greatest relevance to UK clinical practice today.

The choice of comparators was informed by the NICE scope; however, upon restriction of the intended reimbursement population, the primary and sole comparator for the current appraisal is R-GemOx. While Pola-BR is recommended by NICE for R/R DLBCL and is listed as a comparator in the scope, this regimen should no longer be considered a relevant comparator for 2L R/R DLBCL following the approval in March 2023 of Pola-R-CHP in the 1L setting. Since then, Pola-R-CHP has rapidly become standard of care for 1L treatment, with a current market share of [redacted]. Due to BlueTeq restrictions on re-exposure to polatuzumab and a reluctance among clinicians to use bendamustine-containing regimens in the 2L setting to avoid precluding the use of T-cell effecting treatments in 3L+ patients (e.g. CAR-T or bispecific antibodies), this has resulted in Pola-BR being rarely used today for 2L patients. Indeed, most recent market share data indicates this regimen constitutes just [redacted] of the 2L market. UK clinical experts confirmed to Roche at an advisory board meeting that Pola-BR is very rarely used, if at all, and therefore the vast majority of 2L transplant-ineligible DLBCL patients receive R-GemOx in UK clinical practice today (80).

As such, a *de novo* economic analysis was conducted to evaluate the cost-effectiveness of Glofit-GemOx vs. R-GemOx for the treatment of 2L transplant-ineligible R/R DLBCL patients in the UK. The deterministic results indicate that Glofit-GemOx is cost-effective versus R-GemOx at a £20,000 threshold.

Extensive sensitivity analyses have been undertaken, which support the deterministic base case and examine the impact of structural uncertainty, parameter uncertainty and parameter precision. There is no substantial difference between the probabilistic sensitivity analysis estimates and base case analysis, indicating that the deterministic results are likely to be reliable and demonstrates that Glofit-GemOx offers a cost-effective alternative to R-GemOx. Moreover, scenario analyses further support the robustness of the deterministic base case assumptions with all scenario being cost-effective at a £20,000 threshold.

Conclusion

In recent years, there have been great advances in treatment options for R/R DLBCL which have improved the outcomes for many patients. However, these approvals have been for patients in the 3L setting and beyond and, as such, those who have failed initial therapy and are not eligible for ASCT still face a poor prognosis. Therefore, there is a need for innovative

treatment options for 2L transplant-ineligible DLBCL patients that can effectively control disease progression, offer a complete response and improve patient outcomes alongside having a manageable safety profile.

Glofitamab is a ready-to-use CD20xCD3 T-cell engaging bispecific antibody with a unique 2:1 binding format designed to deliver potent anti-tumour efficacy, in a fixed-duration treatment regimen in combination with gemcitabine and oxaliplatin. In the 2L treatment setting, Glofit-GemOx offers a clinically significant benefit, based on improved OS, PFS and CR rate, over R-GemOx. The combination of Glofit-GemOx is well tolerated with a manageable safety profile consistent with the known risks of the individual drugs used.

Overall, the findings of the economic analysis indicate that, compared with R-GemOx, Glofit-GemOx is a cost-effective treatment option for patients with R/R DLBCL NOS who are ineligible for ASCT who have progressed during or after one prior treatment. Based on the available evidence, Glofit-GemOx should be recommended as an option for these patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

Scenario: Comparison to Pola-BR

June 2025

File name	Version	Contains confidential information	Date
ID6202_GlofitGemOx_RR DLBCL_PolaBR scenario_[noCON]_redacted	1.0	No	5 June 2025

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1 Introduction

Polatuzumab in combination with bendamustine and rituximab (Pola-BR) was excluded as a comparator in the company submission based on:

- Feedback from UK clinical experts that Pola-BR is no longer used in the second-line (2L) setting for transplant-ineligible, relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL), (estimated use ranged from 0 to 10%) (1).
- Pola-BR use will continue to decline due to increased uptake of Pola-RCHP in the 1L setting and restrictions in the BlueTeq criteria around re-exposure to polatuzumab (2), which was corroborated by market share data obtained by the company which showed an increase in Pola-RCHP use in 1L DLBCL and a corresponding decrease in 2L Pola-BR use in 2024.
- Furthermore, clinical experts informed the company they are not using Pola-BR in the 2L setting due to lymphotoxic effects of bendamustine, as there is evidence that demonstrates a reduced efficacy of subsequent T-cell engaging therapies, including CAR T-cell therapy and bispecific antibodies (important 3L+ treatment options in DLBCL), in patients with prior bendamustine treatment.

The negative impact of bendamustine treatment on downstream treatment outcomes is now acknowledged in recently published treatment guidelines for R/R DLBCL from the British Society of Haematology (published 19th May 2025) (3). This guideline corroborates the advice received by the Company from UK clinical experts that Pola-BR should be avoided in the 2L treatment of DLBCL. Notably, the section specific to 2L management of patients who are ineligible for high dose chemotherapy and autologous stem cell transplant (HDT-ASCT) on page 3 of the guideline provides the following information to support avoidance of Pola-BR:

- There are currently no data on the activity of Pola-BR for R/R large B cell lymphoma in patients who received polatuzumab in first-line therapy
- Where possible, Pola-BR should be avoided for patients who may be suitable for third-line CAR T-cell therapy given that bendamustine exposure prior to apheresis is associated with increased risk of CAR T-cell manufacturing failure and inferior outcomes after CAR T-cell therapy
- Although definitive data are not yet available and current literature is conflicting, there is concern that prior bendamustine exposure may adversely impact the efficacy of

subsequent CD3xCD20 bispecific antibody (BsAb) therapy, especially if the interval between these therapies is short

Subsequent to the submission of this guideline for publication, there was a presentation at the BSH Annual Scientific Meeting in April 2025 on the retrospective analysis of UK real-world data for the BsAbs, glofitamab and epcoritamab, as 3L+ treatments for large B-cell lymphoma (4). A multivariate analysis was performed on the BsAb-treated evaluable patients (n=312) for progression-free survival (PFS) with several variables, including prior bendamustine treatment. This variable was statistically significantly associated with reduced PFS for the BsAbs with a hazard ratio of 1.68 (95% CI: 1.18-2.39; p=0.004).

The company acknowledges the EAG has identified the exclusion of Pola-BR in the Company submission as a key issue in its report. Three clinicians from expert treatment centres consulted by the EAG stated that Pola-BR is used in 2L to warrant its inclusion as a comparator (estimates of 0–10%, 10–15% and 10–20%). Due to the range of estimated use by clinicians, the Company sought opinion from NHS England regarding the use of Pola-BR in the 2L setting, and it was confirmed that the use was sufficient enough (40%) for the NHS to confirm it should be included as a comparator in the appraisal. Of note, the NHS informed the Company that the clinical experts it consulted were surprised that the use of this regimen is still so high and that this is a reflection of use in regional hospitals, possibly due to a lower uptake of Pola-RCHP and the concerns on bendamustine use in the 2L setting not filtering down from the expert treatment centres.

Irrespective of this, the Company is cognizant that the Committee does not have the evidence available to make a decision on the cost-effectiveness of glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) vs Pola-BR since the EAG did not inquire if this analysis was possible and if data were available. To facilitate decision-making at the upcoming committee meeting, the Company is providing the following scenario analysis that provides evidence for the cost-effectiveness for Glofit-GemOx vs Pola-BR based on a propensity score analysis conducted using 2L patients enrolled in the GO29365 Pola-BR study. However, the Company maintains that Pola-BR is not a relevant comparator for this appraisal given the recently published guidelines for R/R DLBCL (see Section 5 for further details)

2. Propensity score analysis vs Pola-BR

This section provides the methodology and results for the propensity score analysis comparing the 2L patients from STARGLO study (Glofit-GemOx) with the 2L only patients from GO29365 study (Pola-BR).

2.1 Methods

To ensure that the patient cohorts used for the analysis were as homogeneous as possible before attempting any comparisons, the populations from STARGLO and GO29365 studies were subsetted to account for differences in trial enrolment criteria. In the GO29365 study, patients who received Pola-BR had different histology, such as DLBCL NOS, HGBCL, PMBCL, and tFL. However, the STARGLO study only included patients with DLBCL NOS. Thus, only patients with DLBCL NOS in the GO29365 study were included (142 out of 152 patients who received Pola-BR). Moreover, in the GO29365 study, the size of the largest node lesion was used instead of bulky disease ≥10 cm as bulky disease was not available in the data. The size of the large node lesion in both studies was used to match. The population was further subsetted to only account for 2L (i.e. 1 prior line of therapy) population. This resulted in [redacted] patients in the Glofit-GemOx arm, and [redacted] patients in the Pola-BR arm.

In the GO29365 study, there were many missing values for cell type of origin and bone marrow involvement. Therefore, the main analysis was performed without adjusting for these variables. The missing values of other covariates were set to be equal to the mean or mode of each covariate, so that patients were not dropped from the analysis. The full matching method also followed this approach. In the IPTW with multiple imputation analysis, imputation was used to estimate values for cell type of origin, bone marrow involvement, and other covariates, enabling a more complete analysis.

2.1.1 Summary of baseline characteristics

A summary of the baseline characteristics used in the IPTW and their imbalances prior to any adjustment are reported in Table 1. Several baseline characteristics were imbalanced between the Glofit-GemOx and Pola-BR groups, with an absolute SMD >0.1.

After narrowing the population to the 2L only population, refractory to last line of therapy had the same values as refractory to first line therapy. In addition, there were no prior ASCT patients in both arms. Therefore, both variables were removed from the analysis. Lastly, since the population was restricted to 2L only, prior lines of therapy was excluded as a covariate to match for in the analysis.

Table 1: Summary of baseline characteristics for the unadjusted sample

Variable	Glofit-GemOx [redacted]		Pola-BR ([redacted])		SMD	VR
	Mean	SD	Mean	SD		
Age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 2, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III/IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High LDH, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extranodal disease, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPI 3–5, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory first-line, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulky disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since last treatment to first study treatment, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male sex, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SMD, standardised mean difference; ECOG, Eastern Cooperative Oncology Group; Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NA, not applicable; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; SD, standard deviation; SMD, standardised mean difference; VR, variance ratio.

Balanced (defined as <0.1 for aSMD or <2 for VR) or unbalanced covariates are indicated in green and orange, respectively.

Covariate balance after IPTW is shown in Table 2. Figure 1 provides a pictorial representation (love plot) of the relative performance of the unadjusted and IPTW methods in achieving covariate balance, as assessed through absolute SMDs.

Covariate balance improvements were observed after IPTW for all factors. Overall, covariate balance was improved after IPTW compared with the unadjusted models. However, not all variables achieved balance according to the 0.1 threshold for absolute SMD. Furthermore, additional matching resulted in the effective sample size (ESS) for Pola-BR reducing to [redacted].

Table 2: Summary of baseline characteristics after IPTW (all covariates)

Variable	Glofit-GemOx ([redacted])		Pola-BR ([redacted])		SMD	VR
	Mean	SD	Mean	SD		
Age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 2, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III/IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High LDH, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extranodal disease, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPI 3–5, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory first-line, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulky disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since last treatment to first study treatment, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male sex, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SMD, standardised mean difference; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IPI, International Prognostic Index; IPTW, inverse probability of treatment weighting; LDH, lactate dehydrogenase; NA, not applicable; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; SD, standard deviation; SMD, standardised mean difference; VR, variance ratio.

Balanced (defined as <0.1 for aSMD or <2 for VR) or unbalanced covariates are indicated in green, respectively.

Figure 1: Love plots for covariate balance after IPTW

Abbreviations: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; IPTW, inverse probability of treatment weighting; LDH, lactate dehydrogenase; ther, therapy; trt, treatment.

As imbalances still existed after matching, all baseline covariates were adjusted in the outcome regression after the IPTW and full matching was performed. It is important to note that the subsequent adjustment could only be performed for summary statistics but not for KM curves.

2.2 Results

2.2.1 Overall survival

A summary of the PSA results for OS is provided in Table 3, and the KM curves are provided for the unadjusted, IPTW, and full matched samples in Figure 2, Figure 3, and Figure 4, respectively. Note that the risk tables in the adjusted KM curves show the sum of weights, which is different from ESS and should not be interpreted.

The HR for OS [redacted]. Results from the IPTW with multiple imputation and full matching showed similar estimates.

Table 3: Summary of PSA results for OS

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]
IPTW	[redacted]
IPTW with multiple imputation	[redacted]
Full matching	[redacted]

Abbreviations: CI, confidence interval; Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; PSA, propensity score analysis.
HRs presented for the comparison of Glofit-GemOx versus Pola-BR.
HRs <1 favour Glofit-GemOx.

Figure 2: KM plot of OS for the unadjusted sample

[redacted]

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; KM, Kaplan–Meier; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.

Figure 3: KM plot of OS for the IPTW sample

[redacted]

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IPT, inverse probability of treatment; IPTW, inverse probability of treatment weighting; KM, Kaplan–Meier; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.

Note: The risk table shows sum of weights which is different from ESS and should not be interpreted.

Figure 4: KM plot of OS for the full matched sample

[redacted]

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; KM, Kaplan–Meier; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.

2.2.2 Progression-free survival

A summary of the PSA results for PFS IRC-assessed is provided in Table 4, and the KM curves are provided for the unadjusted, IPTW, and full matched samples in Figure 5, Figure 6, and Figure 7, respectively. The PFS definition that censors for NALT in both trials was used.

The HR for PFS [redacted]. Results from the IPTW with multiple imputation and full matching showed similar estimates.

Table 4: Summary of PSA results for (IRC-assessed) PFS

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]
IPTW	[redacted]
IPTW with multiple imputation	[redacted]
Full matching	[redacted]

Abbreviations: CI, confidence interval; Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab; PSA, propensity score analysis.
HRs presented for the comparison of Glofit-GemOx versus Pola-BR.
HRs <1 favour Glofit-GemOx.

Figure 5: KM plot of PFS for the unadjusted sample

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IRC, independent review committee; KM, Kaplan–Meier; PFS, progression-free survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.

Figure 6: KM plot of PFS for IPTW sample

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IPT, inverse probability of treatment; IPTW, inverse probability of treatment weighting; KM, Kaplan–Meier; PFS, progression-free survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.

Note: The risk table shows sum of weights which is different from ESS and should not be interpreted. estimand is ATE.

Figure 7: KM plot of PFS for the full matched sample

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; KM, Kaplan–Meier; PFS, progression-free survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.

2.3 Propensity score analysis: limitations and conclusions

The indirect treatment comparison of Glofit-GemOx vs Pola-BR is associated with significant limitations. Notably, after subsetting the trial populations, and further matching to align the 2L only populations of STARGLO and GO29365, imbalances between covariates of interest still remained. Furthermore, the effective sample size for Pola-BR was reduced to [redacted], indicating the data for this comparison has significant uncertainties.

It should also be noted that clinical experts have confirmed to the Company that the evidence from GO29365 study outperforms the experience of Pola-BR in clinical practice. Real world evidence from UK patients with R/R DLBCL demonstrate that median PFS and OS for Pola-BR was 4.8 and 8.2 months respectively, compared to 9.2 months and 12 months in GO29365 (5).

These limitations should therefore be taken into consideration when considering the robustness of this analysis to inform decision making.

3. Model inputs and assumptions

The economic analysis conducted for this scenario is consistent with that presented in the company submission for the comparison of Glofit-GemOx vs R-GemOx and utilises the same partitioned survival model structure. The patient baseline characteristics that are used in the cost-effectiveness model (CEM) are based on the baseline characteristics for the 2L population enrolled in STARGLO.

The follow up period for PFS and OS in the ITC is shorter than the model lifetime horizon, therefore extrapolations were required from the PFS and OS curves.

3.1 Survival analysis

3.1.1 Progression-free survival

The PFS KM curves for Glofit-GemOx and Pola-BR (Figure 8, panel A) demonstrate that the [redacted]. The Schoenfeld test (p=0.0446) (Figure 8, panel D) suggests the proportional hazards assumption should be

rejected, as indicated by the log-log plot which shows convergence at the earlier time points (Figure 8, panel C). The PFS curves were therefore fitted independently.

Standard parametric distributions were used to extrapolate PFS based on the overall goodness of fit and clinical plausibility of the extrapolations. Analysis of survival and hazard plots suggest a monotonic hazard rate for Glofit-GemOx (with a continuous decline in hazard rate) and for Pola-BR (Figure 8, panel B).

Visual inspection of the curves demonstrates that all distributions poorly fit the observed KM curve data for Glofit-GemOx and Pola-BR (Figure 9). The AIC and BIC values presented in Table 5 demonstrate the Gompertz distribution to be the best fit for Glofit-GemOx; however, when visually evaluating the curves (Figure 9), this distribution yields clinically implausible estimates of long-term PFS. Log-normal was the second-highest ranked distribution, with the log-logistic and generalised gamma distributions being within five points of the log-normal distribution, indicating that there is not a strong rationale for these distributions to be selected over log-normal on the basis of statistical fit (6). The exponential and Weibull distributions were the worst fitting distributions.

For Pola-BR, the generalised gamma was the highest ranked AIC and BIC ranked distribution; however, this overestimates the proportion of patients progression-free at later time points in the model. This is of importance since clinical experts have confirmed to the Company that the evidence from GO29365 study outperforms the experience of Pola-BR in clinical practice (5), therefore the use of generalised gamma will overestimate PFS of Pola-BR. As with Glofit-GemOx, the exponential and Weibull distributions were the worst fitting by AIC and BIC ranking.

Due to clinical experts previously validating log-normal distribution for Glofit-GemOx and NICE DSU TSD 14 recommending fitting the same distribution to both treatment arms, the Company fit the log-normal distribution to the Pola-BR arm for consistency. However, given the poor fit of all distributions to the observed KM data, this distribution is applied to tail of the KM curves to reflect estimates of PFS from the ITC at the early stages of the model. The extrapolation occurs from 20 months as this reflects when the tail on the curve starts for both arms, with approximately [redacted] and [redacted] of patients remaining at risk in the Glofit-GemOx and Pola-BR arms, respectively.

Table 5: Summary of goodness-of-fit data for PFS (standard parametric independent models)

	Exponential	Weibull	Log-normal	Gen gamma	Log-logistic	Gompertz
Glofit-GemOx						

AIC	605.187	598.752	589.321	590.277	591.947	583.988
BIC	607.931	604.242	594.811	598.512	597.436	589.478
AIC Ranking	6	5	2	3	4	1
BIC Ranking	6	5	2	4	3	1
Pola-BR						
AIC	740.620	730.258	709.087	694.347	714.977	712.378
BIC	742.470	733.958	712.787	699.898	718.677	716.079
AIC Ranking	6	5	2	1	4	3
BIC Ranking	6	5	2	1	4	3

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Figure 8: PFS KM, hazard plot, log-log plot and Schoenfeld test for Glofit-GemOx vs. Pola-BR

Figure 9: PFS survival plots considered for Glofit-GemOx and Pola-BR

3.1.2 Overall survival

The OS KM curves for Glofit-GemOx and Pola-BR (Figure 10, panel A) demonstrate [redacted]. The Schoenfeld test (p=0.001) (Figure 10, panel D) suggests the proportional hazards assumption should be rejected, as indicated by the log-log plot which shows convergence (Figure 10, panel C), therefore the OS curves were fitted independently. Analysis of survival and hazard plots suggest non-monotonic hazard rates for both Glofit-GemOx and Pola-BR (Figure 10, panel B), indicating compatibility with log-normal, log-logistic and generalised gamma distributions.

As with PFS, visual inspection of the curves demonstrates that the all distributions poorly fit the observed KM curve data for Glofit-GemOx and Pola-BR (Figure 11). The AIC and BIC values presented in Table 6 indicate that the Gompertz distribution is shown to be the best fit for Glofit-GemOx and Pola-BR; however when visually evaluating the curves (Figure 11), this distribution yields clinically implausible estimates of long-term survival. Log-normal was the second-highest ranked distribution for Glofit-GemOx, with the log-logistic and generalised gamma distributions being within five points of this. For Pola-BR, the generalised gamma was the second-highest ranked distribution for Glofit-GemOx, with the log-normal and log-logistic distributions being within five points of this.

Table 6: Summary of goodness-of-fit data for OS (standard parametric independent models)

	Exponential	Weibull	Log-normal	Gen gamma	Log-logistic	Gompertz
Glofit-GemOx						
AIC	594.355	590.223	582.495	583.761	585.200	576.085
BIC	597.100	595.713	587.985	591.996	590.690	581.575
AIC Ranking	6	5	2	3	4	1
BIC Ranking	6	5	2	4	3	1
Pola-BR						
AIC	712.819	715.902	698.968	693.836	702.820	690.306
BIC	723.669	719.602	702.668	699.387	706.520	694.006
AIC Ranking	5	6	3	2	4	1
BIC Ranking	6	5	3	2	4	1

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Taking the above factors into account the log-normal distribution was chosen for both Glofit-GemOx and Pola-BR base case. As with PFS, this distribution is applied to tail of the KM curves given the poor fit to the observed data. The extrapolation also occurs from 20 months, with approximately [redacted] and [redacted] of patients remaining at risk in the Glofit-GemOx and Pola-BR arms, respectively.

Figure 10: OS KM, hazard plot, log-log plot and Schoenfeld test for Glofit-GemOx vs. Pola-BR

Figure 11: OS survival curves considered for Glofit-GemOx and Pola-BR

3.1.3 Long-term remission

As with the company base case analysis for the comparison of Glofit-GemOx vs R-GemOx, patients alive and progression-free at 3 years in both the Glofit-GemOx and Pola-BR arms enter long-term remission. On entering long-term remission, patients do not continue to progress, revert to near general population utility values (assumed 10% lower vs. general population as per TA927), and do not accrue any further costs. In addition, after 3 years, when the majority of progressed patients in the model have died, mortality risk for the remaining patients reverts to a near general population level (9% excess vs. the general population [in line with value applied from TA559 and TA567, based on a standardised mortality rate (SMR) identified from Maurer 2014], adjusted to account for potential excess comorbidities.

3.2 Additional inputs and assumptions

All inputs and assumptions in the scenario are as per the company base case submission. A scenario is provided for the analysis under the EAG's preferred base case in Section 4.1.

Information on specific inputs relevant to the scenario are provided below.

3.2.1 Adverse events

As with the base case analysis, only treatment-related AEs with a severity grade of 3 or higher that occurred in over 1% of patients were considered and costed for Pola-BR (see Table 7). The cost of adverse events in the Pola-BR arm per cycle is £196.27.

Table 7: Treatment-related adverse events considered in the model – Pola-BR

Grade 3–5 AEs	Pola-BR	Mean cost	Source
Anaemia	20	£153	NHS Ref Costs 2023/24; WF01A service code 306
Diarrhoea	4	£511.30	NHS Ref Costs 23/24; Weighted average of FD10J-M; DC
Febrile neutropenia	7	£2,233.96	From TA649 £1848; inflated to 2024
Leukopenia	16	£38837	NHS Ref Costs 23/24: Weighted average of SA35A-E; DC
Lymphopenia	12	£411.36	NHS Ref Costs 23/24; Weighted average of SA08G-J; DC
Lymphocyte count decreased	12	£411.36	NHS Ref Costs 23/24; Weighted average of SA08G-J; DC
Neutrophil count decreased	22	£388.37	NHS Ref Costs 23/24: Weighted average of SA35A-E; DC
Neutropenia	101	£388.37	NHS Ref Costs 23/24: Weighted average of SA35A-E; DC
Pneumonia	8	£679.86	NHS Ref Costs 23/24; Weighted average of DZ11K-V; NES
Platelet count decreased	7	£346.70	NHS Ref Costs 23/24; Weighted average of SA12G-SA12K; Day Case

Thrombocytopenia	42	£346.38	NHS Ref Costs 23/24; Weighted average of SA12G-SA12K; Day Case
Tumour lysis syndrome	3	£1,323.99	Value reported in TA796 inflated to 2023
Vomiting	4	£511.30	NHS Ref Costs 23/24; Weighted average of FD10J-M; DC
White blood cell count decreased	17	£388.37	NHS Ref Costs 23/24: Weighted average of SA35A-E; DC

AEs, adverse events; DC, day case; NES, non-elective short stay

3.2.2 Subsequent treatments

The costs of the following therapies were applied to the proportion of patients who move from the PFS to PPS health state each cycle upon progression on Pola-BR. The proportions of each regimen received are adapted from feedback from clinical experts for similar 3L therapies but adapted to reduce the proportion of patients receiving CAR-T therapy compared to the amounts received post Glofit-GemOx and R-GemOx.

Table 8: Proportion assumed to take each subsequent therapy by arm following 2L therapy

Subsequent therapy	% post Pola-BR
Other R- chemo regimens	4.0
Other chemo regimens (non-R)	1.0
Clinical trial/other	15.0
Radiotherapy	4.0
Allogenic SCT	1.0
Axicabtagene ciloleucel	10.0
Loncastuximab tesirine	10.0
Glofitamab	25.0
Epcoritamab	30.0

R, rituximab; SCT, stem cell transplant;

3.2.3 Severity modifier

In line with the NICE Methods Manual, an adjustment to the value of a QALY can apply where there is a shortfall in QALYs for people living with a condition, compared with a person without the condition, over the remaining lifetime of the patients.

Baseline characteristics from the STARGLO trial were used to inform the expected total discounted QALYs for the general population ([redacted])

Expected QALYs for a person free from R/R DLBCL were then calculated using the QALY shortfall calculator from McNamara et al 2022, applying the reference case HRQoL norms based on EQ-5D data from the Health Survey for England (waves 2017-2018) (7).

Total QALYs for people living with 2L DLBCL were informed by the discounted QALYs from the cost-effectiveness model. The total QALYs for the current UK population of patients with R/R DLBCL in the 2L setting was set equal to the QALYs associated with Pola-BR.

This resulted in a proportional QALY shortfall in the comparison vs. Pola-BR of [redacted] and an absolute QALY shortfall of [redacted]. As such, no adjustment to the value of Glofit-GemOx QALYs applies for this scenario vs Pola-BR.

Table 9: QALY shortfall analysis

Expected total QALYs for the general population	Assumed current treatment	Total QALYs expected for people living with the condition, under current treatment	Absolute QALY shortfall	Proportional QALY shortfall
9.86	Pola-BR	[redacted]	[redacted]	[redacted]

Note: QALYs discounted at 3.5%
QALY, quality adjusted life year

4. Cost-effectiveness results

The cost-effectiveness results for Glofit-GemOx vs Pola-BR with the current approved PAS discount for both glofitamab and polatuzumab are presented in Table 10. Glofit-GemOx is shown to be cost-effective at a £30,000 threshold versus Pola-BR.

Table 10: Deterministic base-case cost-effectiveness results (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)	NMB at £30,000
Glofit-GemOx	[redacted]	6.30	[redacted]					
Pola-BR	[redacted]	4.68	[redacted]	[redacted]	1.61	[redacted]	£25,462	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years

4.1 EAG preferred base case

The cost-effectiveness results as per the EAG's preferred base case is provided for comparison below:

Table 11: Scenario results with EAG's preferred model assumptions, cumulative results, PAS for glofitamab and obinutuzumab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY.
Company base-case	Glofit-GemOx	[redacted]	[redacted]	£25,462
	Pola-BR	[redacted]	[redacted]	
+ Mortality same as for general population after six years	Glofit-GemOx	[redacted]	[redacted]	£25,745
	Pola-BR	[redacted]	[redacted]	
+ 30% of patients not receiving 3L treatment	Glofit-GemOx	[redacted]	[redacted]	£26,749
	Pola-BR	[redacted]	[redacted]	
+ Utility scores specific to 2L patients	Glofit-GemOx	[redacted]	[redacted]	£26,754
	Pola-BR	[redacted]	[redacted]	
+ GemOx given for 6 cycles in both arms	Glofit-GemOx	[redacted]	[redacted]	£26,069
	Pola-BR	[redacted]	[redacted]	
+ Use revised progression resource use	Glofit-GemOx	[redacted]	[redacted]	£26,067
	Pola-BR	[redacted]	[redacted]	
+ Use terminal costs, rather than weekly healthcare resource use costs	Glofit-GemOx	[redacted]	[redacted]	£23,307
	Pola-BR	[redacted]	[redacted]	
+ Administration cost applied once for each combination of treatments	Glofit-GemOx	[redacted]	[redacted]	£22,614
	Pola-BR	[redacted]	[redacted]	
+ Adverse event: Grade 3 Tumour lysis syndrome in Glofit-GemOx arm	Glofit-GemOx	[redacted]	[redacted]	£22,745
	Pola-BR	[redacted]	[redacted]	
EAG preferred base case assumptions	Glofit-GemOx	[redacted]	[redacted]	£22,745
	Pola-BR	[redacted]	[redacted]	

4.2 Weighted ICER

Table 12 below provides a weighted ICER for the cost-effectiveness of Glofit-GemOx vs R-GemOx and Pola-BR together, based on the NHS market share of Pola-BR of 40% and the remaining use being R-GemOx. In both the company and EAG preferred base case assumptions, the ICER is below £20,000.

Table 12: Weighted ICER – Company base case and EAG preferred assumptions

Comparator	ICER	Market share	Weighted ICER
Company base case			
R-GemOx	£3,412	60%	£12,232.00
Pola-BR	£25,462	40%	
EAG base case assumptions			
R-GemOx	£12,257	60%	£16,452.20
Pola-BR	£22,745	40%	

5. Conclusion

The results from this analysis demonstrates that Glofit-GemOx is cost-effective compared to Pola-BR at a willingness to pay threshold of £30,000 in both the company base case and EAG preferred base case scenarios. Furthermore, taking a weighted average based on the proposed market share of the two comparators in this appraisal, ICERs for both the company and EAG preferred assumptions are under £20,000.

Irrespective of these results, the company maintains that Pola-BR should not be considered a relevant comparator for this appraisal, given the recent guidelines published for R/R DLBCL recommending avoiding the use of Pola-BR in the 2L setting (3).

BSH guidelines are the most relevant form of guidance to inform UK clinical practice in haematology. The previous BSH guideline covering R/R DLBCL was published in 2016 when there were limited data to support standard approaches to the management of patients who were ineligible for HDT-ASCT. The publication of this new guideline should therefore result in more equitable 2L treatment of transplant-ineligible patients across the UK being treated at a broad range of haematology centres, from large academic institutions to regional district general hospitals. Therefore, the Company believes that the use of Pola-BR in this patient population will reduce even further, aligning with recommendations from the BSH.

References

1. Roche Products Ltd. Roche UK HTA Advisory Board Report for Glofitamab-GemOx in Relapsed/Refractory DLBCL - November [data on file]. 2024.
2. NHS England. National Cancer Drugs Fund List. 2025 3rd January 2025.
3. Chaganti S, Fox CP, Maybury BD, Burton C, Barrington SF, Illidge T, et al. Management of relapsed or refractory large B-cell lymphoma: A British Society for Haematology Guideline. British journal of haematology. 2025.
4. Haynes E TW, Wilson, W et al.,, editor Real World Experience of Glofitamab and Epcoritamab: A Retrospective U.K. Multicentre Analysis. BSH 65th AGM; 2025.
5. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D, et al. Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. Blood advances. 2022;6(9):2920-6.
6. Rafferty A. Bayesian Model Selection in Social Research Sociological Methodology. 1995;25:111-63.
7. McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-Adjusted Life Expectancy Norms for the English Population. Value in Health. 2022.

Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

Company email response regarding second-line use of pola-BR

Email from Company:

Although the EAG report cites the exclusion of PolaBR as a comparator as the first key issue, the company was not asked for this analysis during clarification questions. We therefore sought clarification from NHS England to understand its position on the market share of PolaBR in second-line (2L) transplant-ineligible DLBCL to confirm if this aligned with the feedback we received from clinical experts and our own market share data from expert centres that its use is not sufficient (0-10%) to warrant it being a comparator.

We spoke to [redacted] who confirmed that of 411 new registrations for Pola-BR in 2024, 59% of those are in the 2L setting, i.e. 242 patients, and the vast majority of these will be in transplant-ineligible patients. It should be noted that [redacted] commented that the clinical experts he consulted were surprised the usage of PolaBR is this high, and that this is due to use in loco-regional MDTs (non-academic centres). [redacted] also mentioned that the number of new registrations has fallen from 34 per month in 2024 to 28 per month in January to April 2025, indicating that the use of this regimen is declining. However, the proportion of registrations for 2L usage remains at 59% during the first 4 months of 2025, therefore the NHS would conclude PolaBR should be a comparator.

Based on our budget impact model, which assumes [redacted] eligible patients for glofitamb plus gemcitabine and oxaliplatin (i.e. second-line transplant-ineligible, relapsed refractory DLBCL), 242 patients equate to 40% of all 2L patients. This value aligns closely to the [redacted] market share reported in the NHS England budget impact assessment; therefore, the company estimates that 40% of all patients in England are receiving PolaBR.

Despite this, the company still considers PolaBR to be an unsuitable comparator for this appraisal given the recent British Society of Haematology guidelines in relapsed/refractory DLBCL published in May 2025. Within these, it states PolaBR should be avoided for patients who may be suitable for third-line CAR T-cell therapy given that bendamustine exposure prior to apheresis is associated with increased risk of CAR T-cell manufacturing failure and inferior outcomes after CAR T-cell

therapy. The guidelines also cite concerns that prior bendamustine exposure may adversely impact the efficacy of subsequent bispecific antibodies (glofitamab and epcoritamab), especially if the interval between these therapies is short. As such, the company considers the inclusion of PolaBR in decision-making would contradict current recommendations for appropriate clinical practice.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

Summary of Information for Patients (SIP)

February 2025

File name	Version	Contains confidential information	Date
ID6202_GlofitGemOx_RRDLBCL_SIP_[noCON]	1.0	Yes	10 February 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Active ingredients: glofitamab in combination with gemcitabine and oxaliplatin (glofitamab-GemOx). Brand name: Columvi (glofitamab)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after 1 systemic therapy who are ineligible for autologous stem cell transplant (ASCT).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for glofitamab-GemOx is pending and is expected. Please refer to Table 2 in Section 1.2 of the company submission for the anticipated date of approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In 2024 and in 2025 up until 10th February (date of the NICE Company submission), Roche provided the following support to UK-based patient groups that are relevant to the treatment of B-cell lymphomas, such as DLBCL. These included providing funds for the purpose of supporting patients, healthcare, scientific research or education that is independent and free from Roche influence, where Roche did not receive any direct benefit or gains. These included:

- A £20,000 grant to Lymphoma Action to support their work on information, education and support activities for people affected by lymphoma
- A £25,000 grant to Blood Cancer UK to support their "Support Service Transformation" project
- A £15,000 grant to the Blood Cancer Alliance (BCA) to support their work in 2024 in the following specific policy areas: campaigning for specific action to address the needs of blood cancer patients from minority ethnic backgrounds; expanding their Access to Medicine influencing campaign to help more people with blood cancer access innovative treatment options; continuing their "Forgotten Fifth" campaign, with a specific focus on improving early diagnosis of blood cancer

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Main condition that the medicine plans to treat

DLBCL is a fast-growing form of non-Hodgkin lymphoma (NHL) that affects white blood cells called B-lymphocytes. Normally, these lymphocytes help fight infections, but in DLBCL, they become abnormal and accumulate in lymph nodes or other body organs.

Glofitamab-GemOx is a cancer treatment for adult patients with DLBCL that has relapsed or is refractory (R/R) after initial treatment. It is intended for those who are not eligible for a stem cell transplant.

Main symptoms of disease

Main Symptoms: The primary symptom of DLBCL is swollen lymph nodes, usually in the head, neck, armpit, or groin. Depending on the location, other symptoms may include bone pain, skin lumps, coughing, or breathlessness. Additional symptoms, known as 'B-symptoms', can include:

- Fever (above 38°C)

- Recurrent night sweats
- Unexplained weight loss

How many people have the condition

In the UK, about 4,850 people are diagnosed with DLBCL each year (1). This translates to approximately 380 cases per million people, or around 25,000 cases over a 10-year period (2). DLBCL is more common in individuals over 60, with an average diagnosis age of 70 (3). Men are slightly more likely to develop DLBCL than women.

Burden of disease

Most DLBCL patients are diagnosed in advanced stages, suggesting a poor prognosis. About 60% of patients respond well to initial, first-line (1L) chemo-immunotherapy. However, 30-40% of patients experience relapse of their DLBCL or may not respond to treatment (refractory disease).

Relapsing or being refractory to first-line treatment leads to the requirement for second-line (2L) treatment. Most relapses occur within 24 months of starting 1L treatment (4, 5), leading to poorer outcomes (6-8). Some patients may be eligible for 2L treatment with a self (autologous) stem cell transplantation or CAR-T cell therapy, and many patients experience a long-term remission with these therapies. However, about half of patients requiring 2L treatment for DLBCL will not be eligible for these treatments. These patients are usually treated with another line of chemo-immunotherapy. Most patients will experience relapsing disease during or following this treatment, with further requirement for more lines of anti-lymphoma therapies. Patients requiring multiple therapy rounds are more likely to experience further disease progression and treatment side effects (9).

Emotional effects

DLBCL and its treatment can significantly impact patients' quality of life, leading to higher levels of anxiety and depression. Younger patients often feel more anxious, while older patients may experience more depression (10). Men may be more affected emotionally, while women might experience more positive changes, though they may face worse physical functioning than men post-diagnosis (11). Patients with additional health issues alongside DLBCL tend to have increased fatigue, emotional impact, depression, and reduced physical and mental health (11).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How DLBCL is diagnosed

DLBCL is diagnosed by collecting a sample of an affected lymph node or tissue through a surgical biopsy. The sample is then analysed under a microscope to determine the specific type of lymphoma by examining the cells and their characteristics and genetic

features. Additional tests, such as antibody testing or cell analysis, are performed to confirm the diagnosis of DLBCL. In cases where the diagnosis is uncertain, DNA testing methods may be used to look for signs of cancer (12).

Several different types of radiological scans can be used to see where the DLBCL is in the body. The main type of scan used in DLBCL is called a PET/CT scan, which is performed before starting treatment and regularly afterwards to see if the treatment is working. If the DLBCL comes back or is not responsive to treatment, this will be captured on the PET/CT scan, highlighting the need for 2L treatment. PET/CT scans are used before, during and after administration of current 2L therapies. No additional tests are required for the medicine being evaluated in this appraisal compared with the standard treatments used for this condition.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

First-line treatment

Around 80% of patients with DLBCL receive first-line (1L) treatment, with most being treated with chemo-immunotherapies called R-CHOP (rituximab [an immunotherapy] plus chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone).

Another treatment is called Pola-R-CHP. Pola-R-CHP is similar to R-CHOP, but replaces vincristine (‘O’ in R-CHOP) with polatuzumab vedotin, an immunotherapy joined to a potent anticancer drug. Approximately 60% of these patients experience a long-term disease remission after receiving 1L treatment (4, 13). However, a significant proportion of patients either do not respond to 1L treatment, experience a relapse, or encounter treatment-related complications, and therefore require further, 2L treatment (4, 13).

Second-line treatment

For those patients who require 2L therapy for DLBCL, treatment options depend upon eligibility for high dose chemotherapy and autologous stem cell transplant (ASCT). ASCT requires a course of high dose chemotherapy. Patients need to be young enough (usually younger than 70 years) and fit enough, without significant co-morbidities, such as heart or kidney complications, to be able to tolerate high dose chemotherapy. For patients whose

disease is refractory to 1L treatment or if their disease relapses within a year of 1L treatment, CAR-T cell therapy may be an alternative option if they are eligible for an ASCT. About half of patients requiring 2L treatment for DLBCL will not be eligible for these treatment options and they will be considered for alternative chemo-immunotherapies.

Rituximab-based chemotherapy

For patients who are not candidates for ASCT (ASCT-ineligible), less intensive rituximab-based chemo-immunotherapy is an alternative. R-GemOx (rituximab, gemcitabine, and oxaliplatin) is commonly used in the UK for 2L treatment as it is often better tolerated than other similar regimens. The main side effect of R-GemOx is neutropenia, a condition that lowers neutrophil levels and makes patients more susceptible to infections (14, 15).

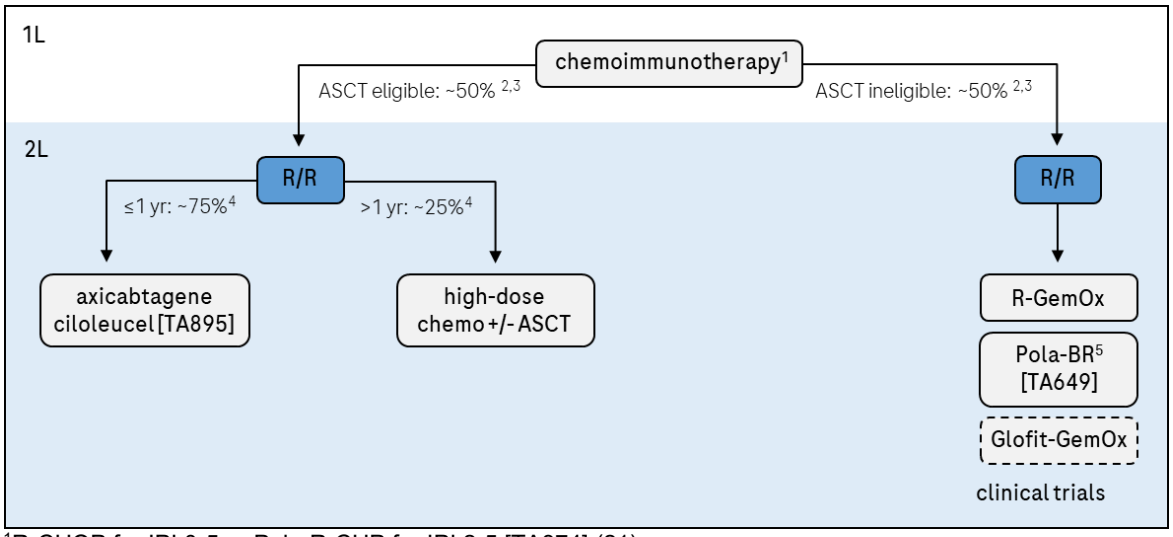
NICE considers R-GemOx as a relevant comparator for glofitamab-GemOx, meaning it will be evaluated for cost-effectiveness relative to R-GemOx.

Polatuzumab vedotin in combination with bendamustine and rituximab

Another option for ASCT-ineligible patients is polatuzumab vedotin (Polivy®) combined with bendamustine and rituximab (Pola-BR). In clinical trials, nearly half of the patients receiving Pola-BR experienced neutropenia and febrile neutropenia, with 30% discontinuing treatment due to side effects. The use of Pola-BR as a 2L treatment in the UK has reduced substantially, as polatuzumab vedotin is increasingly used in the first line (Pola-R-CHP), and patients cannot be retreated with it for a second time (16-18). Additionally, bendamustine can reduce lymphocyte numbers, making third-line (3L) treatments like CAR-T therapy and bispecific antibodies less effective (19, 20). Therefore, Roche does not consider Pola-BR a relevant comparator for glofitamab-GemOx. UK lymphoma clinical experts agreed with this position (18).

The current treatment pathway for R/R DLBCL is summarised below (Figure 1).

Figure 1: Current 1L and 2L treatment pathway for patients with R/R DLBCL



[1]R-CHOP for IPI 0-5 or Pola-R-CHP for IPI 2-5 [TA874] (21)
[2]Sarkozy and Sehn, 2019 (22)
[3]Sehn and Gascoyne, 2015 (13)
[4]Westin and Sehn, 2022 (23)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The Lymphoma Coalition is a group of patient organisations around the world that support people with lymphoma, including patients in the UK. They conduct a survey every two years to learn more about the experiences of people with lymphoma and their caregivers. In 2022, 488 people from the UK (434 patients and 54 caregivers) responded to the survey (24).

Although the proportion of DLBCL patients who responded to the Lymphoma Coalition survey was relatively low (13%), the results may still be relevant across all subtypes of lymphoma. This is because some chemo-immunotherapy treatments used to treat lymphoma have similar side effect profiles, regardless of the specific subtype. Therefore, the survey results can provide valuable insights into the experiences and challenges faced by lymphoma patients and their caregivers, regardless of the subtype they are dealing with.

The key findings from this research in terms of impact on patients and carers are as follows:

- The most common side effects reported by patients (>50%) were fatigue (80%), hair loss (63%), constipation (50%) and changes in sleeping patterns/trouble sleeping (53%).
- Side effects that affected patients' wellbeing the most were hair loss, infections and constipation, and approximately three-quarters of those affected by hair loss or constipation experienced these side effects for more than a year.
- For the majority of those patients with affected sleep patterns, this continued for more than a year, and in approximately 30% of these patients, it lasted more than 2 years.
- In those patients affected by fatigue, for over 70% this was experienced for over a year, with 40% continuing to experience it for over 2 years.
- In those patients reporting lymphoma symptoms and/or treatment side effects, 56% agreed or strongly agreed that symptoms/side effects negatively impacted on close family or friends, 60% agreed or strongly agreed that they had a negative effect on their social life, 65% agreed or strongly agreed that they negatively impacted on every day activities (e.g. exercise, shopping, household chores) and 53% agreed or strongly agreed that they were unable to work or had to change working pattern because of symptoms and/or side effects.
- Psychosocial issues were experienced by 82% of patients over the prior year, with over half of patients (56%) in remission reporting fear of cancer relapse as their biggest concern; other reported effects included anxiety (47%), isolation (38%) and loss of self-esteem (35%).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

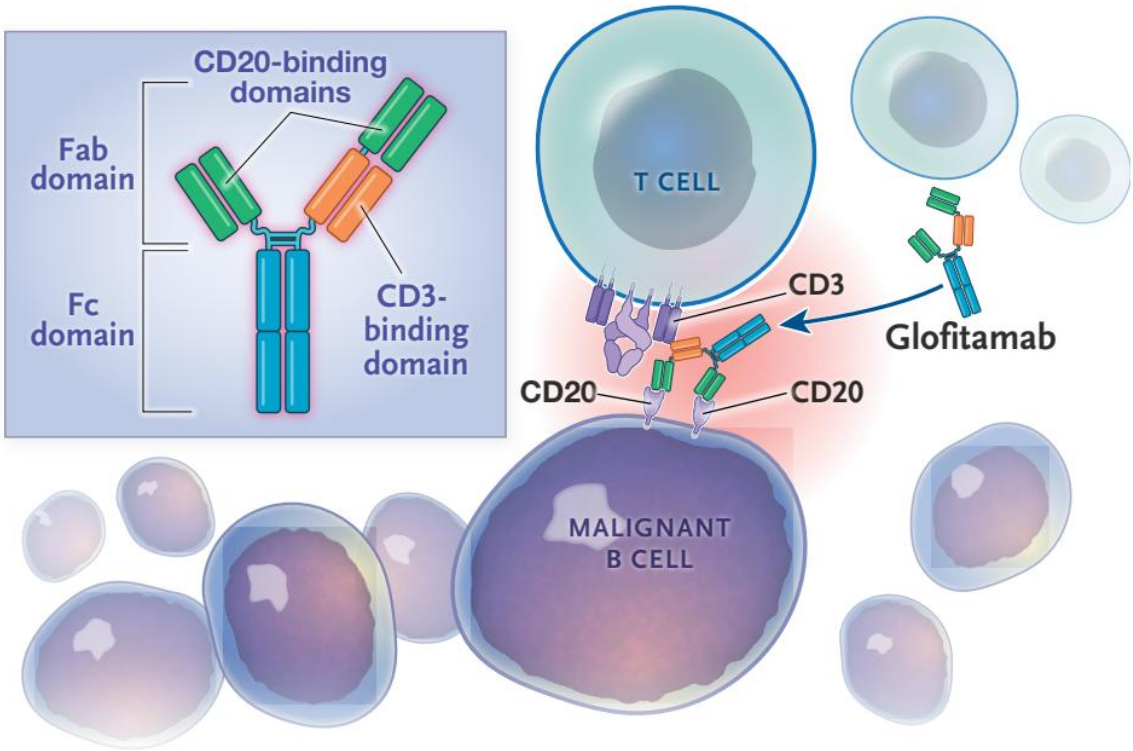
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Glofitamab is a monoclonal (man-made) antibody that binds to two different proteins (bispecific) on the surface of immune system cells: CD20 on B-cells and CD3 on T-cells. By binding to both types of cells, it activates the patient's own T-cells to multiply and destroy the cancerous B-cells that express CD20 (25). This unique mechanism of action supports the patient's own immune system in fighting DLBCL, which is especially important in 2L treatment when the disease has become refractory to 1L chemo-

immunotherapy. See Figure 2 for an illustrated diagram showing how glofitamab works on T-cells and B-cells.

Figure 2: How glofitamab works (27)



3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Glofitamab is to be used in combination with the chemotherapy drugs gemcitabine and oxaliplatin. Gemcitabine works by interfering with the DNA of cancer cells, which stops them from growing and multiplying (26). Oxaliplatin damages the DNA of cancer cells, making it hard for them to repair and survive (27). While these drugs do not target only cancer cells, they make cancer cells more recognisable to the immune system and thus more vulnerable to the effects of glofitamab (28). Gemcitabine and oxaliplatin have favourable safety profiles compared with other chemotherapies, and this is why they are

commonly used as a 2L treatment for R/R DLBCL in combination with rituximab (R-GemOx) (14, 29-31).

One week before patients receive their first dose of glofitamab, they receive a single dose of another antibody, obinutuzumab. Obinutuzumab is used to lower the number of B cells in the patients, which has been shown to reduce the risk of a specific side effect of glofitamab known as cytokine release syndrome (CRS) (32).

A clinical trial found the most common side effects of glofitamab-GemOx to be cytopenias (reduced numbers of blood cells), CRS, nausea, peripheral neuropathy (effects on the nerves in the extremities such as numbness, tingling, burning sensation, pain or discomfort), diarrhoea and increased concentrations of liver enzymes in the blood (28).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Patients will receive obinutuzumab, glofitamab, gemcitabine and oxaliplatin under the supervision of a doctor experienced in cancer treatment, in the haematology unit of a hospital.

Medicines given before glofitamab treatment

Seven days before starting glofitamab treatment, patients will be given a single dose of another medicine, obinutuzumab. This is to lower the number of B-cells in the blood in order to reduce the risk of CRS (32), which is a side effect of glofitamab that some patients may experience and can be severe.

Shortly before glofitamab is given, patients will be given other medicines (pre-medication) to help reduce reactions associated with cytokine release syndrome. These medicines may include:

- A corticosteroid, such as dexamethasone
- A fever-reducing medicine, such as paracetamol
- An antihistamine, such as diphenhydramine

How much and how often glofitamab will be given

Patients will receive 12 treatment cycles of glofitamab. Each cycle lasts 21 days, so the total treatment course is about eight and a half months. Treatment with glofitamab will begin with a low dose and will gradually increase to the full dose.

A typical schedule for glofitamab is shown below.

Cycle 1: This will include a pre-treatment and 2 low doses of glofitamab during the 21 days:

- Day 1 – pre-treatment with obinutuzumab
- Day 8 – starting low glofitamab dose of 2.5 mg
- Day 15 – the second low glofitamab dose of 10 mg

Cycle 2 to Cycle 12: This will be just one dose in each 21 day cycle:

- Day 1 – full glofitamab dose of 30 mg

How much and how often gemcitabine and oxaliplatin will be given

For the first 8 cycles of glofitamab treatment, patients will also receive fixed doses of gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2). Patients will not receive these treatments during the final 4 cycles of glofitamab treatment. For Cycle 1, gemcitabine and oxaliplatin will be given on Day 2, and for Cycles 2-8, these treatments will be given on Day 1 or Day 2, after patients receive glofitamab.

How treatments are given and monitored

Obinutuzumab, glofitamab, gemcitabine and oxaliplatin are given as a drip into a vein (intravenous [IV] infusion). The time required for infusion will depend on how the patients respond to the treatment. Patients will have their temperature and blood pressure monitored to look for signs of CRS. The monitoring time in hospital will depend on how patients react to the treatment. When patients return home, they will be asked to call their haematology care team if they experience any signs or symptoms of CRS, for example fever, fast heartbeat, feeling dizzy or lightheaded, nausea, headache, rash, confusion, chills, shortness of breath. A patient card will be given to all patients to remind them of the symptoms to look out for and who to call if they experience any side effects.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

NP30179 (NCT03075696)

Glofitamab was first tested for its effectiveness and safety as a monotherapy (i.e., without GemOx) in patients with R/R B-cell non-Hodgkin's lymphoma (NHL) in study NP30179. The study found that glofitamab was effective and well tolerated, and it established the step-up dosing schedule of glofitamab used in study GO41944 (32, 33).

GO41944 (STARGLO; NCT04408638)

Study GO41944, also known as STARGLO, is a global trial testing the effectiveness and safety of glofitamab in combination with gemcitabine and oxaliplatin (glofitamab-GemOx)

compared to rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) in patients with R/R DLBCL after at least one prior therapy (28, 34).

The evidence for this NICE submission is taken from a group of patients who, before joining the STARGLO study, had relapsed from or were refractory to one prior therapy (patients who had received more than one prior therapy were excluded from the NICE appraisal). Within this group, 115 patients received glofitamab-GemOx and 57 patients received R-GemOx. The main objective (primary endpoint) of the trial is overall survival (OS). Data collected in March 2023 (the 'primary analysis') showed that patients receiving glofitamab-GemOx in the STARGLO study lived longer than those who received R-GemOx. Since then, further data was collected and an 'updated analysis' was conducted in February 2024, providing an additional 10.5 months of follow-up data on the effectiveness and safety of the study treatments. Results from the updated analysis were recently published in a medical journal (28) and were supportive of the primary analysis when patients were followed up for longer. Further information on the STARGLO study is available on the ClinicalTrials.gov website: https://www.clinicaltrials.gov/study/NCT04408638 (34).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The STARGLO study evaluated the effectiveness and safety of glofitamab-GemOx compared with R-GemOx for patients with R/R DLBCL who had received at least one prior line of therapy. In this study, 183 patients were treated with glofitamab-GemOx and 91 patients were treated with R-GemOx (34). The data was first analysed in March 2023 (the 'primary analysis'), and an 'updated analysis' was carried out in February 2024 with more follow-up time.

The primary endpoint of STARGLO was OS, defined as the length of time between a patient joining the study and dying from any cause. At the updated analysis, there was a 38% reduction in the risk of death in patients treated with glofitamab-GemOx compared to patients treated with R-GemOx. On average, patients treated with glofitamab-GemOx lived nearly twice as long as those treated with R-GemOx (median OS of 25.5 months and 12.9 months, respectively) (28).

The study also looked at progression-free survival (PFS), defined as the length of time between a patient joining the study and showing evidence of disease progression or death, whichever occurred sooner. At the updated analysis, there was a 60% reduction in the risk of a PFS event in patients treated with glofitamab-GemOx compared to those

treated with R-GemOx. Patients remained progression-free for an average of 13.8 months when treated with glofitamab-GemOx, compared to 3.6 months when treated with R-GemOx (28).

At the updated analysis, 59% of patients had a complete response (no evidence of lymphoma on tests or scans) to glofitamab-GemOx, compared to only 25% treated with R-GemOx.

The efficacy data described above represents all patients in the STARGLO study. When joining the study, around two-thirds of patients had received one prior therapy for DLBCL and around one-third of patients had received two prior therapies. Since the Company is seeking reimbursement for glofitamab-GemOx in the 2L, the efficacy data was also analysed in the group of patients who had received one prior therapy. In this '2L subpopulation', the efficacy of glofitamab-GemOx was consistent with the efficacy in the whole population.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The STARGLO study assessed the health-related quality of life (HRQoL) of patients by asking them to complete questionnaires. The results of these questionnaires are known as patient-reported outcomes (PROs).

The EORTC QLQ-C30 questionnaire asked patients about their physical functioning and fatigue levels. The FACT-Lym LymS questionnaire focused on symptoms specific to lymphoma. Patients completed these questionnaires multiple times while undergoing treatment. Both questionnaires were scored using a points system, which researchers used to track changes in HRQoL throughout the study for each patient.

Key Findings:

- Fatigue (EORTC QLQ-C30): The time it took for patients to report an increase in fatigue was similar between those treated with glofitamab-GemOx and those treated with R-GemOx (on average 1.6 months and 1.4 months, respectively).
- Physical Functioning (EORTC QLQ-C30): Patients treated with glofitamab-GemOx took longer to experience a decrease in physical functioning compared to those treated with R-GemOx (median: 23 months vs. 18 months). However, this difference is not statistically significant due to the small sample size.

- Lymphoma Symptoms (FACT-Lym LymS): The time it took for patients to report an increase in lymphoma symptoms was longer for those treated with glofitamab-GemOx compared to R-GemOx (on average 6.2 months vs. 4.5 months). The results were not found to be statistically significant.

Collectively, the PRO data confirms that glofitamab-GemOx does not add additional burden to patients compared with R-GemOx in the areas assessed by the questionnaires.

In addition to the EORTC QLQ-C30 and FACT-Lym LymS questionnaires, patients were asked to complete the EQ-5D-5L health status questionnaire. Data from this questionnaire was used for economic modelling purposes.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Each medicine has its own side effects, and the same medicine can produce different reactions in different people.

The STARGLO study evaluated safety in patients who received at least one dose of the study drugs (obinutuzumab pre-treatment plus glofitamab, gemcitabine, and oxaliplatin) (28, 34).

More patients who received glofitamab-GemOx experienced side effects compared with those who received R-GemOx in the STARGLO study. This is because the average exposure to glofitamab-GemOx was higher than R-GemOx; the average number of treatment cycles in patients receiving glofitamab-GemOx was 12 and it was 4 in the patients receiving R-GemOx. The updated analysis showed that the safety profile of glofitamab-GemOx was consistent with the known risks of the individual study drugs:

- The most common side effects (≥ 30% patients in either group) reported from the STARGLO study included cytokine release syndrome (CRS), low white blood cell count (neutropenia), low iron levels in the blood (anaemia), low levels of platelets (thrombocytopenia), neuropathy, diarrhoea and altered levels of liver enzymes in the blood. Symptoms of CRS may range from a high temperature (fever), nausea and fatigue to low blood pressure and breathlessness that requires treatment in an intensive care unit. However, most of the cases of CRS in the STARGLO study were low-grade with only a fever being experienced.

- Serious side effects occurred in [redacted]% of patients treated with glofitamab-GemOx, with [redacted]% reported to be related to glofitamab treatment.
- [redacted]% of patients treated with glofitamab-GemOx stopped taking treatment because of side effects.
- Overall, the study concluded that the safety profile of glofitamab-GemOx was manageable (28).

The safety data summarised above represents all patients in the STARGLO study. The safety of glofitamab-GemOx was also analysed in the 2L subpopulation, where it was shown to be consistent with the safety in the whole population.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Glofitamab, gemcitabine, and oxaliplatin (glofitamab-GemOx) are ready-to-use medicines administered in a fixed-duration treatment regimen. Glofitamab-GemOx is expected to be positioned alongside rituximab-based chemotherapy (mainly R-GemOx) in the 2L DLBCL setting as an alternative for patients with one prior line of therapy who are not eligible for ASCT.

Glofitamab-GemOx is effective and well tolerated in patients

The STARGLO study confirmed that glofitamab-GemOx is effective and well tolerated in patients with R/R DLBCL (28). The study showed that, in the whole patient population, glofitamab-GemOx significantly increased survival time and the time to progression of disease compared to the current standard treatment for transplant ineligible patients, R-GemOx. Glofitamab-GemOx increased the number of patients who achieved complete response (no evidence of lymphoma on tests or scans) substantially, compared with R-GemOx, and these responses were achieved rapidly (28). The safety profile of glofitamab-GemOx in the whole patient population was manageable and consistent with the known risks of the individual study drugs (28).

The efficacy and safety of glofitamab-GemOx were also shown to be similar for patients in the 2L subpopulation. Therefore, glofitamab-GemOx addresses the unmet need in these patients.

The clinical evidence for glofitamab-GemOx has been well received by UK clinical experts who believe that this novel therapy combination has the potential to enhance access and equity in the treatment of R/R DLBCL (18) for those patients who are not eligible for an autologous stem cell transplant or CAR-T cell therapy.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with other treatments for DLBCL, glofitamab-GemOx might not work for all patients. Clinical study evidence suggests that approximately 6 out of 10 patients will respond to the treatment, while the remaining 4 out of 10 will not (28). Unfortunately, there is no way to predict whether a patient will respond to the treatment when their doctor decides to use glofitamab-GemOx.

Most side effects of glofitamab-GemOx are mild, including the previously mentioned cytokine release syndrome (CRS). However, some patients may experience severe CRS that requires hospital treatment (28). Consequently, all patients receiving glofitamab must stay in the hospital for their first treatment, unlike some other therapies for DLBCL.

3i) 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 economic case presented in this submission is based on an analysis assessing the use of glofitamab-GemOx compared with R-GemOx for the treatment of adult patients with R/R DLBCL who have received one prior systemic therapy and are ineligible for transplant.
- The approach taken to model costs and health benefits is done by splitting patients into three different health states: pre-progression, progressed disease, and death.

This is a common approach used to model the lifetime benefits and costs of treatments used to treat different types of cancer.

- The data used to predict how long patients treated with each treatment would remain in each health state, which informs the amount of costs and health gains they would accrue, is based on data from the STARGLO study (2L only patients).

Modelling how much a treatment extends life

- Based on the economic modelling, it is predicted that people with 2L transplant ineligible DLBCL treated with glofitamab-GemOx will live longer than those treated with R-GemOx. These gains mostly occur from delaying disease progression.
- Data on PFS, OS, time on treatment, quality of life, and adverse events all feed into the economic model. Observed data from STARGLO is used to predict long-term outcomes. The model predicts disease progression, costs and health outcomes over the lifetime of all patients in the model (60-year time horizon).
- Anyone still alive at 3 years is assumed to enter long-term remission, and reverts to a life expectancy near that of the general population (9% increased risk to account for comorbidities).

Modelling how much a treatment improves quality of life

- Quality of life in the economic model is determined by the health state a patient is in, and whether or not they are receiving treatment. The quality of life values assigned to each health state is based on the values collected in STARGLO which was assessed using the EQ-5D-5L quality of life measure. The data were then converted to NICE's preferred EQ-5D-3L measure for the economic analysis.
- Quality of life improvements are achieved if a patient remains progression-free and alive for longer.
- If a person remains progression-free after 3 years, they are assumed to be cured, with their quality of life reverting to near general population levels (10% reduction compared to the general population to account for comorbidities).
- As a partitioned survival model was used for the economic analysis, observed benefits linked to treatment response rates are not likely to be accounted for in the quality of life calculations, as survival outcomes drive the results. Treatment options for patients with DLBCL who have relapsed following or were not responsive to first-line therapy are limited and patients have a poor prognosis, therefore there is an urgent need for innovative second-line treatment options that offer effective, durable remissions and are readily available. As such, the availability of glofitamab-GemOx has the potential to improve quality of life for patients, particularly since this may prevent further hospital visits and additional further lines treatment that in most cases involves additional toxicity and prolonged hospital in-patient stays. The full extent of these benefits are not expected to be fully captured in the economic analysis.

Modelling how the costs of treatment differ with the new treatment

- Overall, the total costs of treatment related to glofitamab-GemOx is expected to be greater than that of R-GemOx. This is driven by increased costs in the progression-free state, where disease progression takes longer to occur for people who receive glofitamab-GemOx compared to R-GemOx. However, treatment costs in the progressed-disease state are greater with R-GemOx due to more patients entering this health state, thereby incurring further costs for receiving subsequent treatments.

Uncertainty

- Due to limited trial follow-up, there is some uncertainty regarding the efficacy estimates included within the economic model, although this is a common obstacle with clinical trial evidence
- The economic analysis included long-term remission/survivorship assumptions, which were plausible for R/R DLBCL in previous 2L+ and 3L+ DLBCL NICE appraisals. There remains uncertainty around the time point after which patients can be considered as long-term survivors in the 2L setting. Given the impact of potential excess comorbidities in this population, the actual quality of life and survival predictions in these patients compared to the general population is also uncertain. However, adjusting these time points in the economic analysis does not change the overall cost-effectiveness conclusion.

3j) 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)

Glofitamab attaches to proteins on the surface of the patient's T-cells and lymphoma cells, bringing them into close proximity (32), stimulating the patient's own T-cells to destroy the cancerous B-cells. This unique "mechanism of action" differs from other antibodies that target only one type of immune cell. Additionally, gemcitabine and oxaliplatin work in various ways to enhance how glofitamab activates the patient's immune system against their disease. Glofitamab is the first bispecific antibody treatment to show an improvement in OS compared with the current 2L standard of care treatment for transplant ineligible patients.

3k) 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

Glofitamab, gemcitabine, and oxaliplatin are available as off-the-shelf medicines, making glofitamab-GemOx a convenient and effective treatment option for both patients and the healthcare system.

There should be no equality issues in accessing this treatment as glofitamab-GemOx should be available in any haematology treatment unit where bispecific antibodies, such as glofitamab, and R-GemOx can be delivered if it is recommended by NICE.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Patient groups and charities:

- Blood Cancer Alliance
- Blood Cancer UK
- Cancer Research UK
- Lymphoma Action
- Macmillan Cancer Support
- Maggie's Cancer Centres

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in HTA: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-hta/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: https://eurohealthobservatory.who.int/publications/i/health-technology-assessment-an-introduction-to-objectives-role-of-evidence-and-structure-in-europe-study

4b) Glossary of terms

Term	Acronym	Description
Ann Arbor Classification System	-	A staging system used for the diagnosis and management of Hodgkin's lymphoma and non-Hodgkin's lymphoma. The system defines four stages of lymphoma, based on the extent of the disease in the body.
Antibody	-	A protein that plays an important role in the body's immune system. Each antibody is unique and recognises a specific part of a germ or other invader. Antibodies can be custom designed for use as drugs.
Autologous stem-cell transplantation	ASCT	A procedure that involves collecting and storing a patient's own stem cells, usually from the bone marrow or blood, and then returning them to the patient after they have undergone intensive chemotherapy or radiation therapy.
Biopsy	-	A process in which a very small part of tissue in the body is removed to look for signs of disease.
Bispecific antibody	-	An antibody or protein that has the ability to bind to two different targets at the same time. In cancer treatment, bispecific antibodies can be designed to recognise and bind to both cancer cells and immune cells, directing the immune cells to attack the cancer cells.
B-lymphocytes/B-cells	-	A type of white blood cell that plays a key role in the immune system. B-lymphocytes are responsible for producing antibodies, which are proteins that help the body identify and neutralise foreign substances such as bacteria and viruses.
Chimeric antigen receptor T-cell therapy	CAR-T	A type of cancer treatment that involves genetically modifying a patient's own immune cells to recognise and attack cancer cells. The process involves removing T-cells (a type of white blood cell) from a patient's blood, modifying them to produce a receptor called a chimeric antigen receptor (CAR)

		that can recognise and attach to a specific protein on the surface of cancer cells, and then infusing the modified T-cells back into the patient's bloodstream. Once infused, the CAR-T cells can identify and destroy cancer cells that express the targeted protein.
Clinical trial	-	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. Also called clinical study. When it is called “Phase III clinical trial”, it tests the safety and how well a new treatment works compared with a standard treatment.
Complete response	CR	A complete disappearance of all signs and symptoms of cancer after treatment. It indicates that no cancer cells can be detected by any of the tests used for the diagnosis of the specific type of cancer that the patient had.
Cytokine release syndrome	CRS	A type of immune system reaction that can occur in some patients receiving certain types of immunotherapy, including CAR-T cell therapy and bispecific antibodies. It happens when the immune system is activated and releases high levels of cytokines, which are proteins that act as messengers between cells. This excessive release of cytokines can cause a range of symptoms, including fever, chills, low blood pressure, difficulty breathing, and organ dysfunction. In severe cases, CRS can be life-threatening and require hospitalisation and treatment in an intensive care unit.
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30	EORTC QLQ-C30	A quality of life questionnaire used to assess the well-being of cancer patients. It was developed by the European Organisation for Research and Treatment of Cancer (EORTC) and is widely used in clinical trials and routine care to measure the impact of cancer and its treatment on patients' daily lives.
Functional Assessment of Cancer Therapy –	FACT-Lym LymS	A patient-reported outcome measure developed by the Functional Assessment of Cancer Therapy (FACT) group to assess the health-related quality of life in patients with lymphoma. It consists of a 44-

Lymphoma – Lymphoma Subscale		item questionnaire that covers areas such as physical, social, emotional, and functional well-being, as well as lymphoma-specific symptoms and concerns. LymS is an abbreviated version of FACT-Lym that includes 15 items.
Immune system	-	A complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases.
Monoclonal antibody	-	Man-made molecules that mimic the immune system's ability to fight off harmful pathogens, such as viruses or cancer cells. They are designed to target specific proteins on the surface of cells and act as a "lock and key" mechanism to bind to these proteins and trigger an immune response to destroy the cells. Monoclonal antibodies are used in the treatment of various medical conditions, including cancer, autoimmune disorders, and infectious diseases.
Overall response rate	ORR	A measure of the proportion of patients in a clinical trial or other study who experience a significant reduction in the size of their tumour or other disease.
Positron Emission Tomography-Computed Tomography scan	PET-CT	A medical imaging technique that combines two types of scans to provide more detailed information about the structure and function of tissues and organs in the body. A PET scan uses a small amount of radioactive tracer to highlight areas of the body with high metabolic activity, while a CT scan provides a detailed image of the body's internal structures.
Prognosis	-	A medical term that refers to the likely course or outcome of a disease or condition. It is an estimate of how the disease will progress in an individual patient, based on factors such as the patient's age, medical history, severity of the disease, and response to treatment.
Quality of life	QoL	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual’s sense of well-being and ability to carry out activities of daily living.
Relapsed or refractory	R/R	Refers to the status of a disease, often cancer, which has either come back (relapsed) after a period

		of remission or has not responded to initial treatment (refractory). In the context of lymphoma, patients who are R/R to 1L therapy (the initial treatment) are often given more aggressive therapies, including clinical trials and stem cell transplantation.
Side effect	-	An unexpected medical problem that arises during treatment with a drug or other therapy. Also known as adverse events, they may be mild, moderate, or severe.
Stem cell transplant	-	The process of providing a patient with healthy stem cells that can replace diseased cells intentionally destroyed by therapy.
Systemic treatments	-	Medications or therapies that affect the entire body instead of just one specific part or organ.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse B-cell lymphoma [ID6202]

Clarification questions

Company Response

March 2025

File name	Version	Contains confidential information	Date
ID6202_GlofitGemOx_RR DLBCL_Clarification_Response_[noCON]	1.0	No	19th March 2025

Abbreviations

Abbreviation	Definition
ASCT	autologous stem cell transplant
CHMP	Committee for Medicinal Products for Human Use
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
EPAR	European Public Assessment Report
ICU	intensive care unit
ITT	intention-to-treat
KM	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
OS	overall survival
PFS	progression-free survival
R/R	relapsed/refractory
SLR	systematic literature review
STC	simulated treatment comparison
TLS	tumour lysis syndrome
TTOT	time to off treatment

Section A: Clarification on effectiveness data

Background

A1. CS section B.1.2, first paragraph of page 19, states *"See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR)."* There is no mention of the EPAR in Appendix C, or any of the other appendices, and it does not appear to be in the reference pack. Could the company please supply the EPAR.

Glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx) was recommended for the STARGLO indication by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 28th February 2025. The EPAR is expected to be published in May 2025 and will be provided when published.

Systematic Literature Review

A2. CS Appendix B.1.1.1.4 describes the tools used in the quality/risk of bias assessment of studies included in the SLR. Could the company provide further information on how many analysts were involved in this process of risk of bias assessment.

Two independent analysts assessed the risk of bias, and any discrepancies were resolved through discussion or the intervention of a third reviewer.

Indirect treatment comparison

A3. CS section B.2.10 paragraph 1 states "*a matching-adjusted indirect comparison (MAIC) feasibility assessment was conducted*". Could the company please provide the feasibility assessment report.

The feasibility assessment report has been provided as a separate document titled "DLBCL 2L+ SLR and Feasibility Assessment Report" alongside these responses.

A4. CS section 2.10 describes feasibility assessment for the MAIC. Did you consider feasibility assessment for a simulated treatment comparison (STC) which may be a more appropriate method of indirect treatment comparison where there is less overlap of study population characteristics?

The objective of the systematic literature review and matching-adjusted indirect comparison (MAIC) feasibility assessment was to assess the clinical evidence available for the treatment of patients with relapsed/refractory (R/R) (second line and beyond [2L+]) diffuse large B-cell lymphoma (DLBCL), to provide a comparison of Glofit-GemOx with comparators of interest. Data for the comparison with R-GemOx is available from the Phase III STARGLO randomised controlled study and is used directly in the model.

However, for the 3L+ comparators listed in the NICE scope that were included in the feasibility assessment (axicabtagene ciloleucel, loncastuximab tesirine and epcoritamab), it was not possible to control for the baseline characteristics either by a MAIC or STC. For instance, the epcoritamab EPCOR-NHL-1 study enrolled a large proportion of patients with PMBCL histology. Since STARGLO only enrolled patients with DLBCL NOS, trial differences could not be adjusted for. As such, comparisons to these comparators were concluded to be infeasible.

STC targets a conditional treatment effect and when working with time-to-event or categorical outcome data, outcome estimates are systematically biased when the link function is nonlinear and consequently non-collapsible (1). Moreover, a MAIC can generate adjusted Kaplan-Meier (KM) curves, which can be used in economic evaluations, whereas the STC approach cannot.

Although there are benefits of fitting STC, i.e. extrapolations when the comparator study does not overlap with the intervention study, the validity of the extrapolation depends on accurately capturing true covariate-outcome relationships (1).

Therefore, the company focused on the MAIC for the feasibility assessment. Based on the reasons above, an STC approach would not be suitable as it would likely be biased and not appropriate for economic evaluations.

A5. CS section B.2.10 page 78 refers to a propensity score analysis. Could the company please provide the results and, if possible, the propensity score analysis report.

As discussed in Section 1.1 of the company submission, the company is seeking reimbursement for Glofit-GemOx in adult patients with R/R DLBCL not otherwise specified (NOS) who are ineligible for autologous stem cell transplantation (ASCT) who have progressed during or after one prior treatment only (i.e. for patients in the second-line [2L] setting). The propensity score analysis discussed on page 78 of the company submission is related to the 3L+ setting.

The rationale for restricting the reimbursement population compared to the proposed marketing authorisation (transplant ineligible patients after at least one prior treatment) is based on:

- **The relevance to NHS clinical practice**: positioning in the 2L aligns with the intended use of Glofit-GemOx in clinical practice according to UK clinical experts given that the greatest unmet need in R/R DLBCL is in the 2L setting.
- **The available evidence base**: Robust indirect treatment comparisons (ITCs) in the 3L+ setting cannot be conducted, while approximately two-thirds of patients enrolled in the STARGLO study received Glofit-GemOx or R-GemOx as a 2L treatment and is therefore not limited by small patient numbers.
- **Optimisation of decision making**: restricting to the 2L only setting reduces uncertainties in the analysis and allows for the most robust case for the cost-effectiveness of Glofit-GemOx to be considered.

Although a propensity score analysis can be conducted vs glofitamab monotherapy in the 3L+ setting, it is associated with considerable uncertainty since only 37.2% of patients received Glofit-GemOx in STARGLO as a 3L+ treatment, therefore resulting in a small ESS of 46.98 for the Glofit-GemOx arm. The results of this comparison are not provided since this does not align with the intended reimbursement population and is therefore not relevant to decision making. This view is supported by clinical experts who stated at an advisory board meeting that the results of the ITC

demonstrates why a 2L only submission should be considered given the unmet need in the 2L setting and that glofitamab is already reimbursed in the 3L+ setting.

STARGLO trial – Patient-reported outcomes

A6. CS section 2.6.3 refers to clinically meaningful differences EORTC QLQ-C30 and FACT-LymS results. The Statistical Analysis Plan defines these differences as 10 points and 3 points respectively. Could the company please provide references to support these definitions in the current study population.

The references used to support the definitions of clinically meaningful differences for the EORTC QLQ-C30 and FACT-Lym LymS results are cited in Section 4.5.10.2 of the Study Protocol, which the Company provided to the EAG upon their request. The references cited for EORTC QLQ-C30 are Osoba et al. 1998 (2) and Cocks et al. 2012 (3), and those for FACT-Lym LymS are Carter et al. 2008 (4) and Hlubocky et al. 2013 (5).

EORTC QLQ-C30

The study by Osoba et al. measured the significance to patients of changes in QLQ-C30 scores by corresponding the category of change from a subjective significance questionnaire with the differences in QLQ-C30 scores among patients with small-cell lung cancer and breast cancer who had received chemotherapy (2). Mean QLQ-C30 scores were around 5–10 for patients indicating “a little” change, around 10–20 for a “moderate” change, and greater than 20 for a “very much” change.

A study by Cocks et al. estimated clinically meaningful changes based on a meta-analysis of published QLQ-C30 data across 11 cancer types along with blinded expert opinions (3). It was found that for most of the 15 QLQ-C30 subscales, a mean increase of 10 points represented “medium” improvement and a mean decrease of 10 points represented “small” deterioration. It is important to note that very few patients in this study had cancers of haematological origin, and their specific cancer types were not reported.

The Company is not aware of any studies to date that have investigated thresholds for clinically meaningful differences in QLQ-C30 scores specifically for patients with

DLBCL. However, several recent clinical studies in patients with R/R DLBCL have defined a clinically meaningful change as 10 points with reference to the Osoba et al. study (6-9). Therefore, the Company considers a within-patient difference of 10 points to be an appropriate threshold to define a clinically meaningful change.

FACT-Lym

Carter et al. validated FACT-Lym (generic scale, FACT-G, plus lymphoma-specific scale, LymS) and estimated thresholds for clinically meaningful change in patients with R/R mantle cell lymphoma. The study estimated a change of 6.5–11.2 points to be clinically meaningful for the total FACT-Lym (FACT-G and LymS) and a change of 2.9–5.4 points for LymS (4). A subsequent study by Hlubocky et al. validated FACT-Lym in a cohort of 84 patients with non-Hodgkin lymphoma, 77 of whom had B-cell lymphoma (5). The original 22-item LymS scale was reduced to 15 items based on patient input, and estimates for clinically meaningful change on the revised subscale were 3–5 points.

Defining a clinically meaningful change in LymS score as a 3-point change from baseline appears to be common practice in clinical studies involving patients with DLBCL (6, 8, 10). Therefore, the Company considers a within-patient decrease of 3 points to be an appropriate threshold for defining clinically meaningful deterioration.

A7. CS Table 18. Please clarify how time to confirmed deterioration was defined for each of the EORTC QLQ-C30 and FACT-LymS outcomes.

The Statistical Analysis Plan (SAP v6) for STARGLO provides the following definitions of time to deterioration endpoints for EORTC QLQ-C30 and FACT-LymS outcomes.

For the EORTC QLQ-C30, time to deterioration in physical functioning is defined as the time from randomisation to the first documentation of a 10-point or more decrease in the scale and time to deterioration in fatigue is defined as the time from randomisation to the first documentation of a 10-point or more increase in the scale.

For the FACT-Lym LymS, time to deterioration in lymphoma-specific symptoms is defined as the time from randomisation to the first documentation of a 3-point or more decrease in the subscale.

Patients who do not have an observed deterioration at the clinical cut-off date were censored at the last non-missing assessment date. Patients without a post-baseline assessment were censored at randomisation.

STARGLO trial – 2L subpopulation

A8. Please would the company clarify how many patients in each arm of the 2L subpopulation of the STARGLO trial were from the UK

Patient recruitment in the UK by the stratification factor, number of prior lines (1 versus ≥2), is included in the summary of baseline disease characteristics by country, referred to in Section 4.5.3 of the updated CSR (Table t_mh_char_bycntry_T_IT_16FEB2024_41944). This table was appended in the updated CSR and not provided in the Company Submission document. In the 2L subpopulation of STARGLO, 4 patients in the R-GemOx arm and 6 patients in the Glofit-GemOx arm were recruited at UK sites. Please see document "A8_Baseline characteristics split by country [confidential]" that has been submitted alongside this response document.

A9. CS section B.2.8 and Figure 10 describe pre-specified subgroup analysis of OS for the ITT population. Could the company please provide the same subgroup analysis of OS for the 2L subpopulation of the STARGLO trial.

The subgroup analysis of overall survival (OS) for the 2L subpopulation of STARGLO is provided in Figure 1 below. All risk factors included in the subgroup analysis of OS for the intention-to-treat (ITT) population are displayed in the 2L subgroup analysis forest plot, with the exception of the number of previous lines of systemic therapy as only patients with 1 prior line of systemic treatment are included in the 2L subpopulation.

It should be noted that many of the subgroups of the 2L subpopulation contain small numbers of patients resulting in wide confidence intervals and therefore the results should be interpreted with caution. The forest plot of OS for the 2L subpopulation is broadly similar to that for the ITT population in STARGLO. The main exception is for age group; in the 2L subpopulation, the proportion of patients aged <65 (42/172; 24%) is lower than that in the ITT population (102/274; 37%), resulting in a very

broad confidence interval for the <65 group with an imprecise point estimate for the OS HR. The main reason for the difference in proportion of older patients in the 2L subpopulation compared with the ITT population is that age, usually >70, is often used as a key criteria for transplant ineligibility (as stated in Section 1.3.2.1.1 of the CS); eligibility for ASCT was an exclusion criterion for 2L patients in STARGLO but not for 3L+ patients (Section 4.1.2 of the STARGLO study protocol), which allowed fewer 2L patients aged <65 years to be recruited into the study.

Figure 1: Subgroup analysis of OS (ITT population; 2L)

A10. Updated CSR (STARGLO_updated_CSR [confidential].pdf) section 5.2.10 provides exploratory analyses of exposure adjusted adverse event rates for the safety evaluable population. Could the company please provide the same exposure adjusted adverse event rates for the 2L subpopulation?

Please see document “A10_exposure_adjusted_AE_rates_2L_safety_evaluable” that has been submitted alongside this response document.

A11. CS Table 26 provides the number of patients who experienced an adverse event leading to treatment withdrawal in each arm of the 2L subpopulation of the STARGLO trial. Could the company provide a breakdown of the AEs leading to treatment withdrawal by MedDRA Preferred Term.

Please see document “A11_treatment_withdrawal_AEs_2L_safety_evaluable” that has been submitted alongside this response document.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION. Please clarify why glofitamab with gemcitabine and oxaliplatin (Glofit-GemOx) treatment for 2L R/R DLCBL was not modelled using

a mixture cure model? Please provide a scenario in the economic model where only patients in the PFS health state have general population mortality and those in the progressed health state have a cancer-related mortality.

The company notes that a mixture cure model may be appropriate for conditions that can be considered to be curative and where there is sufficient evidence available (both clinical and observational) to support an assumption that a proportion of patients may be cured. However, for the current appraisal, the company considered that the available evidence was not supportive of a mixture cure model.

This is primarily due to limited follow up in the STARGLO trial. At the updated analysis, the median follow up for overall survival was 20.7 months. Moreover, while the overall survival Kaplan Meier curves (Figure 4 in the company submission) indicates a plateau, the company notes that there are limited data points at later time points in the model ([redacted] and [redacted] patients at risk at 24 months for Glofit-GemOx and R-GemOx, respectively). A longer follow up time is required to robustly estimate the cure fraction for a mixture cure model, a previous study has demonstrated that even having 11 years follow up was not sufficient to accurately estimate a cure fraction in DLBCL (11).

The company decision to model survival using a standard parametric model with an assumption on long-term remission aligns with previous technology appraisals in R/R DLBCL, including appraisals for bispecific monoclonal antibodies (glofitamab monotherapy [TA927] (12) and epcoritamab [TA954] (13)). Furthermore, it should be noted that a mixture cure model was applied in the company base of TA649 (polatuzumab plus bendamustine and rituximab) (14) but was rejected by the Committee on the basis of uncertainty in the estimated cure fraction since this was based on two year progression-free survival data, as well as a scenario in TA927 but again this was not considered as part of the final decision making. Given the available evidence, precedence from previous appraisals in this disease and guidance provided in TSD19 (15), the company considers a parametric model with an assumption on long-term remission to be more appropriate to reflect the curative potential of treatments for DLBCL.

The model has been adapted to include the scenario requested by EAG (see cell F21 of the Model Inputs tab). This scenario changes the model structure from a PSA to a state transition model (STM), with state transition probabilities derived from the STARGLO trial to enable the application of distinct transition probabilities for the two health states: general population mortality for the progression-free health state and cancer-related mortality for the progressed health state. To implement this scenario, the weekly hazard of progression was calculated from the STARGLO trial PFS curve, while the probability of progression was deduced by subtracting the mortality hazard from the progression hazard. The modified overall survival was recalculated by consecutively applying the general population mortality rate to patients in the progression-free health state and the mortality rate derived from the OS curve of the STARGLO trial to patients in the progressed health state. The modified progression-free survival was similarly recalculated based on the updated state transition probabilities as a result of this scenario. The columns that were adjusted to implement this scenario are highlighted in purple in the Glofit+GemOx and R+GemOx sheets of the cost-effectiveness model.

The results from this scenario are provided below in Table 1 alongside the updated base case results from the model following the incorporation of changes to modelled adverse events (question B3), costs (B4-B6) and corrections on time-on-treatment (B7) highlighted by the EAG. The requested scenario generates an ICER of £27,251 (PAS price).

However, the company believes this scenario generates clinically implausible results. Applying the general population mortality rate to R/R DLBCL patients in the progression-free health state underestimates mortality and progression in both arms, as can be seen by the increased life years gained (LYG) compared to the updated base case. Indeed, the LYG for Glofit-GemOx (11.26) is similar to that gained for Polatuzumab plus R-CHP and R-CHOP in 1L DLBCL ([redacted] and 11.83, respectively), which is clinically implausible as 2L R/R patients have a worse prognosis than 1L patients, and greater than that seen for glofitamab monotherapy in 3L+ DLBCL (ranging from [redacted] to [redacted] depending on comparator). Although R-GemOx is standard of care for transplant ineligible 2L DLBCL patients in the UK, survival outcomes with this regimen are poor, with UK clinical experts describing this

treatment as a ‘stepping stone’ in order to access approved 3L treatments. Therefore, it should be expected that the LYG be similar to those seen in the 3L+ setting.

Similarly, utilising the mortality rate derived from patients transitioning from either a progression-free or progressed health state to death for those in the progressed health state may also underestimate mortality, as the mortality rate may be higher than this combined rate. Therefore, the company considers that this scenario results in clinically implausible estimates of PFS and OS for both the treatment and control arms, and is therefore not appropriate for decision making.

Table 1: Scenario requested by EAG

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)
Updated base case (PAS price applied)							
Glofit-GemOx	[redacted]	6.73	[redacted]				
R-GemOx	[redacted]	4.31	[redacted]	[redacted]	2.42	[redacted]	£3,412
STM Scenario (PAS applied)							
Glofit-GemOx	[redacted]	11.26	[redacted]				
R-GemOx	[redacted]	6.22	[redacted]	[redacted]	5.05	[redacted]	£27,251

B2. PRIORITY QUESTION. We note that the proportion of patients with PFS remains constant in the two arms in the company base case (Glofit-GemOx from 3 to 11 years and R-GemOx from 3 to 20 years). However, the CS states that these patients will die according to the general population mortality rate. Please correct the model so that patients in the PFS health state die according to the general population mortality rate.

As explained in Section 3.3.4.1 of the CS, the "long-term remission/survivorship assumptions" option in the Model Inputs sheet allows the setting of two timepoints in the model:

1) Utilities and costs for progression-free survival (PFS) are assumed to be equal to those of the general population after 'x' years (where 'x' is specified by the **ltr_time** parameter). By setting ltr_time to 3 years, the company's base case assumes that patients who do not progress within the first 3 years are considered to be in long-term remission until the next event (death) occurs. This assumption implies that the patients in long-term remission will have utility values 10% lower than the general population values aligned to TA927 (12), to account for the excess comorbidities these patients face after having had R/R DLBCL. Thus, the probability of disease progression remains constant until the 11th and 20th years for the Glofit-GemOx and R-GemOx treatment arms, respectively (not the proportion of patients as highlighted in the question). At these timepoints, the probability of mortality overtakes the fixed progression probability, which is set at 3 years in the base case according to the company's model. This mortality is also adjusted to be similar to that of the general population, as explained below.

2) Mortality for the cohort (progression-free and progressed health states) is assumed to be equal to the general population after y years (where 'y' is specified by the **lts_time** parameter): In the company's base case, the second timepoint (**lts_time**) is also set to 3 years. At this point, when most of the progressed patients in the model have died, the mortality risk for the remaining patients reverts to a level close to that of the general population, with a 9% excess mortality rate compared to the general population. This adjustment is in line with the values applied from TA872 (16), TA927 (12) based on a standardised mortality rate (SMR) identified from Maurer et al., 2014 (17), and it accounts for potential excess comorbidities. This parameter (lts_time) enables the model to set the mortality rate to be nearly equal to that of the general population after this timepoint. The application in the Glofit+GemOx (column BK) and R+GemOx (column BJ) sheets of the model is as follows:

=IF(AND(lts_scenario="Yes",C13>lts_time),BK12*(1-CHOOSE(MATCH(dm_mortality,dm_mortality_optn,0),**'Life tables'!AQ12,'Life tables'!AS12)),BC**13)

Column BC refers to the OS curve calculated by the mortality rate from the trial with the general population mortality adjustment. This adjustment involves capping the trial-derived mortality rate at the level of general population mortality. This means that if at any point the trial-related mortality rate falls below the general population mortality rate, the latter will be used in place of the former. This situation is expected to occur, if at all, only at the tail end of the survival curve.

'**Life tables'!AQ** column (used when the 'Age distribution as in trial' option in the cell F19 of the Model Inputs sheet is selected) and **'Life tables'!AS** column (used when the 'Average cohort age' option is selected) refer to the general population mortality values listed in the Life tables sheet.

B3. CS section B.3.3.7 states that only treatment-related adverse events with a severity grade of 3 or higher were considered in the model (listed in CS Table 35). However, CS Appendix D Table 19 shows that in the 2L subpopulation of STARGLO:

- **Three (5.5%) patients in the R-GemOx arm and two (1.9%) patients in the Glofit-GemOx arm experienced grade 3 tumour lysis syndrome.**
- **Three (2.8%) patients in the Glofit-GemOx arm experienced grade 3 atrial fibrillation.**
- **Three (2.8%) patients in the Glofit-GemOx arm experienced grade 3+ sepsis.**

Please explain why these adverse events were not considered in the model.

The economic model includes costs for treatment-related adverse events, grade 3–5 with an incidence ≥1%. Table 19 in Appendix D of the company submission presents all grade 3–5 adverse events by preferred term with a frequency of ≥1% in either arm for the 2L subpopulation of STARGLO, irrespective of whether they were considered to be treatment-related or not.

Of the adverse highlighted in the question, only tumour lysis syndrome (TLS) in the three patients receiving R-GemOx were related to treatment. The model has now been updated to include the cost of TLS for patients receiving R-GemOx. The cost of TLS was applied based on the value reported in TA796 (£1,232.73) (18) and inflated

to 2023 based on NHS inflation indices reported in the Unit Costs of Health and Social Care 2023 manual (£1,323.99).

B4. In CS Table 59, the cost of MRI is £246. However, the total HRG cost for this code is £165. Please give further details on how this cost has been derived.

The value of £246 reported in the company submission and economic model was using the cost for MRI in community diagnostic centres rather than for outpatient imaging. The model has now been updated to reflect this value (which is cited as £156 on the 2023/24 NHS Reference Costs Power BI platform), to be consistent with previous appraisals in R/R DLBCL.

B5. In CS Table 51, the cost of intensive care unit hospitalisation cost (ICU) is £2,277. We are unable to obtain this cost for ICU. Please give further details on how this cost has been derived (The EAG obtains £2,444 using code XC01Z – XC06Z for non-specific general adult critical care).

The value of £2,277 for the cost of ICU hospitalisation was generated from the weighted average of codes XC01Z – XC07Z for adult critical care, as per the summary HRG tab of the 2023/24 NHS reference costs Power BI platform.

The company has updated the cost of managing cytokine release syndrome (CRS) in the economic model so that it reflects the cost identified by the EAG to focus on non-specific general adult critical care only.

B6. In CS Table 51, the unit cost for pharmacist time is £31.20 (1 hour). The EAG is unclear how the cost has been estimated from the source cited (TA812). Please give further information on how this cost was derived.

There is a typo in Table 51 of the company submission as the source for the pharmacist cost should be TA649 (as mentioned in the economic model), not TA812. This calculation was based on the assumption that preparation of an infusion takes 39 minutes of a pharmacist's time, which based on the hourly rate of £48 for a hospital pharmacist results in a cost of £31.20.

The hourly rate of £48 was as reported in the PSSRU 2018 unit costs manual. Inflating this to 2023 values results in an hourly rate of £53.87, therefore a cost of £35.02 per infusion preparation. The economic model has been updated to reflect this.

B7. CS section B.3.3.6 explains that the STARGLO trial time on treatment Kaplan-Meier data were complete, and that these were used to model treatment duration without needing to fit a distribution curve. We note that most of the modelled estimates for the R-GemOx arm fit the corresponding K-M data closely. However, the modelled oxaliplatin time on treatment (half cycle corrected oxaliplatin) is quite different to the K-M data (solid and dotted orange lines in the figure below). Please would you explain the discrepancy.

[redacted]

The discrepancy was caused by an error in the formula in column DU on the R-GemOx sheet in the submitted model (which is now column EG in the updated model). The formula was referring to an incorrect column; this has now been corrected to refer to column AD (PFS used) in the updated model. Similarly, the company identified the same error in columns DM (TTOT Gemcitabine) and CS (TTOT Rituximab), and these errors have been corrected accordingly. The corrected modelled and KM curves of oxaliplatin TTOT of the R-GemOx arm are shown in Figure 2.

Figure 2: Time to off treatment (TTOT)

[redacted]

In addition to this correction, the company identified another error in the same sheet of the model. The column calculating the accumulated 'Drug cost of Rituximab' (column EL in the updated model) erroneously included the costs of Gemcitabine and Oxaliplatin. This was corrected by removing the calculation steps for these drugs, as their costs are already accounted for in subsequent columns of the sheet.

Please refer to the supporting appendix for the updated base case results with these corrections (plus additional changes on costs and TLS adverse events) incorporated.

B8. CS section B.3.4.2 states "a distinction between PFS on- and off-treatment was made to account for the potential impact of treatment related factors (such as toxicities, burden of administration, etc.) on utility." Please could the company provide a graph of mean patient health-related quality of life over time, by treatment arm, for the STARGLO ITT and 2L populations for progression-free survival.

Table 2 presents the utility estimates for the ITT population grouped by progression status and treatment arm.

Table 2: Utility estimates (ITT population)

	Estimate	bStderr	2.5% bCL	97.5% bCL
PFS_GLOFIT_GEMOX	0.7587741	0.0130771	0.73454175	0.78439525
PFS_R_GEMOX	0.75101946	0.02011215	0.71068953	0.790149
PPS_GLOFIT_GEMOX	0.6873425	0.01804033	0.65130169	0.72049951
PPS_R_GEMOX	0.67958786	0.02300007	0.63632542	0.72456378

Figure 3 presents the mean pre-progression (PFS) utility estimates for the ITT population for each month by treatment arm.

Figure 3: Mean pre-progression utility estimates (ITT population)

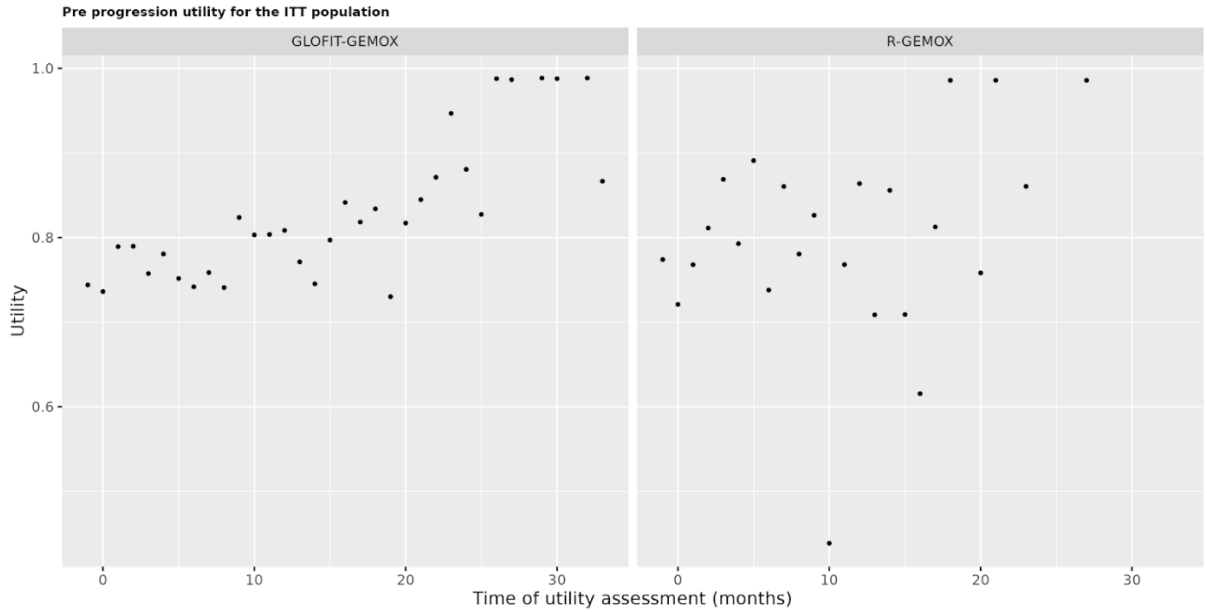


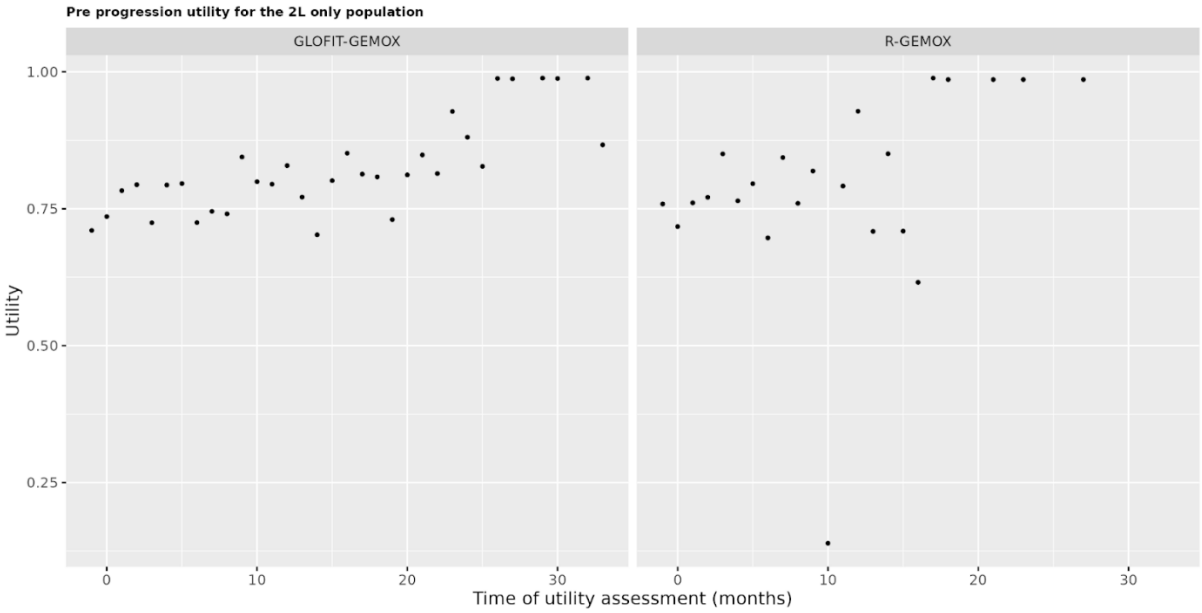
Table 3 presents the utility estimates for the 2L population grouped by progression status and treatment arm.

Table 3: Utility estimates (2L population)

	Estimate	bStderr	2.5% bCL	97.5% bCL
PFS_GLOFIT_GEMOX	0.75957774	0.01419095	0.73234492	0.78684993
PFS_R_GEMOX	0.75139225	0.02213927	0.70967536	0.79405758
PPS_GLOFIT_GEMOX	0.69429683	0.02337879	0.64902061	0.74142003
PPS_R_GEMOX	0.68611134	0.02713419	0.63560951	0.74120994

Figure 4 shows the mean pre-progression (PFS) utility estimates for the 2L population for each model by treatment arm.

Figure 4: Mean pre-progression utility estimates (2L population)



B9. Are you aware of any published cost effectiveness studies or HTA studies for relapsed or refractory diffuse large B-cell lymphoma that have been published since you conducted your systematic literature review?

The systematic literature review for cost-effectiveness studies in R/R DLBCL was last updated on 19th August 2024, which is within 6 months of our evidence submission date of 10th February 2025. The company is not aware of any additional studies or HTA studies that have been published since then.

B10. Please clarify how the hazard plot for PFS (CS Figure 13 panel B) and hazard plot for OS (CS Figure 15 panel B) were produced from data in the economic model. Alternatively, please provide the data and calculations that produced the two hazard plots.

The Company used the muhaz function in muhaz R package to obtain the smoothed hazard. Sometimes the smoothed hazard did not work as expected when the number at risk is very low. Therefore, the maximum time was limited so that the number at risk was at least 10.

The R-code that was used to generate the smoothed hazard is provided below:

```
sfit <- survfit(Surv(int_data0$AVAL, int_data0$CNSR == 0) ~ 1)
```

```
endz <- approx(sfit$n.risk, sfit$time, xout = max(10, min(sfit$n.risk)))$y
max.time <- ifelse(is.na(endz), sfit$time[length(sfit$time)-2], endz)
h_int <- muhaz::muhaz(int_data0$AVAL, 1 - int_data0$CNSR, max.time = max.time)
```

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse B-cell lymphoma [ID6202]

Clarification questions

Company Response: Appendix (Updated Results)

March 2025

File name	Version	Contains confidential information	Date
ID6202_GlofitGemOx_RR DLBCL_CQ Response_Appendix_[noCON]	1.0	No	19th March 2025

This appendix reports updated results from the cost-effectiveness model following the incorporation of tumour lysis syndrome adverse events in the R-GemOx arm, an update to costs (MRI, ICU hospitalisation and pharmacist resource use) and corrections on time-on-treatment as per the company responses to the EAG's clarification questions.

1. Updated base-case results

The updated base case cost-effectiveness results for Glofit-GemOx with the current approved PAS discount (see Section 3.5.2.2 in the company submission) are presented in Table 1. Please note also that as with the company submission, the PAS price for obinutuzumab is applied to all of the results reported. Glofit-GemOx is shown to be cost-effective at a £20,000 threshold versus R-GemOx.

Table 1: Deterministic base-case cost-effectiveness results (glofitamab PAS price, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at £20,000	NMB at £30,000
Glofit-GemOx	[redacted]	6.73	[redacted]						
R-GemOx	[redacted]	4.31	[redacted]	[redacted]	2.42	[redacted]	£3,412	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years

2. *Exploring uncertainty*

2.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specific distributions summarised in Table 63 of the company submission

The median probabilistic incremental costs and QALYs gained from Glofit-GemOx vs. R-GemOx with the PAS discount considered for 1,000 iterations are given in Table 2. The pairwise cost-effectiveness acceptability curves are presented in Figure 1. Assuming a willingness-to-pay (WTP) threshold of £20,000 and £30,000 per QALY gained, the probability of Glofit-GemOx being the most cost-effective treatment vs. R-GemOx was [redacted] and [redacted], respectively. The incremental results of each iteration in the PSA are displayed in Figure 2. The results from the probabilistic analysis are consistent with the original analysis in the company submission, that is, they are in line with those of the deterministic analysis in terms of the estimated QALY and LY gains and the estimated incremental costs. This demonstrates that the deterministic base case results are robust as they are likely to represent the average experience per person treated with Glofit-GemOx.

Table 2: Probabilistic base-case cost-effectiveness results (glofitamab PAS price, comparator and subsequent treatment list price)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at £20,000
Glofit-GemOx	[redacted]	6.70	[redacted]					
R-GemOx	[redacted]	4.25	[redacted]	[redacted]	2.45	[redacted]	£3,561	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years

Figure 1: Cost-effectiveness acceptability curve (glofitamab PAS price, comparator and subsequent treatment list price)

Figure 2: Incremental cost-effectiveness plane (glofitamab PAS price, comparator subsequent treatment list price)

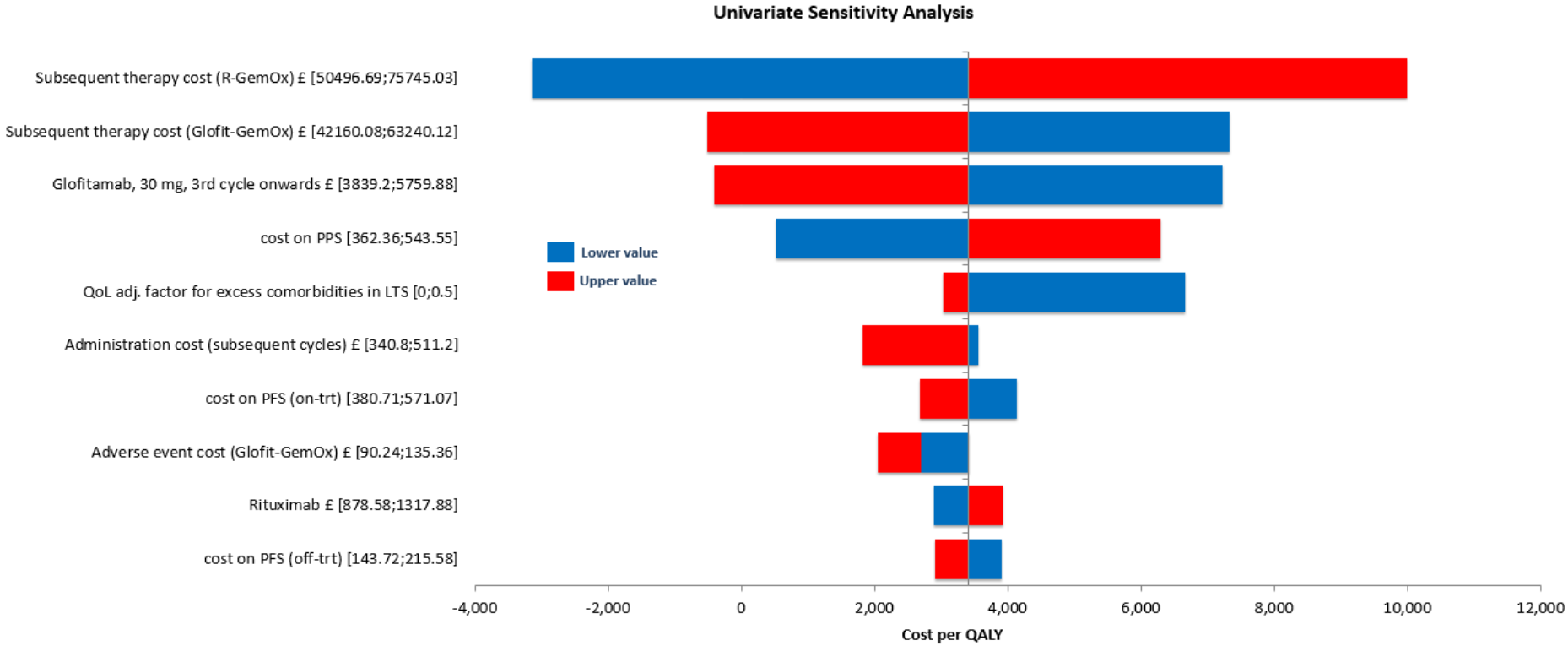
2.2 Deterministic sensitivity analysis

Figure 3 and Figure 4 presents the ten most influential parameters on cost-effectiveness with descending sensitivity when Glofit-GemOx is compared to R-GemOx. These remain consistent with the findings in the company submission. For all parameters presented in the tornado plot, none were shown to an exert a significant impact compared to the deterministic base case with respect to NMB at a WTP of £20,000, thereby indicating a low level of uncertainty around the cost-effectiveness conclusion.

Figure 3: Tornado diagram showing OWSA results on NMB – Glofit-GemOx vs. R-GemOx (glofitamab PAS price, comparator and subsequent treatment list price)

[redacted]

Figure 4: Tornado diagram showing OWSA results on cost per QALY – Glofit-GemOx vs. R-GemOx (glofitamab PAS price, comparator and subsequent treatment list price)



2.3 Scenario analyses

The results of the updated scenario analyses are summarised in Table 3. These remain consistent with the results presented in the company submission.

Table 3: Scenario analysis results (glofitamab PAS price, comparator and subsequent treatment list price)

Parameter modifier	ICER vs. R-GemOx	% change from base-case	NMB at £20,000	% change from base-case
Base case	£3,412	-	[redacted]	[redacted]
Time horizon				
Time horizon, 30 years	£3,515	3.02	[redacted]	[redacted]
Time horizon, 40 years	£3,437	0.73	[redacted]	[redacted]
Time horizon, 50 years	£3,416	0.12	[redacted]	[redacted]
Approach to modelling background mortality				
Average cohort age (35 year time horizon)	£3,130	-8.26	[redacted]	[redacted]
Survival modelling and long-term remission				
PFS distribution – generalised gamma	£19,613	474.82	[redacted]	[redacted]
PFS distribution – log-logistic	£6,497	90.41	[redacted]	[redacted]
OS distribution – generalised gamma	£1,396	-59.09	[redacted]	[redacted]
OS distribution – log-logistic	£3,978	16.59	[redacted]	[redacted]
Cure point (PFS and OS) – 2 years	Dominant	-	[redacted]	[redacted]
Cure point (PFS and OS) – 5 years	£11,144	226.62	[redacted]	[redacted]
No QoL adjustment in long-term remission	£3,041	-10.87	[redacted]	[redacted]
No excess mortality in long-term remission	£2,889	-15.32	[redacted]	[redacted]
Standard mortality rate source (Howlader et al. 2017)	£5,158	51.17	[redacted]	[redacted]
Utilities				
STARGLO – EQ-5D-5L from 2L only	£3,418	0.18	[redacted]	[redacted]
Proximity to death utilities	£2,359	-30.86	[redacted]	[redacted]
TA649	£3,387	-0.73	[redacted]	[redacted]
Discounting				
1.5% discounting for costs and effects	£1,227	-64.04	[redacted]	[redacted]
Comparator and subsequent treatment PAS				
25%	£5,797	69.90	[redacted]	[redacted]
50%	£8,596	151.93	[redacted]	[redacted]

75%	£11,396	234.00	[redacted]	[redacted]

2L, second-line; EQ-5D-5L, EuroQol five-dimensional five-level; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QoL, quality of life

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

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 ensure 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.**	• Roche £20,000 towards helpline, information provision and preparing for treatment project • AbbVie £25,000 towards preparing for treatment project, helpline and information provision • Bristol-Myers Squibb £8,000 towards provision of support groups
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with diffuse large B-cell lymphoma (DLBCL). We combined the information gathered from this with our experiences of working with these patients and 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?	Lymphoma is a type of blood cancer, where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most common type, with around 14,200 people diagnosed each year in the UK. There are many different types of NHL which can be classified in two main ways. Firstly, they can be grouped depending on the type of lymphocyte they developed from: B cells or T cells. B-cell lymphomas are much more common, accounting for 90% of cases. Secondly, they can be grouped into low-grade and high-grade based on how fast they grow. The most common high-grade lymphoma is diffuse large B-cell lymphoma (DLBCL) which affects 5,500 new people every year in the UK. It can affect adults of any age but tends to be malignancy found in older people, with an average age of 65 and older. Most people with DLBCL first notice painless lumps which are enlarged lymph nodes. These are commonly in the neck, groin or armpit. Due to the high-grade nature of DLBCL the lymph nodes tend to enlarge very quickly. Sometimes the cancer can develop in other lymph nodes deep inside the body, or outside of the lymph nodes. This can cause a range of symptoms including cough, shortness of breath and abdominal pain. A third of patients will also have B symptoms when they are diagnosed. These can be night sweats, weight loss, loss of appetite, itch and fatigue as experienced by this patient, *"I had been feeling more tired and run down before I initially went to the doctor".* Our patients often describe fatigue as being particularly debilitating and difficult to deal with. One patient said, *"fatigue affects all areas of life".* Very similar to fatigue, brain fog is something which patients with lymphoma often complain of. This makes people struggle to think and focus and can impact on many things including work. One patient described how it again can impact on all aspects of life.

	A diagnosis of DLBCL does not just have an impact on the person diagnosed. These people will more often than not have spouses, partners, children, or elderly parents to look after. These people are also impacted by the diagnosis of lymphoma. It can be mentally difficult as well as time consuming for these family members as they may have to transport their loved one to hospital appointments, collect medications, visit them in hospital or look after dependents on their own. Due to this they miss out on many aspects of normal life as described by this patient, *"some aspects of life have had to be put on hold for my husband in particular".* It can also be a struggle for the family members to fully understand how their loved one is feeling. They can often all end up feeling helpless, anxious, and alone. *"We have two grown up sons and I think that when I first told them they found it difficult to hear that I was unwell…I do not know if my husband talks to them about the situation when I am not there".* DLBCL is treated with the aim of cure, unfortunately however up to 45% of people become refractory to treatment, or relapse after treatment. The prognosis for these people is poor, and the current treatment regimens available only confer a median survival of twelve months. The psychological impact of a diagnosis of lymphoma is enormous. Patients have described insomnia, anxiety and a constant fear of dying to us. Being then told that you have relapsed, or that the treatment has not worked increases all of this further. Having refractory or relapsed disease brings about prolonged symptoms, further courses of treatment as well as an increased mental strain. People describe the worry of relapsing or not responding to treatment, and then if they do, the worry that there will not any further treatment options available. One patient said, *"Worrying about how long I have raises its head from time to time from a mental health perspective".* Another said, *"I lived in fear of recurrence".* The psychological impact of relapsed or refractory disease cannot be underestimated. *"Relapse in my case was for me very disappointing and upsetting as you think about what the outcome of this relapse is going to be and what that will look like, how long it will take to become ill and die".*

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 is a regimen of chemo-immunotherapy. This is usually a combination of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP) or polatuzumab vedotin, rituximab, cyclophosphamide, hydroxydaunorubicin and prednisolone (Pola-R-CHP). Chemo-immunotherapy although often successful is very intense requiring multiple visits to the hospital. Chemo-immunotherapy also causes a number of short- and long-term side effects. Our patients have reported fatigue, sickness, diarrhoea, hair loss and recurrent infections due to neutropenia. These can all be incredibly debilitating and upsetting. One of our patient's described how upsetting they found the hair loss, *"Losing my hair the first time with RCHOP was distressing, I covered up all the mirrors in the house as I did not want to see myself".* Long term side-effects can include prolonged fatigue and peripheral neuropathy, *"My fingertips and soles of my feet have varying degrees of feeling like they have cotton wool in them sometimes".* Younger patients may also experience fertility issues which can be particularly difficult to deal with. If people do unfortunately relapse, or do not respond to treatment they require further treatment which is usually in the form of salvage chemotherapy and if well enough a stem cell transplant (SCT). This requires a long hospital stay away from friends and family. They can feel very isolated and have described their lives as being on hold during this time. Also relapsing after treatment can make the side effects even more difficult on the patient's mental health. *"When I was given the R-ICE I lost the hair on my head again. I think the most annoying aspect of this was fact it didn't work, so I did not need to lose my hair".* The next treatment option would be CAR-T therapy, or bispecific antibody therapies. These require people to be fit enough at this point, which after multiple treatments becomes less likely.

8. Is there an unmet need for patients with this condition?	Our patients are very complimentary and thankful for the treatment they have received but worry that options will run out, or they will not be well enough to receive any further treatment if they need it. Patients feel that there are multiple treatment options available currently, but as people relapse or become refractory to treatment these treatment options run out. There is therefore an unmet need for these patients and having more options available earlier would be hugely beneficial.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Our patients feel that having glofitamab available as a second line treatment provides them with another option which seems to be well tolerated and effective. One patient described the quick impact it had on her disease, *"What was interesting was the difference the medication made to my lymph nodes and the mass growing on the side of my neck as it visibly decreased and continued to do so up to and including the 2nd reduced dose the following week…Not only that but I also noticed I was not really experiencing any breathlessness and felt so much healthier, more energy".* This patient also described the few side effects she had with glofitamab and how it was a *"completely different kettle of fish"* compared to the numerous side effects she had with chemotherapy and CAR-T therapy. Our patients also feel that having another treatment option available after the first relapse or treatment failure would be a huge advantage of this treatment. They felt that having to wait for multiple relapses made a chance of cure smaller, and also potentially caused more physical side effects and a prolonged mental impact.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The only disadvantage identified by our community was the potential risk of cytokine release syndrome (CRS) with glofitamab and the resulting hospital stay. One patient described how she developed CRS when receiving glofitamab: *"I know I had CRS, but my overall experience of this treatment has been incredibly positive, I felt so much more physically and mentally… I had more energy, I was no longer breathless when I exerted myself, I didn't lose my hair. Me feeling more positive must make me easier to live with, less down days."*

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.	None were identified by our patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None were identified by our patients.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• DLBCL is the commonest high-grade lymphoma with 5,500 new diagnoses each year • Relapsed or refractory DLBCL often has a poor response to treatment with a poor prognosis • Current treatment options have a significant side effect profile • There is need for more treatment options which are well tolerated and effective •

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Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

Clinical expert statement

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The deadline for your response is **5pm** on **Thursday 29 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating relapsed or refractory diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	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 relapsed or refractory diffuse large B-cell lymphoma? ☐ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or 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.	None

8. What is the main aim of treatment for **relapsed or refractory diffuse large B-cell lymphoma?**(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To achieve cure, to delay time to next treatment and at least to control the considerable symptoms of R/R DLBCL.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Achieving partial response (<50% disease) but aiming for complete response.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes
11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of 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?	There are recently published BSH guidelines on R/R DLBAL (published 19th May 2025). These include the indication for this consultation as it is acknowledged that for transplant ineligible patients, there are limited second line options for patients. For transplant eligible pts who have relapsed within 12 months of first line treatment, they are eligible for CAR-T therapy. For transplant eligible pts who have relapsed beyond 12 months of first line treatment, they are eligible for a stem cell autograft. For transport ineligible patients, treatment options are limited, this is due to the availability of treatments (many of which are available 3rd line and beyond) and the fact that some permitted treatments impact negatively on the efficacy of subsequent therapies. There is therefore a gap in treatment for the majority of patients who relapse after 2nd line therapy and many are given treatments with limited benefit and then receive 3rd line therapies when ultimately relapse as occurs in the majority of transplant ineligible patients due to inferior 2nd line treatments.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used for 2nd line R/R DLBCL in the transplant ineligible population. It will be delivered in secondary/tertiary health care settings. These hospitals have experience of glofitamab monotherapy and GemOx so will simply be the

• 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)	administration of the combination and the trial data shows toxicity equivalent to the 2 approaches without increased toxicity for the combination. Practising haematology units should be used to delivering these agents.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes because there was an overall survival benefit with G-GemOx vs R-GemOx (with the latter being the standard of care). From the trial data increase length and quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Anyone unable to tolerate a bispecific antibody +/- chemotherapy due to allergies or comorbidities
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)	Should be broadly equivalent to current therapies used – see response to point 12.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
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	No
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?	It is a stepchange as provides a potentially curative 2nd line option and for many patients there is not a curative 2nd line option available.
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?	There are specific side effects with bispecific seg cytokine release syndrome and neurotoxicity. The rates are low but do occur so this need to be counselled and managed appropriately.
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, trial was conducted in UK patients

• 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?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma)	No
23. How do data on real-world experience compare with the trial data?	UK patients were entered into trial so RWE within trial
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: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Overall survival benefit with Glofitamab and GemOx

Limited treatment options for transplant ineligible 2nd line patients

Toxicity of combination comparable to stand alone agents

Patients currently receive suboptimal 2nd line treatment to allow them to access approved 3rd line treatments

Deliverable in most secondary and tertiary settings

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Part 1: Treating relapsed or refractory diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Sridhar Chaganti
2. Name of organisation	Roche Ltd
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☒ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or 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.	None

8. What is the main aim of treatment for **relapsed or refractory diffuse large B-cell lymphoma?**(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Ideally cure is the aim but is currently only achieved in a proportion of patients treated with either a stem cell transplant or CAR T-cell therapy. For patients not eligible or suitable for either of these, treatment is given with a non-curative intent but hoping to achieve a durable complete remission.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A complete response to treatment as assessed by PET-CT scan.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	For patients not eligible or suitable for either a stem cell transplant or CAR T-cell therapy, there remains a significant unmet need as current treatment options are all non-curative and at best will induce a short-lived response in some patients.
11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of 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?	Treatment depends upon the age and fitness of patient as well as response to prior treatment and duration of remission if achieved. BSH guidelines for relapsed/ refractory large B-cell lymphoma are widely followed in the NHS. These were recently updated. Chaganti S, Fox CP, Maybury BD, Burton C, Barrington SF, Illidge T, Kalakonda N, Eyre TA, McKay P, Kuhnl A, Cwynarski K, Davies AJ; BSH Committee. Management of relapsed or refractory large B-cell lymphoma: A British Society for Haematology Guideline. Br J Haematol. 2025 May 19. doi: 10.1111/bjh.20129. Epub ahead of print. PMID: 40384597. The pathway for 2nd and subsequent lines of therapy has undergone major changes in recent years with availability of new therapies but is generally well defined. There is however some variability, especially with reference to definition of transplant-eligibility. The current technology would be an important addition to current available treatment options for patients not eligible or suitable for stem cell transplant or CAR T-cell therapy in the 2nd line treatment setting and beyond.

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)	GemOx chemotherapy and glofitamab are both already in use in routine NHS clinical practice as individual treatments. With this new technology, the 2 treatments will be delivered as a combination. There is no difference in healthcare resource required to deliver this new treatment compared with current care in the NHS. This treatment can be delivered in all secondary and tertiary care centres in the NHS. No additional investment or training is required to introduce this technology for centres which are already delivering the two treatments individually.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. In the pivotal Phase 3 randomised Starglo trial, there was a significant improvement in overall survival with Glofit-GemOx combination compared with current standard of care R-GemOx chemo regimen (median OS of 25 months vs 12 months). Median PFS with glofit-GemOx was much longer at 13.8 months compared with 3.6 months for R-GemOx. HR QoL is expected to be better for patients with a longer duration of disease control.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Within the pivotal clinical trial, there were major differences in outcomes between different geographical territories. The benefit with glofit-GemOx was largely confined to patients treated in Asia. However, this subgroup analysis is limited by lack of adequate power and there is no scientific or biologic rationale for racial or ethnic variation in treatment response.
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?	In terms of treatment administration and management, the technology is similar to current care and should be deliverable in most centres already treating patient with these regimens individually.

(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?	Stopping rules will follow standard tests for response assessment and assessment for toxicity.
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	Administration of treatment is similar to current care. Improvements in QALY are expected due to better and more durable remissions.
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?	This technology represents an improvement over the current offering for patients. It offers the potential to improve survival for patients with relapsed/ refractory DLBCL who are neither candidates for a stem cell transplant or for CAR T-cell therapy.
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?	Treatment appears well tolerated with a manageable safety profile as expected with these regimens
20. Do the clinical trials on the technology reflect current UK clinical practice?	• In the UK practice this would be an important option and replace R-GemOX chemotherapy.

• 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?	• OS and PFS benefit • N/A • N/A
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 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma)	Loncastuximab and Cd3 x CD20 BsAb (epcoritamab and glofitamab) are also options for some patients in the 3rd line and beyond setting.
23. How do data on real-world experience compare with the trial data?	Pola BR real world data is much worse than the pivotal 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	This treatment is likely to be delivered across most treatment centres and therefore should be more accessible compared to transplant or CAR T-cell therapies.

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: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Glofit-Gemox offers survival benefor compared to current care for patients with relapsed or refractory DLBCL who are not candidates for a stem cell transplant or CAR T-cell therapy

If approved, Glofit-GemOx is expected to replace the current SoC R-GemOc chemotherapy regimen in this setting

The combination has a manageable safety/ toxicity profile which most treatment centres should already be familiar with.

No new or additional resource is required for adoption of this technology in the NHS

This treatment will represent a significant step forward for patients with relapsed/ refractory DLBCL

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CDF clinical lead submission

Email from Peter Clark:

1. An analysis of pola-BR in Jan-Dec 2024 showed a blueteq registration rate of 34/mo, n=411. Of these, 18% had refractory disease to 1L and had not rec'd any 2L treatment. 41% had relapsed disease after 1L and had not rec'd any 2L therapy. 59% therefore were receiving pola-BR as 2L.

2. An analysis of pola-BR in Jan-April 2025 showed a blueteq registration rate of 28/mo, n=112. Of these, 15% had refractory disease to 1L and had not rec'd any 2L treatment. 44% had relapsed disease after 1L and had not rec'd any 2L therapy. 59% therefore were receiving pola-BR as 2L.

3. Although pola-BR use is slowly diminishing since the incorporation of pola into 1L therapy, 2L pola-BR remains in play at present. The use of pola-BR pre-SCT is likely to be very small. The use of pola-BR prior to 2L CAR T has in effect stopped. The current 28/mo pola-BR rate therefore applies to the population in the glofit-gemox appraisal.

4. My DLBCL experts were surprised at the significant and continued use of pola-BR as 2L therapy. Whilst they were quick to point out that their views apply to specialist centres, it is clear that more loco-regional MDTs think otherwise.

5. NHSE’s conclusion therefore is that pola-BR remains a comparator for glofit-gemox in ID6202.

University of Southampton

SHTAC

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma

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Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Fay Chinnery, Research Fellow, Health economics Emma Maund, Research Fellow, Evidence synthesis Keith Cooper, Principal Research Fellow, Health economics David Alexander Scott, Professorial Research Fellow, Statistics Geoff Frampton, Principal Research Fellow, Evidence Synthesis
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Dr Harriet Walter, Associate Professor of Medical Oncology, University of Leicester and University Hospitals Leicester

Dr David Wrench, Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust

We also thank Jonathan Shepherd (Principal Research Fellow) and Marcia Takahashi (Research Fellow) of Southampton Health Technology Assessments Centre (SHTAC), for providing a quality assurance review of the draft report. We additionally thank Lois Woods, (Senior Research Assistant) of SHTAC, for critically appraising the systematic literature review search strategies

Declared competing interests of the authors and advisors

The authors and Dr Wrench declare none.

Dr Smith received financial support from Roche (manufacturer of glofitamab) for travel, accommodation and conference fees to attend the 2024 European Haematology Association Conference in Madrid. He confirms that he did not contribute to any company work relating to glofitamab or the specified comparators for diffuse large B-cell lymphoma.

Dr Walter received a medical education grant from Pfizer (gemcitabine, vincristine) for developing 'A multi- Targeted Approach to improving Clinical Trials Access – South Asian cohort (TACTA- SA)'. This was not related to a specific drug or trial but to improve inclusivity in research activities. Dr Walter also received a medical grant from BeiGene. This was not related to diffuse large B-cell lymphoma nor bispecific therapies.

Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Emma Maund critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Alexander Scott critically appraised the indirect treatment comparisons and drafted the report; Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report and is the guarantor.

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2L	Second-line
3L	Third-line
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine transaminase
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine in combination with rituximab
BSH	The British Society for Haematology
CAR-T	Chimeric antigen receptor T cell
CI	Confidence interval
CON	Commercial in confidence
CNS	Central Nervous System
CRD	Centre for Reviews and Dissemination
CRS	Cytokine Release Syndrome
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DOCR	Duration of complete response
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMC	Electronic Medicines Compendium
eMIT	Electronic market information tool (drugs and pharmaceutical)
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol 5-dimension health questionnaire, 3 Levels

EQ-5D-5L	EuroQol 5-dimension health questionnaire, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire
FACT-Lym LymS	Functional Assessment of Cancer Therapy−Lymphoma subscale
Glofit	Glofitamab
Glofit-GemOx	Glofitamab in combination with gemcitabine and oxaliplatin
HMRN	Haematological Malignancy Research Network
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICU	Intensive care unit
IPD	Individual patient level data
IPI	International Prognostic Index
IRC	Independent review committee
ITT	Intention to treat
LYG	Life-years gained
MedDRA	Medical Dictionary for Regulatory Activities terminology
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NALT	New alternative lymphoma therapy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
ORR	Objective Response Rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PET	Positron emission tomography
PFS	Progression-free survival

Pola-BR	Polatuzumab vedotin in combination with bendamustine and rituximab
Pola-R-CHP	Polatuzumab vedotin, rituximab, doxorubicin, cyclophosphamide and prednisolone
PS	Performance status
PPS	Post-progression survival
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
R-CHOP	Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone
R-CHP	Rituximab in combination with doxorubicin, cyclophosphamide and prednisolone
R-DECC	Rituximab in combination with dexamethasone, etoposide, chlorambucil and lomustine
R-GDP	Rituximab in combination with gemcitabine, dexamethasone, and cisplatin
R-GemOx	Rituximab in combination with gemcitabine and oxaliplatin
R-MitCEBO	Rituximab in combination with prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine
R/R	Relapsed or refractory
RR	Relative risk/risk ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System Organ Class
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
ToT	Time-on-treatment
TSD	Technical Support Document

UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of Key Issues identified by the EAG

ID	Summary of issue	Report sections
Issue 1	Exclusion of Pola-BR (polatuzumab vedotin in combination with bendamustine and rituximab)	2.3
Issue 2	Over-estimation of survival estimates	4.2.6.1.2 and 4.2.6.1.3
Issue 3	Proportion of patients not receiving third-line treatment	4.2.8.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are listed in section 1.6.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost effectiveness ration (ICER) is the ratio of the extra cost for every QALY gained.

Following their response to the Clarification Questions, the company updated their economic model. The company's revised deterministic base case cost-effectiveness results are shown in Table 2 with a confidential patient access scheme (PAS) discount applied for glofitamab and obinutuzumab (administered as a pre-treatment prior to cycle 1 and made by the same company). The ICER is £3,412 per QALY for glofitamab with gemcitabine and oxaliplatin

(Glofit-GemOx) versus rituximab with gemcitabine and oxaliplatin (R-GemOx), with a QALY gain of [redacted] and an additional cost of [redacted].

Table 2 Company revised base case results with PAS for glofitamab and obinutuzumab

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Glofit-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	£3,412
R-GemOx	[redacted]	[redacted]			

Source: Clarification Response Appendix Table 1
Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; R-GemOx, rituximab with gemcitabine and oxaliplatin

1.3 The decision problem: summary of the EAG's key issues

Exclusion of the second-line comparator regimen Pola-BR (polatuzumab vedotin in combination with bendamustine and rituximab)

Report section	2.3
Description of issue and why the EAG has identified it as important	For the intervention in the NICE scope, i.e. Glofit-GemOx (glofitamab plus gemcitabine and oxaliplatin), Pola-BR is a relevant second-line comparator. However, the company have excluded this comparator as they argue that, according to clinical expert opinion, Pola-BR is "very rarely used" ("0-10% estimated") as a second-line treatment today (CS Table 1 and CS section 1.3.2.1.2). The EAG's three clinical experts agreed that its use has declined due to the availability of Pola-R-CHP (polatuzumab vedotin in combination with rituximab, doxorubicin, cyclophosphamide and prednisolone) as a first-line treatment (NICE TA874). The estimated range of use of Pola-BR provided by the EAG's clinical experts suggested that it may currently be up to 10-20% for transplant ineligible patients.
What alternative approach has the EAG suggested?	An indirect treatment comparison (ITC) might be feasible to compare Glofit-GemOx against Pola-BR. However, having

	excluded this comparison, the CS does not discuss this possibility. The EAG is aware that potentially relevant Pola-BR studies exist, for example the GO29365 trial comparing Pola-BR against bendamustine plus rituximab which informed NICE TA649. However, an updated systematic literature review and ITC feasibility assessment would be required to confirm which studies, if any, could be incorporated into a second-line ITC.
What is the expected effect on the cost-effectiveness estimates?	Unknown, since this comparison has not been performed.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion to clarify the extent to which Pola-BR is used as a second-line treatment for relapsed or refractory DLBCL in clinical practice and whether this use would be expected to change given that Pola-R-CHP is now available for first-line treatment. Feasibility assessment for second-line ITC if appropriate (see section 3.3.1).

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Over-estimation of survival estimates

Report section	4.2.6.1.2 and 4.2.6.1.3
Description of issue and why the EAG has identified it as important	The company set the cure point to three years. After this time, the mortality risk for the remaining patients reverts to a near general population level (9% excess vs. the general population based on a standardised mortality rate (SMR) identified from Maurer 2014), adjusted to account for potential excess comorbidities. The EAG notes that, at three years in the model, about 14% of patients in the Glofit-GemOx arm and about 18% of patients in the R-GemOx are alive and that their disease has progressed. We consider that mortality for patients who are progression-free should match the general population mortality, but that patients whose disease has progressed should continue to experience disease-related mortality. Furthermore, the overall survival estimates at five years appear to be overestimated compared to estimates in the literature and from our clinical experts.

What alternative approach has the EAG suggested?	In the model, the majority of patients with progressed disease have died by six years. Consequently, we set the cure point to six years and assume patient mortality is the same as general population mortality after this time.
What is the expected effect on the cost-effectiveness estimates?	Delaying the cure point to six years reduces long-term overall survival estimates in both treatment arms and increases the company base ICER to £9,851 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice about when all patients with DLBCL whose disease has progressed in the second-line setting would have died.

Underestimation of the proportion of patients not receiving third-line treatment

Report section	4.2.8.3
Description of issue and why the EAG has identified it as important	CS Table 55 shows the distribution of subsequent treatments for the patients who receive third-line therapy in the company's base case (100% of patients). Clinical advice to the EAG is that a significant proportion of patients (range: 20% - 50%) would be too frail to tolerate third-line therapy and would receive palliative care instead.
What alternative approach has the EAG suggested?	We take an average of our clinical experts' estimates and set the proportion of patients not receiving third-line treatment in the model to 30%. We conduct scenario analyses setting this proportion to 20% and 50%.
What is the expected effect on the cost-effectiveness estimates?	Reducing total post-discontinuation treatment costs in both arms by 30% increases incremental costs, increasing the company's base case ICER to £7,381 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice about the proportion of patients with DLBCL whose disease has progressed in the second-line setting who would receive palliative care only.

1.5 Other key issues: summary of the EAG's view

We have identified several other aspects of the company base case with which we disagree (listed below in section 1.6), but we note that these changes have a negligible effect on the ICER result.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Our preferred model assumptions are the following:

- Mortality (for patients who are progression-free or whose disease has progressed) is assumed to be same as general population mortality after six years, instead of three years (section 4.2.6.1.3; Key Issue 2 – see section 1.4)
- Proportion of patients not receiving third-line treatment: 30% (section 4.2.8.3; Key Issue 3 – see section 1.4)
- Utility scores specific to second-line patients, rather than from the ITT (Intention to Treat) population (section 4.2.7.3)
- GemOx given for 6 cycles in both arms, rather than 8 cycles (section 4.2.8.1.2)
- Use the one-off progression resource use shown in Table 23 (section 4.2.8.4)
- Terminal end-of-life costs (Table 24) used, rather than the weekly healthcare resource use costs (section 4.2.8.4)
- Administration cost applied once for each combination of treatments, rather than for each treatment (section 4.2.8.1)
- Adverse event costs included for tumour lysis syndrome included in Glofit-GemOx arm (section 4.2.8.5)

Table 3 shows the cumulative cost-effectiveness results using the EAG's preferred assumptions. When using these assumptions, the ICER increases to £12,257 per QALY for Glofit-GemOx versus R-GemOx.

Table 3 EAG's preferred model assumptions, cumulative results, PAS for glofitamab and obinutuzumab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY.
Company base-case	Glofit-GemOx	[redacted]	[redacted]	£3,412
	R-GemOx	[redacted]	[redacted]	
+ Mortality same as for general population after six years	Glofit-GemOx	[redacted]	[redacted]	£9,851
	R-GemOx	[redacted]	[redacted]	
+ 30% of patients not receiving 3L treatment	Glofit-GemOx	[redacted]	[redacted]	£13,396
	R-GemOx	[redacted]	[redacted]	
+ Utility scores specific to 2L patients	Glofit-GemOx	[redacted]	[redacted]	£13,398
	R-GemOx	[redacted]	[redacted]	
+ GemOx given for 6 cycles in both arms	Glofit-GemOx	[redacted]	[redacted]	£13,123
	R-GemOx	[redacted]	[redacted]	
+ Use revised progression resource use	Glofit-GemOx	[redacted]	[redacted]	£13,122
	R-GemOx	[redacted]	[redacted]	
+ Use terminal costs, rather than weekly healthcare resource use costs	Glofit-GemOx	[redacted]	[redacted]	£12,708
	R-GemOx	[redacted]	[redacted]	
+ Administration cost applied once for each combination of treatments	Glofit-GemOx	[redacted]	[redacted]	£12,181
	R-GemOx	[redacted]	[redacted]	
+ Adverse event: Grade 3 Tumour lysis syndrome in Glofit-GemOx arm	Glofit-GemOx	[redacted]	[redacted]	£12,257
	R-GemOx	[redacted]	[redacted]	
EAG base case	Glofit-GemOx	[redacted]	[redacted]	£12,257
	R-GemOx	[redacted]	[redacted]	

Source: EAG created table
2L, second line; 3L, third line; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life-year; R-GemOx, rituximab with gemcitabine and oxaliplatin

The model results are most sensitive to using the mortality the same as the general population after six years and 30% of patients not receiving third-line treatment. All other changes have only minimal effect on the model results. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Roche on the clinical effectiveness and cost effectiveness of glofitamab in combination with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL). It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the External Assessment Group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 25th February 2025. A response from the company via NICE was received by the EAG on 20th March 2025 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on diffuse large B-cell lymphoma

CS section 1.3 provides key background information on diffuse large B-cell lymphoma (DLBCL), covering incidence and prevalence, diagnosis and staging, prognostic factors, risk factors, and quality of life. We summarise the key facts of relevance from the CS together with supplemental information, where appropriate, below.

DLBCL is a type of blood cancer that affects white blood cells called B lymphocytes or B cells. DLBCL is a high grade (fast growing) lymphoma, with a median survival of one year if left untreated. In the UK, approximately 5440 people are diagnosed with DLBCL each year.[1] The incidence of DLBCL increases with age, with a median age at diagnosis in the UK of approximately 70 years, and is slightly more common in males than females.[1] There are various subtypes of DLBCL.[2] However, approximately 90% of cases are classified as DLBCL not otherwise specified (DLBCL NOS).[1] The EAG's clinical experts commented that rarer subtypes of DLBCL can have poorer prognosis than DLBCL NOS. However, the experts differed in opinion on whether rarer DLBCL subtypes would be managed differently to DLBCL NOS.

The most common symptom of DLBCL is one or more painless swellings at single or multiple nodal (lymph node) or extranodal (non-lymph node) sites. These swellings or lumps are caused by the accumulation of abnormal B cells and result in damage to local and surrounding tissues and organs. Other common symptoms, referred to as "B symptoms", include excessive sweating at night, unexplained fever and weight loss.

Clinical experts advised the EAG that DLBCL is diagnosed preferably through surgical excisional biopsy, or needle core biopsy if this not possible. The experts agreed that the extent of disease, which predicts prognosis and contributes to treatment options, can be classified using the Ann Arbor and/or Lugano staging classification systems.

DLBCL prognosis is predicted using the International Prognostic Index (IPI). The IPI consists of five risk factors: Age at diagnosis (>60 years); serum lactate dehydrogenase level (> upper limit of normal); Eastern Cooperative Oncology Group (ECOG) performance status (PS) (≥2); Ann Arbor Stage (stage III or IV); and number of extranodal sites (>1 site). Each risk factor present scores one, giving rise to an IPI score ranging from 0 (no risk factors present) to 5 (all 5 risk factors present). Based on the IPI score, patients are assigned to one of four risk groups in the original IPI: low (IPI score 0 or 1), low-intermediate (IPI score 2), high-intermediate (IPI score 3), high (IPI score 4-5);[3] or to one of three risk groups in the revised IPI: very good' (IPI score 0), 'good' (IPI score 1-2) and 'poor' (IPI score 3-5).[4] The IPI score is used to inform first-line treatment options. Other prognostic factors include cell-of-origin; MYC, BCL2 and/or BCL 6 gene and protein expressions; and TP53 mutations; however, these currently do not inform treatment options.

2.2.2 Treatment pathway for DLBCL

2.2.2.1 First-line treatment

Approximately 80% of patients diagnosed with DLBCL receive treatment at first line. For first-line treatment, the British Society of Haematology (BSH) recommends rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) for patients with advanced stage disease and an IPI score of 1 and polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone (Pola-R-CHP) or R-CHOP for an IPI score of 2-5.[5] Pola-R-CHP treatment regimen is recommended by NICE in technology appraisal TA874.[6] Clinical expert advice to the EAG is that 50% of patients who receive first-line treatment receive R-CHOP and 50% Pola-R-CHP. The CS states that of the patients who receive R-CHOP at first-line, approximately 60% will be cured and the remaining 40% will either be refractory to treatment (progressive disease or non-response from the start of first-line treatment) or relapse (return of disease after complete response to first-line treatment). Clinical expert advice to the EAG is that refractory DLBCL is typically defined as disease that either does not respond adequately to first-line treatment or returns within 6 months, i.e. refractory DLBCL includes early relapse within 6 months of completion of first-line treatment. Relapse is typically considered as disease recurrence after 6 months. One expert, however, highlighted that there is variation in how refractory is

defined in the literature, with relapse 3 months, 6 months or 12 months post first-line treatment. Relapse is more likely to happen within two years of the end of first treatment.[7] Clinical expert opinion to the EAG is that for patients receiving Pola-R-CHP, the percentage cured will be slightly higher compared to that with R-CHOP while the percentage of patients who are refractory to, or relapse after Pola-R-CHP is likely to be slightly less than with R-CHOP.

2.2.2.2 Second-line treatment

CS section 1.3.2.1 states that approximately 31% of patients diagnosed with DLBCL are estimated to receive second-line treatment. The EAG could not locate this data in the cited source, Elstrom et al., 2010.[8] However, clinical expert advice to the EAG is that this is a reasonable estimate. The EAG's clinical experts confirmed there are no current national or European guidelines for treating refractory or relapsed DLBCL, but they occasionally refer to the USA National Comprehensive Cancer Network guideline. The EAG received confirmation from the BSH that their guideline "Management of Relapsed or Refractory Large B-cell Lymphoma' is awaiting publication.[9] Treatment options depend on whether the patient is eligible for autologous stem cell transplant (ASCT) or not. CS section 1.3.2.1.1 states there are no standardised criteria for selecting patients for ASCT but, in general, patients will need to be young enough (e.g. aged <70 years) and fit enough (e.g. acceptable cardiac and renal function, ECOG performance score <2). The EAG's clinical experts agreed that there are no standardised criteria. One expert highlighted that age is not a criterion for ASCT, as there are fit patients in their 70s who may be transplanted. This expert described assessing patient fitness for ASCT as a typically individualised process that takes into account medical fitness, comorbidities,[10] previous treatment and disease status.

2.2.2.2.1 ASCT-eligible treatment option

Approximately 50% of patients who receive second-line treatment for DLBCL are ASCT eligible.[11, 12] Twenty five percent of ASCT eligible patients receive high dose salvage chemotherapy and, upon evidence of complete or partial response consolidation with ASCT.[13] The remaining 75% of ASCT eligible patients are those who did not respond to first-line therapy or had an early relapse within 12 months of completing first-line therapy.[13] These patients may be eligible for autologous chimeric antigen receptor (CAR) T-cell therapy as second-line treatment. The current CAR-T therapy available for this indication in the NHS are axicabtagene ciloleucel (TA895),[14] under the managed access agreement under the Cancer Drugs Fund, and lisocabtagene maraleucel (TA1048) (routine commissioning).[15] It should be noted that final guidance for lisocabtagene maraleucel was published by NICE on 26 March 2025 and therefore this therapy is not included in the NICE scope.

2.2.2.2.2 ASCT ineligible treatment options

It is estimated that 50% of patients who receive second-line treatment for DLBCL are ineligible for ASCT.[11, 12] For these patients, three treatment options are available: i) rituximab in combination with one or more chemotherapy regimen, ii) polatuzumab vedotin with rituximab and bendamustine, and iii) participation in a clinical trial of an investigation drug. These are described in more detail below.

2.2.2.2.2.1 Rituximab in combination with one or more chemotherapy regimen

Examples of rituximab in combination with one or more chemotherapy drugs specified in the NICE scope are:

- Rituximab with gemcitabine and oxaliplatin (R-GemOx)
- Rituximab with gemcitabine (R-Gem)
- Rituximab with prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine (R-P-MitCEBO)
- Rituximab with dexamethasone, etoposide, chlorambucil, lomustine (R-DECC)
- Bendamustine with rituximab (BR)

CS section B.1.3.2.1.2 states that R-GemOx is the standard of care regimen and is considered representative, in terms of efficacy and safety, of the rituximab-chemotherapy combinations. However, there was a lack of consensus among the EAG's clinical experts as to whether R-GemOx is a standard of care regimen. Two of three clinical experts advising the EAG use R-GemOx as a standard of care regimen whilst the third expert uses rituximab in combination with gemcitabine, dexamethasone, and cisplatin (R-GDP). Furthermore, two of the experts stated that the rituximab-chemotherapy regimen varies depending on local practice and preference, whilst the third expert considered it mostly consistent across the country. All three experts stated that the other rituximab-chemotherapy regimens included in the NICE scope are rarely if ever used in clinical practice and one expert commented that R-Gem and R-P-MitCEBO are inferior to other combinations listed in the NICE scope. However, all experts agreed that, overall, R-GemOx can be considered representative of all rituximab-chemotherapy regimens used second-line for non-transplant candidates in terms of efficacy and safety outcomes.

R-GemOx is well-tolerated but survival outcomes are poor with five-year survival rates of 13.9%.[16]

2.2.2.2.2.2 Polatuzumab vedotin with rituximab and bendamustine

Polatuzumab vedotin (Polivy®) in combination with bendamustine and rituximab (Pola-BR) is recommended by NICE for the treatment of adult patients with relapsed or refractory DLBCL who are not candidates for ASCT (TA649).[17]

UK clinical experts consulted by the company suggested that Pola-BR is very rarely used in the second-line (0-10% estimated) due to: i) the approval of Pola-R-CHP as a first-line DLBCL therapy,[18] ii) BlueTeq restrictions to prevent re-exposing patients to polatuzumab, and iii) a reluctance to prescribe bendamustine-containing regimens in this setting as this may preclude the use of T-cell effector therapies (CAR-T, bispecific monoclonal antibodies) in later lines. All three clinical experts advising the EAG agreed that overall use of Pola-BR has declined since polatuzumab has been recommended as a first-line treatment.[18] However, all EAG experts agreed that Pola-BR is still used in a sufficient number of patients to be considered a relevant comparator for this appraisal (estimates of the use of Pola-BR by each of our clinical experts were: ≤10%, 10-15%, 10-20%).

2.2.2.2.2.3 Clinical trials

The EAG's clinical experts suggested that ≤10% of patients may be suitable to participate in clinical trials in the second-line setting.

2.2.2.3 Third and later lines of treatment

Third-line and later treatments are specified comparators in the NICE scope. However, the CS does not provide any background information on these, as they are excluded from the company's decision problem (section 2.3).

To support their decision problem the company investigated the availability and suitability of comparative evidence for third and later lines of therapy for potential inclusion in indirect treatment comparisons. The company concluded that such analyses would not be reliable (see discussion in section 3.3.2 below).

2.2.3 Background information on glofitamab with gemcitabine and oxaliplatin

CS Table 2 gives a summary description of glofitamab in combination with gemcitabine and oxaliplatin (henceforth referred to as Glofit-GemOx). Glofitamab is a T-cell engaging bispecific monoclonal antibody that binds bivalently to the protein CD20 on B-cells and monovalently to the protein CD3 on T-cells. Simultaneously binding to these proteins facilitates the formation of immunological synapses, subsequent T-cell activation and proliferation, and resultant T-cell mediated lysis of CD20-expressing B-cells.[19]

Gemcitabine and oxaliplatin are cytotoxic chemotherapy drugs. Gemcitabine is a nucleoside analogue that becomes incorporated into DNA of cells undergoing DNA replication.[20] Oxaliplatin is a platinum-based alkylating compound that causes DNA lesions.[21] Gemcitabine and oxaliplatin have been shown to have immunomodulatory effects on the tumour microenvironment, which enhances the immunogenicity of tumours without inhibiting cytotoxic T-lymphocyte function.[22, 23] The CS states that these factors support the combination of gemcitabine and oxaliplatin with a T-cell engaging therapy such as glofitamab. The CS also notes that gemcitabine has been shown to upregulate CD20, which could lead to increased CD20 bispecific antibody-binding capacity of the tumour.[24]

The MHRA granted marketing authorisation for glofitamab as a monotherapy, for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systematic therapy, in October 2023. UK marketing authorisation for glofitamab in combination with GemOx is expected in [redacted]. The proposed indication is: [redacted]. The EAG note that glofitamab monotherapy has a broader indication, i.e. for DLBCL, compared to the glofitamab combination therapy, i.e. DLBCL NOS.

Treatment with glofitamab consists of twelve 21-day cycles. All patients require pre-treatment with obinutuzumab (a monoclonal antibody immunotherapy treatment which depletes circulating B-cells) and other prophylactic agents on cycle 1 day 1 to reduce the risk of cytokine release syndrome. Glofitamab is administered as an intravenous (IV) infusion. It must be administered according to a dose step-up schedule in cycle 1 (2.5mg on Day 8 and 10mg on Day 15) leading to the recommended dose of 30 mg in cycle 2 Day 1 and on Day 1 of cycles thereafter. Glofitamab is given in combination with IV gemcitabine (1000 mg/m^2) and IV oxaliplatin (100mg/m^2) at cycles 1-8 and as monotherapy at cycles 9-12. The draft SmPC for Glofit-GemOx and the current SmPC for glofitamab monotherapy, state that all patients must be monitored for signs and symptoms of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) following glofitamab administration.[25, 26] Furthermore, at least 1 dose of tocilizumab (a monoclonal antibody that blocks the activity of pro-inflammatory cytokines) must be available prior to glofitamab infusion at Cycles 1 and 2 in order to treat an event of cytokine release syndrome.[25, 26]. One of the EAG's clinical experts commented that cytokine release syndrome is the biggest risk associated with glofitamab monotherapy. All EAG clinical experts had experience of using

glofitamab as a monotherapy and were familiar with the management of cytokine release syndrome.

CS sections 1.1.1 and 1.3.3 state that UK clinical experts consulted by the company at a recent advisory board were in agreement that there is an unmet need for a second-line therapy in transplant-ineligible patients since current treatments are ineffective and are only used as a 'stepping stone' to allow patients to progress to more effective treatments in the third-line setting.[27] Clinical experts advising the EAG considered this more nuanced in that the use of rituximab in combination with one or more chemotherapy agents in transplant-ineligible patients often necessitates access to third-line treatments.

2.2.4 The position of Glofit-GemOx in the treatment pathway

CS Figure 1, reproduced in Figure 1 below, shows the company's proposed position of Glofit-GemOx in the relapsed or refractory disease management pathway for patients who are ineligible for autologous stem cell transplantation (ASCT).

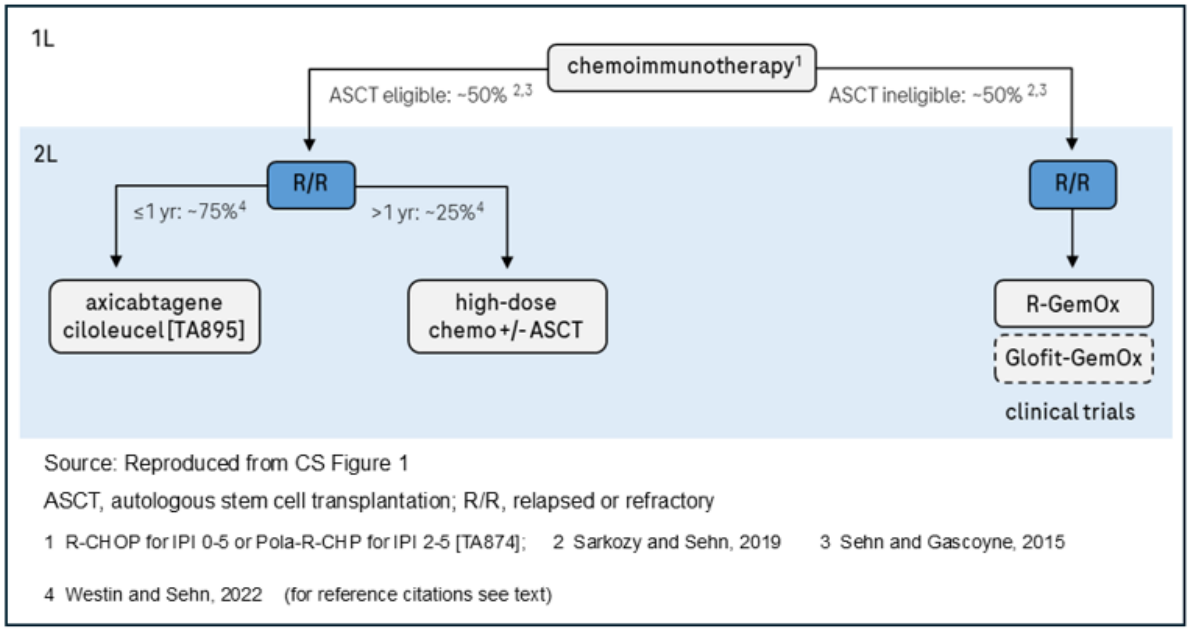

Figure 1 Proposed position of Glofit-GemOx in the treatment pathway

The anticipated licence indication includes [redacted] (CS section B.1.). However, the company proposes Glofit-GemOx for patients who are ineligible for ASCT who have progressed during or after one prior treatment only i.e. the company does not consider Glofit-GemOx as an option for adult patients with relapsed or refractory diffuse large B-cell

lymphoma after 2 or more systemic therapies (see section 2.3 below for discussion). The EAG's clinical experts agreed that the company's positioning of Glofit-GemOx specifically as a second-line therapy is appropriate.

EAG conclusion

The CS provides a detailed and comprehensive background description of DLBCL and current clinical practice, drawing on available British guidelines, NICE technology appraisals and UK clinical experts' opinion. The EAG's clinical experts agree with the company's assertion that there is an unmet need for a second-line therapy for relapsed or refractory patients with DLBCL NOS who are unsuitable for autologous stem cell transplant. Our experts consequently agreed with the company's positioning of Glofit-GemOx as a second-line therapy for this population.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the company's decision problem in relation to the final scope issued by NICE and the EAG's comments on this.

In summary, the company's decision problem is narrower than the NICE scope in the following four respects:

- **DLBCL subtype.** The condition specified in the NICE scope is diffuse large B-cell lymphoma (DLBCL). The company's decision problem is specifically limited to people with DLBCL not otherwise specified (DLBCL NOS), as this was the population included in the company's pivotal trial, STARGLO and is consequently the condition specified in the expected marketing authorisation.
- **Exclusion of the second-line comparator Pola-BR.** The company have excluded polatuzumab vedotin in combination with bendamustine and rituximab (Pola-BR) because they believe it is rarely used as a second-line therapy. However, the EAG's clinical experts estimated that 10-20% of second-line patients may receive Pola-BR and therefore we have questioned the appropriateness of excluding this comparator. The EAG consider this a Key Issue (see Key 0, section 1.3)
- **Assumption that R-GemOx is representative of other second-line rituximab-based regimens.** The company assume that rituximab plus gemcitabine and oxaliplatin (R-GemOx) is representative of the clinical efficacy and safety of other rituximab-chemotherapy regimens and have excluded these regimens as comparators. The EAG's clinical experts agreed that overall, R-GemOx could be considered representative of all rituximab-chemotherapy regimens in terms of efficacy and safety so the company's approach is appropriate
- **Exclusion of third-line Glofit-GemOx and comparators from the decision problem.** The company argue that the greatest unmet need for Glofit-GemOx is in the second-line setting, and that there is insufficient robust evidence to conduct indirect comparisons to establish the relative clinical efficacy and safety of comparators at the third line and beyond. The EAG's clinical experts agreed that the company's approach is appropriate.

Table 4 Summary of the decision problem

	Final scope issued by NICE[a]	Company's decision problem[a]	Rationale if different from the final NICE scope[a]	EAG comments
Population	Adults with relapsed or refractory **diffuse large B-cell lymphoma:** • after 1 systemic therapy when autologous stem cell transplant is not suitable or • after 2 or more systemic therapies	Adult patients with relapsed or refractory (R/R) **diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS)** who are ineligible for autologous stem cell transplantation (ASCT) who have progressed during or after one prior treatment only (CS section 1.1), **i.e. for patients in the second-line setting**	The proposed reimbursement population is narrower than the full market authorisation because: • A feasibility assessment confirmed that ITCs versus regimens in the 3L setting are not possible. • UK clinical experts confirmed that the greatest unmet need in R/R DLBCL is in the 2L setting. • The 2L setting is where the available evidence base is most robust (e.g. 2L setting in the pivotal trial STARGLO) and allows for the most robust case for the cost-effectiveness of Glofit-GemOx to be considered	**DLBCL subtype:** The company's decision problem is specifically limited to people with DLBCL not otherwise specified (DLBCL NOS), which is the population of the pivotal trial but narrower than the NICE scope which does not specify DLBCL subtypes. The EAG note that approximately 90% of cases of DLBCL are classified as DLBCL NOS. **Unmet need:** The EAG's clinical experts agree with the company's assertions that the greatest unmet need for Glofit-GemOx is in the 2L setting. One clinical expert commented that while there are many treatment options in the 3L setting this is not the case for the 2L setting.
Intervention	Glofitamab with gemcitabine and oxaliplatin	In line with the NICE scope	Not applicable	The intervention matches the NICE scope
Comparators	After 1 systemic therapy and when autologous stem cell transplant is not suitable: • R-chemotherapy regimen e.g.:	After 1 systemic therapy and when autologous stem cell transplant is not suitable: • R-GemOx	**Exclusion of Pola-BR:** The company does not consider Pola-BR to be a relevant comparator for 2L	**Exclusion of Pola-BR:** The EAG's clinical experts all agreed with the company that 2L use of Pola-BR has declined due to the use of Pola-R-CHP as a 1L

	Final scope issued by NICE[a]	Company's decision problem[a]	Rationale if different from the final NICE scope[a]	EAG comments
	• R-GemOx • R-Gem • R-P-MitCEBO • R-DECC • BR • Pola-BR After 2 or more systemic therapies: • R-chemotherapy regimen • Pola-BR (only when stem cell transplantation is not suitable) • Axicabtagene ciloleucel • Glofitamab • Loncastuximab tesirine (only if previously treated with polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated) • Epcoritamab (only if previously treated with polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated)		R/R DLBCL (see CS section B.1.3.2.1.2). The rationale for excluding Pola-BR from the analysis is based on the opinion of UK clinical experts advising the company, which is that Pola-BR is very rarely used in the 2L today (0-10% estimated). **Exclusion of all 2L R-chemotherapy regimens except R-GemOx:** R-chemotherapy regimens are reflected by R-GemOx only as the company considers this is the standard of care for 2L transplant-ineligible DLBCL. UK clinical experts advising the company confirmed that this regimen is representative of all 2L R-chemo regimens in terms of efficacy and safety outcomes. **Exclusion of 3L comparators:** Due to the restriction of reimbursement to 2L patients, the company considers 3L comparators are no longer relevant.	treatment. However, the experts all disagreed with the company's exclusion of Pola-BR as a 2L therapy, since 10-20% of patients still receive this. The EAG consider this a Key Issue (see Key 0, section 1.3). **Exclusion of all 2L R-chemotherapy regimens except R-GemOx:** The EAG considers the company's assertion that R-GemOx is standard care for 2L transplant-ineligible DLBCL may not reflect the variation in NHS clinical practice but we agree, based on clinical expert advice, that R-GemOx can be considered representative of all R-chemotherapy regimens in terms of efficacy and safety outcomes. **Exclusion of 3L comparators:** Due to the company's restriction of the Glofit-GemOx indication to 2L patients, and limitations in the availability of 3L evidence (see section 3.3.2), the EAG agrees that it is appropriate to exclude 3L comparators from the company's decision problem.

	Final scope issued by NICE[a]	Company's decision problem[a]	Rationale if different from the final NICE scope[a]	EAG comments
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	In line with the NICE scope	Not applicable	The outcomes match the NICE scope
Subgroups	None specified	None specified	Not applicable	The company's decision problem population is a post hoc subgroup of the total population of the company's pivotal trial, STARGLO.
Special consider-ations including issues related to equity or equality	None specified	None specified	Not applicable	Not applicable

Source: Partly reproduced from CS Table 1, CS section 1.1
1L, first line; 2L, second line; 3L, third line; BR, rituximab and bendamustine; DLBCL, diffuse large B-cell lymphoma; EAG, evidence assessment group; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; N/A, not applicable; Pola-BR, polatuzumab vedotin with rituximab and bendamustine; R-chemotherapy, rituximab with chemotherapy; R-DECC, rituximab with dexamethasone, etoposide, chlorambucil, lomustine R-GDP, rituximab with gemcitabine, dexamethasone and platinum (usually cisplatin); R-Gem, rituximab with gemcitabine; R-GemOx, rituximab with gemcitabine and oxaliplatin; R-P-MitCEBO, rituximab with prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin and vincristine; R/R DLBCL, relapsed or refractory diffuse large B-cell lymphoma.
[a] Abridged version of information provided in CS Table 1.

EAG conclusion on the company's decision problem

The company's decision problem is narrower than the scope of the appraisal in four respects regarding the population and comparators. (i) The EAG and EAG's clinical experts agree with the company's clinical justifications of restricting the population to second-line patients (i.e. excluding. excluding third and later lines of therapy from comparison). (ii) The company's pivotal trial and hence the decision problem restricts the population to those patients with DLBCL NOS, which is narrower than the NICE scope. (iii) The EAG's clinical experts consider the company's exclusion of Pola-BR inappropriate as it is still used in clinical practice, albeit to a reduced extent. The EAG therefore consider this a Key Issue (section 1.3). (iv) The company has excluded all second-line rituximab-chemotherapy regimens from comparison except R-GemOx, which they consider to be standard of care and representative of the other regimens in terms of efficacy and safety. The EAG's clinical experts varied in what they consider as standard second-line therapy. However, they all agreed that R-GemOx can be considered representative of all rituximab-chemotherapy regimens and therefore the company's approach was appropriate.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

In CS Appendix B the company describe their systematic literature review (SLR) to identify clinical evidence evaluating Glofit-GemOx as a second-line or later treatment of relapsed or refractory DLBCL. Additionally, in response to Clarification Question A3 the company provided a detailed SLR Report which includes a feasibility assessment for indirect treatment comparisons. The EAG's appraisal of the SLR methods is summarised below in Table 5. Overall, the EAG considers the SLR methods to be methodologically sound, except for lack of clarity around some aspects of the SLR results and study selection process in the SLR Report as they relate to indirect treatment comparisons (see section 3.3.2 below).

Table 5 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	CS Appendix B section 1.1, CS Appendix Table 1, and the company's SLR Report provide details of eligibility criteria for the clinical SLR. Inclusion criteria were broader for interventions and comparators than that of the NICE final scope.
Were appropriate sources of literature searched?	Yes	Data sources searched are reported in CS Appendix B section 1.1.1.2, CS Appendix Table 2 and the company's SLR Report. Searches covered sufficient databases and included grey literature.
What time period did the searches span and was this appropriate?	Yes	Time periods for searches are reported in CS Appendix B section 1.1.2 and CS Appendix Tables 3 to 14. There was an original search (from database inception) and four update searches. There were no gaps in coverage between search updates. The last update search was conducted in August 2024. The EAG considers the searches sufficiently to date as we are not aware of any new studies of Glofit-GemOx versus R-GemOx, although we are less certain about whether any recently-published studies could be relevant to indirect treatment comparisons (see section 3.3).

Systematic review components and processes	EAG response	EAG comments
Were appropriate search terms used and combined correctly?	Yes	The search terms are all relevant (CS Appendix B Tables 3 to 14). They included broader terms for DLBCL so there is comprehensive disease coverage. CS Appendix B.1.1 states that the strategies for the original search and the first update searches did not restrict by line of therapy. However, all searches including the original and first update search strategies, do limit to lines of therapy (2nd, 3rd or 4th line). The EAG do not consider this an issue.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	CS Appendix B section 1.1.1.3 and CS Appendix Table 1 specify the inclusion and exclusion criteria, which were broader for the intervention and comparator than the NICE scope.
Were study selection criteria applied by two or more reviewers independently?	Yes	Title/abstract and full-text screening was conducted by two independent analysts with any disagreement resolved by consensus or discussion with a project manager (CS Appendix B section 1.1.1.3)
Was data extraction performed by two or more reviewers independently?	Yes	Data extraction was carried out by one analyst and checked by a second (CS Appendix B section 1.1.1.3).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company used the seven criteria outlined in section 2.5 of the NICE single technology appraisal user guide for RCTs.[28] Non-randomised studies were assessed using the Downs and Black checklist (CS Appendix B section 1.1.1.4). The EAG consider this appropriate.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Company Clarification Response A2 states that risk of bias assessments were conducted by two independent analysts with any discrepancies resolved through discussion or the intervention of a third reviewer.
Is sufficient detail on the individual studies presented?	Yes	CS sections 2.2 to 2.8, CS Appendix B sections 1.2 and 1.3, and CS Appendix D provide methodological details and results from the STARGLO trial. The updated trial CSR was also provided.

Systematic review components and processes	EAG response	EAG comments
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	Direct evidence was available from the STARGLO trial. This is the only study in line with the company's decision problem, that compared Glofit-GemOx to R-GemOx in the second line setting (see section 2.3). No pairwise meta-analysis, ITC was therefore undertaken.
Source: Partly reproduced from CS sections 2.2 to 2.8; CS Appendix B sections 1.1, 1.1.2, 1.1.1.2, 1.1.1.3, 1.1.1.4, 1.2, and 1.3; CS Appendix D; CS Appendix Tables 1 to 14; Company SLR Report CSR, clinical study report; DLBCL, diffuse large B-cell lymphoma; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ITC, indirect treatment comparison; RCT, randomised controlled trial; R-GemOx, rituximab with gemcitabine and oxaliplatin; SLR, systematic literature review.		

3.2 Critique of studies of the technology of interest, and the company's analysis and interpretation

3.2.1 Included studies

The company's original and updated searches and selection process identified 505 records reporting 304 unique studies that met the SLR's inclusion criteria (CS Appendix B section 1.1.2.1). Of these studies, only one, the STARGLO trial, is relevant for the company's decision problem.

3.2.1.1 Study characteristics

STARGLO (GO41944; NCT04408638) is a company sponsored, ongoing, phase III, multicentre, open-label randomised trial comparing the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) against rituximab in combination with gemcitabine and oxaliplatin (R-GemOx). The population is patients with relapsed or refractory DLBCL not otherwise specified (NOS), who were ineligible for autologous stem cell transplant (ASCT). Patients had to have at least one line of prior systemic therapy to be eligible for the trial. Randomisation was stratified by lines of previous systemic therapy for DLBCL NOS (1 or ≥ 2) and outcome of last systemic therapy (relapsed or refractory). The trial results support the company's application for regulatory approval of Glofit-GemOx. The trial has one primary outcome, overall survival (OS). Patients were enrolled from 13 countries, including 6% from the UK (CS Table 7).

The population addressed in the company's submission i.e. patients who only had one previous line of therapy (second-line subpopulation), is a post-hoc subgroup (n=172) of the

whole trial population (n=274). Evidence from this subgroup directly informs the company's decision problem (CS section 1.1) and economic model (CS section 3.3)

Table 6 below summarises the STARGLO trial methodology.

Table 6 Summary of STARGLO trial methodology

Study characteristics	
Trial design	Randomised controlled trial (RCT) Open label, except that progression and response were assessed by a blinded independent review committee (IRC) 2 trial arms: • Arm 1: Glofit-GemOx (n=183) • Arm 2: R-GemOx (n=91)
Randomisation	2:1 Stratified by: • Lines of previous systemic therapy for DLBCL (1 or ≥ 2) • Outcome of last systemic therapy (relapsed or refractory) • N=274 patients randomised (including 16 from the UK). N=172 had 1 previous line of therapy, i.e. the second-line subpopulation (including [redacted] from the UK; Clarification Response A8).
Study status	Trial start date: 23/02/2021 – **ongoing**. • Data cut of interim and primary analysis: **29 March 2023** (median follow-up for the primary outcome 11.3 months). Used in the Primary clinical study report (CSR) and in the CS. • Data cut of updated analysis: **16 February 2024** (median follow up for primary outcome 20.7 months). Used in the updated CSR, the CS and company economic model. • Next data cut: **due May 2025.**
Median treatment duration at the latest data cut (16 February 2024)	**Glofit-GemOx:** Glofitamab: 7.2 months; gemcitabine: 4.8 months; oxaliplatin: 4.8 months. **R-GemOx:** Rituximab: 2.1 months; gemcitabine 2.1 months; oxaliplatin: 2.1 months.
Location	62 sites in 13 countries: **Europe** (Belgium, Denmark, France, Germany, Poland, Spain, Switzerland, United Kingdom) **Asia** (China, Republic of Korea, Taiwan) **North America** (United States) **Other** (Australia)
Included population	• Age ≥18 years with histologically confirmed DLBCL NOS • Relapsed or refractory disease (Relapsed: disease that had recurred following a response that lasted 6 months after completion of the last line of therapy. Refractory: disease that did not respond to, or that progressed < 6 months after, completion of the last line of therapy)

Study characteristics	
	• At least one (≥ 1) line of prior systemic therapy (Patients may have undergone autologous stem cell transplant (ASCT) prior to recruitment. Chimeric antigen receptor T cell (CAR T-cell) plus bridging therapy were counted as one line of therapy. Local therapies (e.g., radiotherapy) were not considered as lines of therapy) • Patients who had failed only one prior line of therapy and were not a candidate for high-dose chemotherapy followed by ASCT (i.e. met at least one of the following criteria: left ventricular ejection fraction ≤ 40%; creatinine clearance or glomerular filtration rate ≤ 45 mL/min; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≥ 2; age ≥ 70 years; patient refused high-dose chemotherapy and/or transplant; patient had insufficient response to pre-transplant chemotherapy to be able to proceed to transplant; other comorbidities or criteria that precluded the use of transplant based on local practice standards/investigator opinion) • At least one bi-dimensionally measurable (≥ 1.5 cm) nodal lesion, or one bi-dimensionally measurable (≥ 1 cm) extranodal lesion, as measured on computed tomography scan • ECOG Performance Status of 0, 1, or 2
Excluded population	• Key exclusion criteria: • Patients who had failed only one prior line of therapy and were a candidate for stem cell transplantation • History of transformation of indolent disease to DLBCL • High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, and high-grade B-cell lymphoma NOS, as defined by 2016 WHO guidelines • Primary mediastinal B-cell lymphoma • Primary or secondary central nervous system (CNS) lymphoma at the time of recruitment or history of CNS lymphoma • Prior treatment with glofitamab or other bispecific antibodies targeting both CD20 and CD3 • Prior treatment with R-GemOx or GemOx
Intervention (Glofit-GemOx)	All cycles were 21 days in length. **Obinutuzumab (pre-treatment to mitigate cytokine release syndrome):** Single 1000 mg intravenous (IV) dose administered on Day 1 of Cycle 1

Study characteristics	
	Glofitamab: Step-up dosing; 2.5 mg administered on Day 8 of Cycle 1, 10 mg on Day 15 of Cycle 1, and 30 mg on Day 1 of cycles 2-12. Administered before gemcitabine and oxaliplatin in cycles 2-8. **Gemcitabine:** 1000 mg/m^2 administered IV on Day 2 of Cycle 1 and Day 1 or 2 of cycles 2-8 (per local practice). Administered after glofitamab. Administered before oxaliplatin on the same day **Oxaliplatin:** 100 mg/m^2 administered IV on Day 2 of Cycle 1 and Day 1 or 2 of cycles 2-8 (per local practice). Administered after glofitamab**.** Administered after gemcitabine on the same day
Comparator (R-GemOx)	**Rituximab:** 375 mg/m^2 administered IV on Day 1 of cycles 1-8. Administered before gemcitabine and oxaliplatin **Gemcitabine and oxaliplatin**: same dose and scheduling as in the intervention arm
Concomitant medications	See CS Table 7 for permitted/prohibited concomitant medications
Primary outcome	Overall survival (OS)
Secondary outcomes informing the economic model	Progression free survival (IRC assessed; second-line subpopulation) Adverse events (treatment-related with a severity grade of 3 or higher occurring in >1% of patients; second-line subpopulation HRQoL (EQ-5D-5L; ITT population)
Other secondary outcomes specified in the NICE final scope	**Efficacy:** Response rates (IRC assessed): complete response (CR), objective response rate (ORR), duration of objective response, duration of CR) **HRQoL:** EORTC QLQ-C30; FACT-Lym LymS subscale **Safety:** Type, incidence, severity and seriousness of adverse events (AEs), adverse events of special interest, treatment discontinuation due to adverse events

Source: Partly reproduced from CS Table 7, CS section B.2.11.1, CS section B.2.12, CS section B.3.3, updated CSR Table *t_mh_char_bycntry_T_IT_16FEB2024_41944*, company Clarification Response A8

2L, second-line; CNS, central nervous system; CS, company submission; CSR, clinical study report; DLBCL, diffuse large B-cell lymphoma; DLBCL NOS, Diffuse large B-cell lymphoma not otherwise specified; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire; EQ-5D-5L: EuroQol 5-dimension health questionnaire, 5 Levels; FACT-Lym LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; HRQoL, Health-related quality of life; ITT, intention to treat; R-GemOx, rituximab with gemcitabine and oxaliplatin

Two of the EAG's clinical experts remarked that STARGLO's eligibility criteria are standard criteria for a clinical trial of DLBCL NOS. A third expert commented on the generalisability of the criteria, highlighting that the criteria differ in two respects from UK clinical practice. First, patients aged ≥18 years were eligible for inclusion in the trial, yet in clinical practice those aged 16 and 17 years would also be considered adults, which is the age group specified in the NICE scope. Second, patients had to meet at least one criterion to be considered ineligible for high-dose chemotherapy followed by ASCT which included being aged ≥ 70 years. However, in clinical practice, using an age cut-off of ≥70 years for transplant ineligibility is not recommended. Instead, the decision on transplant eligibility should be based on holistic fitness, since some patients aged over 70 years are fit enough to receive a transplant whilst some younger patients are not.

3.2.1.2 Patients' baseline characteristics

CS section 2.3.3 presents baseline characteristics for the STARGLO whole randomised trial population, i.e. the intention to treat (ITT) population (CS Table 8) and for the STARGLO second-line subpopulation, i.e. the subgroup who had received only one previous line of systemic therapy for DLBCL NOS (CS Table 9). The CS states that baseline characteristics for the ITT population and second-line subpopulation were [redacted] with the exception that [redacted] of patients in the second-line subpopulation ([redacted]) were refractory to their previous (last) line of therapy compared to the ITT population ([redacted]). The EAG in general agrees with the company's statement but we note that a [redacted] of patients were aged ≥ 65 years in the ITT population ([redacted]) compared to the second-line subpopulation ([redacted]).

Key baseline characteristics of the ITT population and second-line subpopulation were as follows:

- The median age of patients in the ITT population was 68 years (range 20-88) and [redacted] years (range [redacted]) in the second-line subpopulation.
- There were [redacted] men than women in [redacted] the ITT population (58% versus 42%) and [redacted].
- There were slightly more Asian patients than White patients in the ITT population (50% versus 42%) [redacted].
- The percentage of Black or African American patients was very low in [redacted] the ITT population (1.1%) and [redacted].

- The proportions of patients with ECOG PS of 0 and 1 were similar in the ITT population (43% and 47%) and [redacted].

3.2.1.2.1 Generalisability

One of the EAG's clinical experts commented that the baseline ECOG PS shows that patients in the second-line subpopulation were fitter than those usually seen in clinical practice, as is typical in clinical trials. Otherwise, the second-line subpopulation is similar to what they would expect to see in clinical practice. Two of the EAG's experts commented that the racial representation in STARGLO is not representative of UK clinical practice, noting that while the UK has a very diverse population, the majority is White whereas only 42% of the STARGLO ITT population were White. A third expert said that the virtual absence of Black or African American patients from the trial does not reflect their inner-city London practice or accurately reflect the racial demographic of the UK. The EAG note previous clinical expert advice to the NICE committee in TA649 (polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma) that "ethnicity is not a factor when considering efficacy or toxicity".[17] Two of the EAG's clinical experts thought that whilst race might affect metabolism of some drugs used in DLBCL treatment they believed this unlikely to have a major direct impact. However, one of the experts highlighted that race or ethnicity may come with varying behavioural, cultural, emotional and language aspects which could impact compliance with, tolerability of, or outcome of treatment and, hence, indirectly influence efficacy and safety. In that sense, they disagreed with the conclusion in TA649 that "ethnicity is not a factor when considering efficacy or toxicity".

3.2.1.2.2 Between-arm population differences

The CS states that baseline demographic data and disease characteristics were generally well-balanced between study arms (CS section 2.3.3). While the EAG in general agrees with the company's statement, we note the following imbalances between the trial arms with respect to the ITT population and the second-line subpopulation:

ITT population (CS Table 8):

- A lower proportion of patients were Asian in the Glofit-GemOx arm compared to the R-GemOx arm (47% versus 56%)
- A greater proportion were White in the Glofit-GemOx arm compared to the R-GemOx arm (45% versus 36%)

- A greater proportion of patients had Ann Arbor staging I-II at study entry, indicating lesser involvement of lymph nodes and overall a lower extent of DLBCL disease, in the Glofit-GemOx arm compared to the R-GemOx arm (33% versus 22%)

Second-line subpopulation (CS Table 9):

- A [redacted] of patients were Asian in the Glofit-GemOx arm compared to the R-GemOx arm ([redacted] versus [redacted])
- A greater proportion of patients had Ann Arbor staging I-II at study entry in the Glofit-GemOx arm compared to the R-GemOx arm (35% versus 21%)

With respect to the second-line subpopulation, one of the EAG clinical experts considered that the difference between the two treatment arms regarding Ann Arbor staging is notable and was concerned that might be a confounding factor and favour one arm. However, our other two experts did not think the difference was sufficient to bias the study results.

EAG conclusion on included study

STARGLO is a an ongoing, phase III, multicentre, open-label randomised trial comparing the efficacy and safety of Glofit-GemOx against R-GemOx. The population is patients with relapsed or refractory DLBCL not otherwise specified (NOS), who were ineligible for autologous stem cell transplant (ASCT). It is used as the pivotal trial to support the company's application for regulatory approval of Glofit-GemOx and is the sole source to directly inform the economic model for this appraisal. The EAG's clinical experts do not consider the population of STARGLO representative of the UK population in terms ethnicity. Our experts consider the population is also fitter than those usually seen in clinical practice but note this is typical in clinical trials.

3.2.2 Risk of bias assessment

The company's methodological quality assessment (also referred to as risk of bias assessment) of the STARGLO trial was conducted using section 2.5 of the NICE single technology appraisal user guide for RCTs.[28] An overview of the company's assessment is presented in CS document B Table 13 and their full assessment, which includes justification for their judgements, is presented in CS Table 17. The EAG independently critically appraised the trial using the same criteria. A comparison of the company and EAG judgements are shown in Table 7 below; disagreements between the company and EAG

judgements are in bold. The company did not frame their answers in terms of the risk of bias; the EAG has provided this interpretation.

Table 7 Overview of company and EAG risk of bias judgements

	Company judgement	EAG judgement
Was randomisation carried out appropriately	Yes	Yes (low risk of bias)
Was the concealment of treatment allocation adequate?	**No**	**Yes** (low risk of bias) as participants were assigned to trial groups via an interactive voice or web response system that generated the random allocation sequence)
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes (low risk of bias)
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No	No (High risk of bias) For the primary and response outcomes results were assessed by an Independent Review Committee (IRC) who were blinded to treatment assignment. However, the trial was otherwise open label so investigators administering patient care and data analysts, as well as patients, were not blinded.
Were there any expected imbalances in dropouts between groups?	No	Survival outcomes: No (low risk of bias) Other outcomes: Unclear (unclear risk of bias) as the full extent of missing data for response and patient-reported outcomes is not clear (see Table 9).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Unclear Primary outcome: Yes (low risk of bias), all randomised patients were included, and censoring methods appear appropriate (see Table 9). But note that the second-line subpopulation did not include all randomised patients so cannot strictly meet the definition of ITT, although proportionately the ITT principle does apply to this subpopulation. Secondary outcomes: No (unclear risk of bias for response outcomes as number of missing data unclear; high risk of bias for patient-reported outcomes as ITT approach not followed) (see Table 9).
Source: Partly reproduced from CS Appendix B Table 17 EAG, External Assessment Group; ITT, intention to treat		

EAG conclusion on the risk of bias

Overall, the EAG considers that as STARGLO was an open-label trial the trial outcomes could potentially be at high risk of bias.

3.2.3 Outcomes assessment

3.2.3.1 Efficacy outcomes

The key clinical effectiveness outcomes from the STARGLO trial, and their definitions, are summarised in Table 8. Of these, overall survival (OS) (the primary outcome of the STARGLO trial), progression-free survival (PFS), and (after mapping and aggregating scores) the EuroQol 5-dimension health questionnaire (EQ-5D) inform the company's economic model.

Table 8 Clinical efficacy outcomes relevant to this technology appraisal

Outcome		Definition (CS Table 7)	Informs economic model
Primary outcome	Overall survival (OS)	Time from randomization to date of death from any cause	Yes
Key secondary outcomes	Progression-free survival (PFS)	Time from randomization to the first occurrence of disease progression or death from any cause, whichever occurs first. Assessed by IRC.	Yes
	Best overall complete response (CR) rate	Proportion of patients whose best overall response is a CR on positron emission tomography/ computed tomography (PET/CT) during the study. Assessed by IRC.	No
	Duration of complete response (DOCR)	Time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first.	No
Other secondary outcomes	Best objective response rate (ORR)	Proportion of patients whose best overall response is a partial response (PR) or a CR during the study. Assessed by IRC.	No
	Duration of objective response (DOR)	Time from the first occurrence of a documented objective response (CR or PR) to disease progression, or death from any cause, whichever occurs first	No
	EORTC QLQ-C30	Time from randomisation to first documentation of a ≥10-point increase (CSR section 5.1.3.8.2). The CS focuses on the physical functioning and fatigue subscales.	No
	FACT-Lym LymS Lymphoma-specific symptoms	Time from randomisation to first documentation of a ≥3-point decrease in mean score (CSR section 5.1.3.8.2).	No
Exploratory outcomes	EQ-5D 5L (not listed as an outcome in CS Table 7)	Aggregate EQ-5D-3L results, mapped from EQ-5D-5L results from the STARGLO trial, inform utility values in the economic model (CS section 3.4.2). Original (pre-mapping) EQ-5D scores are not reported in the CS but	Yes

		are provided in the CSR for the whole-trial population (pages 2147-2156).	
	Mean changes from baseline in EORTC QLQ C-30 and FACT-Lym Lym S scores	Includes all remaining subscales of the EORTC QLQ-C30 (see section 3.2.3.2 below for the subscales)	No
	Proportion of patients experiencing a clinically meaningful improvement (responder analysis)	Defined as stated, but not listed as a relevant outcome in CS Table 7.	No
	Incidence and outcomes of CAR T-cell therapy after study treatment	Incidence of treatment with CAR T-cell therapy and survival following CAR T-cell therapy, defined as time from date of CAR T-cell therapy to date of death from any cause.	No

Source: EAG created table.
CAR, chimeric antigen receptor; CR, complete response; CSR, clinical study report; CT, computed tomography; DOCR, duration of complete response; DOR, duration of objective response; EORTC QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire; EQ-5D, EuroQol 5-dimension health questionnaire; FACT-Lym LymS, Functional Assessment of Cancer Therapy−Lymphoma subscale; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

In the STARGLO trial PFS, the complete response (CR) and objective response rate (ORR) were each assessed both by the study investigators and by an independent review committee (IRC). For the economic analysis of PFS the IRC-assessed results were used; the CS does not mention whether these differed from the investigator-assessed results. The company did not provide these comparisons for the second-line subpopulation; summaries of the results of these comparisons in the whole-trial population are given in the results section 3.2.4 below.

The secondary response outcomes do not inform the economic analysis and are immature (median duration of complete and objective responses was not reached in the Glofit-GemOx arm). We have therefore only summarised those response outcomes in this report that are reported in the CS, i.e. the complete response rate (section 3.2.5.3 below) and the duration of complete response (section 3.2.5.4 below).

The exploratory outcomes relating to responder and CAR-T cell therapy analyses listed in Table 8 above do not influence interpretation of the structure or results of the economic analysis and are not discussed further in this report.

3.2.3.2 HRQoL outcomes

Aside from the EQ-5D which is a standard health-related quality of life (HRQoL) measure for providing utility estimates in health technology appraisals and informs the economic analysis, the CS reports two patient-reported HRQoL and function-related outcomes, the European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy−Lymphoma subscale (FACT-Lym LymS). Note that these two outcomes do not inform the company's economic analysis. The EAG's clinical experts commented that these patent-reported outcomes are not used for decision making in clinical practice but considered them appropriate for DLBCL trials

EQ-5D, EORTC QLQ-C30 and FACT-Lym Lym S results are not reported in the CS for the second-line subpopulation group of the STARGLO trial. Second-line results for these three outcomes were requested by the EAG before the clarification stage of the technology appraisal and were provided by the company on 25th February 2025.

3.2.3.2.1 EORTC QLQ-C30

As noted in CS section 2.4.3, the EORTC QLQ-C30 is a general instrument that has been validated for assessing functional response and HRQoL for a broad range of cancers. However, the validations either included no patients,[29] or very few patients [30] who had haematological cancers and so the relevance to DLBCL is uncertain (Clarification Response A6). The EORTC QLQ-C30 consists of 30 questions that assess the following, each transformed to an 0-100 score:

- five domains of patient functioning (physical, emotional, role, cognitive, social) – higher scores indicate better HRQoL
- three symptom scales (fatigue, nausea and vomiting, pain) – higher scores indicate worse HRQoL
- global health status/ quality of life – higher scores indicate better HRQoL
- six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial problems) – higher scores indicate worse HRQoL

The CS reports EORTC QLQ-C30 results for the time to deterioration of physical functioning and time to deterioration of fatigue but the company do not explain why these two specific domains were selected. The CS states that all remaining scales of the EORTC QLQ-C30 were assessed in an exploratory analysis (CS Table 7) but results of these analyses are not provided in the CS.

The company define a minimum clinically meaningful change in the EORTC QLQ-C30 score as ≥10-points. This appears appropriate to cover all subscales,[29, 30] although changes in EORTC QLQ-C30 subscales have been found to be relatively small in practice, which might reflect response shift (patients adapting to their changing health status).[30]

3.2.3.2.2 FACT-Lym LymS

As stated in CS section 2.4.3, the FACT-Lym LymS was developed and validated to assess lymphoma-specific HRQoL in patients with non-Hodgkin lymphoma. The FACT Lym LymS assesses B symptoms, and the effects of a patient's symptoms and treatment toxicity on their HRQoL. Scores range from 0 (worst) to 60 (best) HRQoL. Clarification Response A6 explains that validation of the instrument included patients with DLBCL and so this is a relevant disease-specific measure of symptoms.

The company define clinical deterioration as a ≥3-point decrease in the FACT Lym LymS score. Clarification Response A6 justifies that this threshold for a clinically meaningful change is commonly used in recent DLBCL studies.[31-33]

3.2.3.3 Safety outcomes

According to CS section 2.4.4, assessment of safety included exposure to study treatment, adverse events, changes in laboratory test results and in vital signs and ECGs. Relevant test results for the safety analysis are those which support the interpretation of adverse events and as such are already captured within the adverse events data. Note that the exposure to study treatment was longer in the Glofit-GemOx arm than the R-GemOx arm of the STARGLO trial (CS section 2.3.1).

The key adverse events of importance in this technology appraisal are those which inform the economic analysis and those which are important for a patient's clinical risk and management. The adverse events included in the economic analysis are treatment-related adverse events of severity grade 3 or higher (CS Table 45) and all-cause mortality (CS section 3.3.5). The EAG's clinical experts commented that adverse events which have the largest implications for patients, including need for intensive care unit (ICU) admission and/or delayed subsequent treatment, are cytokine release syndrome and febrile

neutropenia. The difference between neutropenia and febrile neutropenia is important since isolated neutropenia without infection may have little consequence for the patient whereas febrile neutropenia typically needs urgent hospital admission to manage serious infection or sepsis which would involve intravenous antibiotics and granulocyte colony stimulating factor therapy.

Parameters informing the economic analysis that are indirectly related to adverse events are treatment discontinuation rates and the total time on treatment (CS section 3.3.6).

EAG conclusion on the outcomes assessment

The outcomes assessed by the company are appropriate. Febrile neutropenia is a more important safety outcome than neutropenia alone (however this affected very few patients in the STARGLO trial and would not markedly influence the economic analysis – see section 4.2.6.4). The EORTC QLQ-C30 and Fact-Lym LymS are relevant patient-reported outcomes for clinical trials on DLBCL but are not used for decision making in clinical practice.

3.2.4 Statistical methods of the included studies

Key aspects of the statistical analysis approach are summarised in Table 9 below.

Table 9 Summary of the statistical methods for the STARGLO trial

Methodology components	EAG comments
Analysis populations (CS Table 10)	The analysis populations of the STARGLO trial were: **Intention to treat (ITT):** All patients randomised. The statistical analysis plan (SAP, section 5.1) states that analysis was according to the originally randomised groups. However, whilst the ITT analysis population is appropriate, the second-line subpopulation for the company's decision problem (section 2.3) does not follow this approach since only 172 of the 274 randomised patients are included. **Patient-reported outcome (PRO)-evaluable:** People who have a baseline and at least one post-baseline PRO assessment. **Safety-evaluable:** All randomized patients who receive any amount of any study treatment, grouped according to treatment received (study protocol section 6.5).

	The definitions of the PRO-evaluable and safety-evaluable populations are relevant for the second-line subpopulation but are subject to a smaller sample size than when applied to the whole trial population.
Sample size calculation (CS section 2.4.1)	The STARGLO trial had a total randomised sample size of N=274 which should be sufficient (N=270) to provide 80% power for the ITT population to detect a between-group difference in median OS of 7.3 months (HR=0.6), assuming median OS from published R-GemOx trials is 11 months and annual dropout is 2%. The CS does not report statistical power for the second-line subpopulation or for other outcomes. Given that the second-line subpopulation had a smaller sample size (total N=172 randomised) the EAG assumes that the second-line statistical analysis was not powered statistically to detect differences in any of the outcomes between the Glofit-GemOx and R-GemOx groups. However, the EAG's three clinical experts considered the survival results in the second-line subpopulation clinically meaningful.
Analysis of outcomes (CS section 2.3.1)	Two analyses were conducted: **Interim analysis:** 29 March 2023. This became the **primary analysis** since the pre-specified primary outcome threshold for statistical significance was met (p≤0.0148). **Updated analysis:** 16 February 2024 (additional 10.5 months median follow up), reported in the CS in addition to the primary analysis. Overall, the statistical analysis approaches appear appropriate, being based on standard survival analysis methods for OS and PFS. Details of the statistical tests and estimand approaches are not provided in the CS but are stated in the SAP (Tables 2, 7, and 8 and section 5.1 in the SAP) and appear appropriate.
Methods to account for multiple testing (CS section 2.3.1)	**Primary analysis:** A hierarchical testing sequence (OS → PFS → CR rate → DOCR) with controlled 2-sided study-wise error rate was employed for the primary outcome (OS hazard ratio, threshold p≤0.0174) and key secondary outcomes (PFS, CR, DOCR rate, threshold p≤0.03244). Other secondary outcomes and exploratory outcomes should be interpreted descriptively only.

	Updated analysis: Descriptive analysis only. This includes the second-line subpopulation analysis.
Handling of missing data (primarily reported in the SAP)	The censoring rules for missing survival data are not stated in the CS but are reported in SAP Table 3 for OS and SAP Table 7 for PFS and appear appropriate. Sensitivity analyses with/without the following censoring were conducted as follows: • For OS deaths, discontinuations or drug supply interruptions related to COVID-19 were censored (SAP section 5.3.3). • For PFS, missing data or assessments due to COVID-19 and any losses to follow-up or discontinuation of PFS assessments that were not due to a PFS event were censored (SAP section 5.5.2). • For PFS, as indicated in CS Figures 5 and 6, patients who received any new anti-lymphoma therapy (NALT) (which could include a range of therapies as shown in CS Table 19) were censored. The sensitivity analyses were conducted on PFS without censoring for NALT, and censoring for NALT without HSCT (SAP section 5.5.2) Results of the COVID-19 sensitivity analyses for OS differed slightly from those of the primary analysis but not to an extent that would affect clinical conclusions (CSR Table 20). COVID-19 sensitivity analyses were not conducted for IRC-assessed or investigator-assessed PFS because fewer than 5% of patients in either treatment group had data missing due to COVID-19 (CSR section 5.1.3.1). The analyses without censoring for NALT gave similar results to those with censoring for IRC-assessed PFS (CSR Table 27) and investigator-assessed PFS (CSR section 5.1.3.2.1). For response outcomes the sample size reported (CS section 2.6.2.2) is for the randomised population but without indication of how many missing data were imputed or how.

	Patient-reported outcomes were analysed according to available cases: patients who had a baseline and at least one post-baseline assessment were included, except for the time to deterioration outcomes which were based on ITT analysis (CS Table 10). The CS acknowledges that PRO completion rates declined over time as expected due to attrition (CS section 2.6.3) but no imputation approach is specified for achieving the ITT population for the time to deterioration outcomes. The number of data missing for these outcomes is not reported in CS Table 18.
Sensitivity & post-hoc analyses	To recap, the second-line subpopulation of the STARGLO trial which is the focus of the company's decision problem as discussed above (section 2.3) is a post hoc subgroup of the trial population that was not specified in the trial protocol. We refer to the "second-line subpopulation" in this report to distinguish this analysis population from the following other subgroup analyses conducted by the company: A pre-specified subgroup analysis of OS for a range of 25 patient demographic and disease characteristics was intended for the ITT population of the STARGLO trial (CS Table 7). CSR section 5.1.2.3 refers to the subgroup analyses as being exploratory. Results for 10 of these subgroups are reported in CS Figure 10, with no explanation of why results for the remaining 15 analyses have been omitted. The company provided the corresponding subgroup analysis results for the second-line subpopulation in Clarification Response A9, except that the subgroup 'number of previous lines of therapy' is not relevant so the clarification response contains nine subgroups. CS section 2.8 mentions that clinical efficacy of Glofit-GemOx varied by race and geographic region for the trial ITT population. However, whilst race is one of the 25 subgroups specified in CS Table 7 this was not included among the subgroup results in CS Figure 10 or Clarification Response A9. For discussion of the subgroup analysis results see section 3.2.5.6

	The CSR reports additional post hoc exploratory analyses of OS and PFS in CSR section 5.1.5 which primarily aimed to understand the mechanisms of the observed effects of geographical region seen in the main analyses, but these are not discussed in the CS.

EAG conclusion on the study statistical methods

The overall approach to trial statistics appears appropriate and the EAG's clinical experts all considered the survival analysis results clinically meaningful. However, statistical analyses on the second-line subpopulation do not include all randomised patients, were not pre-specified, and should be interpreted as exploratory. Immaturity of the survival outcomes data adds further uncertainty whilst the extent of missing data for patient-reported outcomes is unclear (although the latter do not inform the economic analysis). Results have only been provided for 10 of 25 pre-specified subgroup analyses; race appears to be a subgroup of interest according to the CS but is not reported.

3.2.5 Efficacy and safety results of the intervention studies

As discussed above (sections 3.2.3 and 3.2.4), the results presented here should be interpreted in the context of their limitations. The second-line subpopulation is a post hoc subset of the STARGLO randomised trial ITT population meaning that statistical inferences are descriptive (i.e. can only be considered exploratory). The survival outcomes data are relatively immature whilst for patient-reported outcomes and time to deterioration analyses the extent of missing data is unclear.

3.2.5.1 Overall survival

Survival analysis results for OS are shown in CS Table 14. The hazard ratio for the second-line subpopulation (only reported in the CS for the updated analysis, 16 February 2024) is shown in Table 10 below. The longer follow-up data from the updated analysis for the second-line subpopulation are those used to inform the economic analysis (p-values for this analysis are illustrative, as they were not adjusted for multiple testing). [redacted]

Table 10 Overall survival in the STARGLO trial

Outcome	Primary analysis		Updated analysis			
	ITT population Median follow-up 11.3 months		ITT population Median follow-up 20.7 months		2L subpopulation Median follow-up xxxx months	
	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=115	R-GemOx N=57
Median OS, months (95% CI)	NE (13.8, NE)	9.0 (7.3, 14.4)	25.5 (18.3, NE)	12.9 (7.9, 18.5)	NE ([redacted])	15.7 ([redacted])
Stratified HR (95% CI)	0.59 (0.40, 0.89); p=0.011		0.62 (0.43, 0.88); p=0.006 [a]		[redacted]	

Source: Reproduction of CS Table 14 with adjusted layout.
2L, second-line; ITT, intention to treat; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; N, sample size; NE, not evaluable; OS, overall survival
[a] p-values are illustrative, not adjusted for multiple testing.

Kaplan-Meier curves for the updated analysis are provided in CS Figures 3 and 4 for the ITT and second-line subpopulations respectively. The OS curve for the second-line subpopulation is reproduced in Figure 2 below.

Figure 2 Overall survival in the second-line subpopulation of the STARGLO trial, updated analysis

3.2.5.2 Progression-free survival

Survival analysis results for PFS are shown in CS Table 15. The hazard ratio for the second-line subpopulation (only reported in the CS for the updated analysis, 16 February 2024) is shown in Table 11 below. The secondary outcome of IRC-assessed PFS in the ITT population met the criterion for statistical significance at the primary analysis according to the pre-specified hierarchical testing procedure (CS section 2.6.2.1). The longer follow-up data from the updated analysis of the second-line population are those used to inform the economic analysis (p-values for this analysis are illustrative, as they were not adjusted for multiple testing).

Table 11 Progression-free survival in the STARGLO trial

Outcome	Primary analysis		Updated analysis			
	ITT population Median follow-up 7.2 months		ITT population Median follow-up 15.7 months		2L subpopulation Median follow-up [redacted] months	
	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=115	R-GemOx N=57
Median OS, months (95% CI)	12.1 (6.8, 18.3)	3.3 (2.5, 5.6)	13.8 (8.7, 20.5)	3.6 (2.5, 7.1)	20.4 [redacted]	5.6 [redacted]
Stratified HR (95% CI)	0.37 (0.25, 0.55) p<0.000001		0.40 (0.28, 0.57); p<0.000001 [a]		[redacted]	

Source: Reproduction of CS Table 15 with adjusted layout.
2L, second-line; ITT, intention to treat; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; N, sample size; NE, not evaluable; PFS, progression-free survival
[a] p-values are illustrative, not adjusted for multiple testing.

Comparisons of median PFS between IRC and investigator assessments and between stratified and unstratified hazard ratios were not provided by the company for the second-line subpopulation of STARGLO. For the ITT population these comparisons are reported in CSR sections 5.1.3.1 and 5.1.3.2 and show that IRC and investigator analyses, using both stratified and unstratified hazard ratios gave similar results.

Kaplan-Meier curves for the updated analysis are provided in CS Figures 5 and 6 for the whole-trial and second-line populations respectively. The PFS curve for the second-line population is reproduced in Figure 3 below.

Figure 3 Progression-free survival in the second-line population of the STARGLO trial, updated analysis

3.2.5.3 Complete response rates

Complete response rates are reported in CS Table 16. Results for the second-line subpopulation (only reported in the CS for the updated analysis, 16 February 2024) are shown in Table 12 below. The secondary outcome of IRC-assessed complete response in the ITT population met the criterion for statistical significance at the primary analysis according to the pre-specified hierarchical testing procedure but p-values for the updated analysis are illustrative, as they were not adjusted for multiple testing (CS section 2.6.2.2).

Table 12 Complete response rates in the STARGLO trial

Outcome	Primary analysis		Updated analysis			
	ITT population		ITT population		2L subpopulation	
	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=115	R-GemOx N=57
Median OS, months (95% CI)	50.3 (42.8, 57.7)	22.0 (14.0, 31.9)	58.5 (51.0, 65.7)	25.3 (16.8, 35.5)	[redacted]	[redacted]
Difference (95% CI)	28.3 ([redacted]); P<0.0001		33.2 (20.9, 45.5); p<0.0001 [a]		[redacted]	

Source: Partial reproduction of CS Table 16.
2L, second-line; CI, confidence interval; CR, complete response; IRC, independent review committee; N, sample size; ITT, intention to treat;
[a] p-values are illustrative, not adjusted for multiple testing.

Comparisons of complete response rates between IRC and investigator assessments were not provided by the company for the second-line subpopulation of STARGLO. For the ITT population these comparisons are reported in CSR sections 5.1.3.4.1 and 5.1.3.4.2 and show that IRC and investigator assessments gave similar results.

3.2.5.4 Duration of complete response

The CS reports the duration of complete response in CS Table 17. Data for this IRC-assessed secondary outcome were immature at the primary analysis for the ITT population (median follow-up 6.4 months) and did not meet the pre-specified threshold for statistical significance (CS section 2.6.2.3); p-values at the updated analysis are illustrative, as they were not adjusted for multiple testing. Results for the second-line subpopulation (only reported in the CS for the updated analysis, 16 February 2024) are shown in Table 13 below. Median duration of complete response was not reached in the Glofi-GemOx arm for the ITT population [redacted].

Table 13 Duration of complete response in the STARGLO trial

Outcome	Primary analysis		Updated analysis			
	ITT population Median follow-up 6.4 months		ITT population Median follow-up [redacted] months		2L subpopulation Median follow-up not reported	
	Glofit-GemOx [redacted]	R-GemOx [redacted]	Glofit-GemOx [redacted]	R-GemOx [redacted]	Glofit-GemOx [redacted]	R-GemOx [redacted]
Median OS, months (95% CI)	14.4 (14.4, NE)	Not reached	Not reached	24.2 (6.9, NE)	[redacted]	[redacted]
Unstratified HR (95% CI)	0.59 (0.19, 1.83); P=0.3560		0.59 (0.25, 1.35); p=0.2040 [a]		[redacted]	

Source: Partial reproduction of CS Table 17 and CS section 2.6.2.3.
2L, second-line; CI, confidence interval; DOCR, duration of complete response; HR, hazard ratio; IRC, independent review committee; N, sample size; NE, not evaluable.
[a] p-values are illustrative, not adjusted for multiple testing.

Comparisons of the duration of complete response between IRC and investigator assessments were not provided by the company for the second-line population of STARGLO. For the ITT population these comparisons are reported in CSR sections 5.1.3.5.1 and 5.1.3.5.2. The unstratified hazard ratio was less favourable to Glofit-GemOx in the IRC assessment (HR=0.59; 95% CI 0.25 to 1.35) than in the investigator assessment

(HR=0.41; 95% CI 0.18 to 0.93). However, median duration of complete response was not reached in the Glofit-GemOx arm and so the data are immature and subject to uncertainty.

3.2.5.5 HRQoL outcomes

3.2.5.5.1 EQ-5D

As noted above (section 3.2.3.2), EQ-5D-5L results for the second-line subpopulation are not included in the CS but were provided by the company separately (prior to the clarification stage) on request from the EAG. The company provided results for the individual EQ-5D-5L subscales (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) but not for the overall EQ-5D score which is used in the economic analysis. Therefore, we were unable to check whether the EQ-5D data used in the economic modelling accurately reflect those collected in the STARGLO trial.

3.2.5.5.2 EORTC QLQ-C30

Time to deterioration

The CS reports the proportions who had clinically meaningful deteriorations in the EORTC QLQ-C30 physical functioning and fatigue subscales (CS section 2.6.3) and the time to deterioration in these subscales (CS Table 18) only for the full STARGLO trial population. These results indicate [redacted] between the R-GemOx and Glofit-GemOx groups which the company interpret to indicate that Glofit-GemOx [redacted] in these subscales. However, corresponding time to deterioration results for the second-line population group, and results for other subscales than physical functioning and fatigue, have not been provided by the company.

Changes from baseline

As noted above (section 3.2.3.2), changes from baseline in EORTC QLQ-C30 scores (an exploratory outcome) are not included in the CS but were provided separately by the company (prior to the clarification stage) for the second-line subpopulation on request from the EAG. The company provided results for 15 EORTC QLQ-C30 scales for a range of timepoints but did not include an interpretation of these. We have summarised the changes from baseline at 12 months (Table 14) since attrition substantively reduced the sample size after this timepoint. Most of the changes from baseline did not achieve the 10-point threshold to be considered clinically meaningful (section 3.2.3.2). Overall, with the exception of cognitive function, the direction of the differences between groups is favourable to Glofit-GemOx when compared to R-GemOx, although differences in the Global health status and pain scales are marginal. There is a signal that cognitive functioning may have been worse on Glofit-GemOx than R-GemOx therapy (Table 14). However, the EAG's clinical experts

generally suggested these results should not be over-interpreted given the relatively small sample sizes, and the fact that EORTC QLQ-C30 has not been specifically validated for DLBCL patients.

Table 14 Change in EORTC QLQ-C30 scores for the STARGLO trial second-line subpopulation at month 12, updated analysis

Assessment scale	Mean (SD) change from baseline	
	R-GemOx N=16	Glofit-GemOx N=31
Scales where an increasing score indicates improvement		
Cognitive functioning	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]
Global heath status/QoL	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]
Scales where a decreasing score indicates improvement		
Appetite loss	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Nausea & vomiting	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Source: Adapted by the EAG from a document provided by the company separately from the CS and clarification responses		

3.2.5.5.3 FACT-Lym LymS

Time to deterioration

The CS reports the proportions who had clinically meaningful deteriorations in lymphoma-specific symptoms (CS section 2.6.3) and the time to deterioration in the FACT-Lym LymS score (CS Table 18) only for the full STARGLO trial population. These results indicate [redacted] between the R-GemOx and Glofit-GemOx groups which the company interpret to indicate that Glofit-GemOx [redacted] in

symptoms. However, corresponding time to deterioration results for the second-line subpopulation have not been provided by the company.

Changes from baseline

As noted above (section 3.2.3.2), changes from baseline in the FACT-Lym LymS lymphoma-specific symptom score (an exploratory outcome) are not included in the CS but were provided separately for the second-line subpopulation by the company (before the clarification stage) on request from the EAG. The mean (SD) change in FACT-Lym LymS score from baseline at 12 months was [redacted] in the R-GemOx group and [redacted] in the Glofit-GemOx group (we refer to the changes at 12 months since attrition substantively reduced the sample size at later timepoints). These changes represent clinically meaningful deteriorations in symptoms in both groups, as might be expected on cancer treatment, with the deterioration larger for the R-Gem-Ox group. However, these results are not definitive given the relatively small sample sizes and all the other concerns mentioned above relating to the post hoc subpopulation.

3.2.5.6 Subgroup analyses

As noted above (Table 9), the CS reports OS subgroup analysis results by patient characteristics for 10 of the 25 pre-specified subgroups for the STARGLO trial ITT population. In Clarification Response A9 the company provided corresponding subgroup analysis results for the second-line population group (for 9 rather than 10 subgroups as the number of prior lines of therapy is not a relevant analysis for the second-line setting).

The subgroup analysis for the second-line population group (Figure 1 in Clarification Response A9) shows a broadly similar picture to that for the ITT population (CS Figure 10), except with wider confidence intervals reflecting the smaller sample size. The second-line population group did, however, have a different age distribution to the full trial population, with fewer patients aged below 65 years, which increases the uncertainty (i.e. gives a wider confidence interval) for those aged <65 years in the second-line group. The company explain that this reflects that in the STARGLO trial eligibility for ASCT was an exclusion criterion for second-line but not third-line patients, hence fewer second-line patients aged <65 years were recruited.

In the ITT population [redacted] differences between geographical regions are evident, with Glofit-GemOx favoured over R-GemOx in the Rest of the World subgroup but not in the Europe or North America subgroups. The company commented that clinical experts found these geographical differences challenging to interpret due to small sample sizes and wide confidence intervals (CS section 2.8). As mentioned above (section

3.2.1.2), the EAG's clinical experts noted that Black patients are underrepresented in the STARGLO trial and so the clinical efficacy and safety of Glofit-GemOx in this subgroup is unknown. As we noted above (Table 9) race was one of 15 pre-specified subgroups in the STARGLO trial for which the CS has not reported results for the second-line subpopulation.

3.2.5.7 Safety outcomes

Data on adverse events is reported in CS section B.2.11 and CS Appendix D (both for the whole safety evaluable population the STARGLO trial and for the second-line subpopulation of this). Additional adverse event data for the whole safety evaluable population is reported in the updated CSR, and for the second-line subpopulation in data tables provided by the company (CS confidential reference pack, and Clarification Responses A10 and A11). All data presented are from the 16 February 2024 data cut.

In the CS and updated CSR, adverse event data for the Glofit-GemOx arm are presented separately for patients who received any dose of glofitamab *or* obinutuzumab (referred to in the CS as "any treatment exposed"); and for those who received any dose of glofitamab (referred to in the CS as "glofit-exposed"). The numbers of patients and safety findings were very similar between these two exposure groups for both the whole safety evaluable population and the second-line subpopulation.~~.~~ The EAG therefore preferentially report data for the second-line subpopulation with the glofit-exposed group in the following sections, except where data from the whole safety evaluable population provides additional insight.

3.2.5.7.1 Exposure to study treatments

CS section B.2.11.2 cautions that comparation of safety data for Glofit-GemOx and R-GemOx should be considered in the context of the substantially different treatment exposures. The CS reports data on treatment exposure (CS section 2.11.1 and CS Tables 23 and 24) but does not report any data on exposure-adjusted adverse event rates.

Exposure to study treatments was the same in:

- the Glofit-GemOx arm of the whole safety evaluable population and the second-line subpopulation: median and range of number of cycles of glofitamab and GemOx was 11 ([redacted]) and 8 ([redacted]), respectively
- the R-GemOx arm of the whole safety evaluable population and of the second-line subpopulation: median and range of number of cycles for all treatments was 4 ([redacted]).

The Updated CSR (section 5.2.10) reports post-hoc exploratory analyses of exposure-adjusted adverse event rates (AE rate per 100 patient-years) for the whole safety evaluable population. The EAG requested the company to provide exposure-adjusted adverse event rates for the second-line subpopulation. In company Clarification Response A10, exposure adjusted event rates for the second-line subpopulation were provided at the highest level term, System Organ Class, only of the adverse event coding dictionary MedDRA. Exposure adjusted event rates at the System Organ Class level are available for the whole population in Updated CSR Table 86.

For both the whole safety evaluable population and the second-line subpopulation, exposure adjusted adverse event rates for the Glofit-GemOx arm were [redacted] for the R-GemOx arm except for [redacted] The Updated CSR states the [redacted]

3.2.5.7.2 Overview of adverse events

3.2.5.7.2.1 Any adverse event

All patients in the Glofit-GemOx arm ([redacted]) and almost all (98.2%) in the R-GemOx arm experienced at least one adverse event (CS Table 26). The most common adverse event in the Glofit-GemOx arm was cytokine release syndrome ([redacted]) and in the R-GemOx arm nausea ([redacted]) (company Table *t_ae_ctc_bypl_SE_16FEB2024_41944).* The proportion of patients experiencing nausea was [redacted] in the Glofit-GemOx arm ([redacted])

3.2.5.7.2.2 Serious adverse events

Serious adverse events were defined using standard criteria (CS Table 12). The proportion of patients in the Glofit-GemOx arm who experienced a serious adverse event was [redacted] that of the R-GemOx arm ([redacted] versus xxxxx (CS Table 26).

3.2.5.7.2.3 Adverse events with a severity grade ≥3

The proportion of second-line subpopulation patients experiencing an adverse event with a severity grade ≥3 in the Glofit-GemOx arm was almost double that of the R-GemOx arm ([redacted] versus 41.8% respectively; CS Table 26). The most common type of grade 3 events in the second-line subpopulation and whole population were [redacted] (company Table *t_ae_ctc2_GA35_SE_2L_16FEB2024_41944*, CS section B.2.11.2).

The proportion of second-line subpopulation patients in the Glofit-GemOx arm who experienced an adverse event with a severity grade ≥3 related to rituximab/glofitamab was

approximately double that of the R-GemOx arm ([redacted] versus [redacted] CS Table 26). The company's economic model includes the treatment-related adverse events with a severity grade ≥3 or more, occurring in ≥1% of patients, in at least one treatment arm in the STARGLO second-line subpopulation. These events are reported in Table 18 below.

3.2.5.7.2.4 Fatal adverse events

Grade 5 adverse events i.e. fatal adverse events are reported in CS Table 36, CS Appendix Table 19 and company Table *t_ae2_FATAL_SE_2L_16FEB2024_41944*). Overall, in the second-line subpopulation there were three times as many fatal adverse events in the Glofit-GemOx arm compared to the R-GemOx arm ([redacted] versus 1.8% respectively), although numbers were small (n=[redacted] versus n=1) (CS Table 26). In the second-line subpopulation, fatal adverse events in the Glofit-GemOx arm included [redacted] The [redacted] fatal adverse event in the R-GemOx arm was [redacted] (company Table *t_ae2_FATAL_SE_2L_16FEB2024_41944*).

3.2.5.7.2.5 Adverse events leading to treatment discontinuation

The proportion of patients in the Glofit-GemOx arm who discontinued treatments due to adverse events was approximately [redacted] that of the R-GemOx arm ([redacted] versus [redacted]) (CS Table 26). The [redacted] adverse event for treatment discontinuation was COVID-19 in both the Glofit-GemOx arm and the R-GemOx arm ([redacted] and [redacted] respectively) (table provided in Clarification Response A11)

3.2.5.7.3 Company specified adverse events of special interest

CS section 2.11.4 states the following adverse events related to glofitamab treatment were of special interest given that they may have implications for prescribing decisions and patient management:

- Grade ≥ 2 cytokine release syndrome
- Grade ≥ 2 neurologic adverse events
- Tumour lysis syndrome
- Febrile neutropenia
- Grade ≥ 2 aspartate transaminase (AST), alanine transaminase (ALT) or total bilirubin elevation
- Grade ≥ 2 tumour flare
- Pneumonitis or interstitial lung disease (ILD)

- Colitis.

Results for these events in the second-line subpopulation are reported in CS Table 29. In addition, CS section 2.11.4 also reports on cytokine release syndrome of any grade (CS section 2.11.4.1), and neurologic adverse events of any grade (CS section 2.11.4.2; whole population only). Data on neurologic adverse events in the second-line subpopulation are reported in company Table *t_ae_ctc2_NEUR_SE_2L_16FEB2024_41944*. It is unclear to the EAG how neurologic adverse events are defined: CS section 12.11.4.2 states they include "preferred terms (PTs) reported from the Nervous System Disorders and Psychiatric Disorders system organ classes". However, company Table *t_ae_ctc2_NEUR_SE_2L_16FEB2024_41944* additionally includes some preferred terms from nine other system organ classes e.g. Ear and Labyrinth Disorders.

The proportion of second-line patients in the Glofit-GemOx arm experiencing grade ≥ 2 cytokine release syndrome was [redacted] (CS Table 29).

The proportion of second-line patients experiencing Grade 2 ≥ neurologic adverse events in the Glofit-GemOx arm was [redacted] that compared to R-GemOx arm ([redacted] versus [redacted]) (CS Table 29).

The proportion of second-line patients who experienced Grade ≥ 2 AST, ALT, or total bilirubin elevation in the Glofit-GemOx arm was [redacted] than in the R-GemOx arm ([redacted] versus [redacted]). Conversely, the proportion of patients experiencing tumour lysis syndrome in the R-GemOx arm was [redacted] than in the Glofit-GemOx arm ([redacted] versus [redacted] respectively) (CS Table 29).

[redacted] proportions of second-line patients experienced febrile neutropenia in the Glofit-GemOx and R-GemOx arms ([redacted] and [redacted] respectively; CS Table 29). However, in the whole population the proportion of patients with febrile neutropenia was almost [redacted] in the Glofit-GemOx arm than the R-GemOx arm ([redacted] versus 1.1%) (CS Table 28).

A [redacted] proportion of second-line patients experienced pneumonitis or interstitial lung disease ([redacted]) or colitis ([redacted]) in the Glofit-GemOx arm than the R-GemOx arm ([redacted]) (CS Table 29).

3.2.5.7.3.1 Cytokine release syndrome (any grade)

Almost [redacted] of second-line patients in the Glofit-GemOx arm ([redacted]) experienced cytokine release syndrome of any grade (CS Table 32). [redacted] of these events were considered

serious adverse events (CS Table 33), but only [redacted] events were considered grade 3 in severity. There were [redacted] grade 4 or 5 events.

Overall, the EAG's clinical experts considered the cytokine release syndrome profile of Glofit-GemOx in the second-line subpopulation of the STARGLO trial consistent with their experience of using glofitamab as a monotherapy in clinical practice. Furthermore, they were familiar with how to manage such events. One expert advised that given the less fit (non-transplant eligible) population, care will be needed to ensure that the prophylaxis protocol is maintained, and that clinical vigilance and early intervention is applied regarding cytokine release syndrome management.

3.2.5.7.3.2 Neurologic adverse events

Neurologic adverse events in the second-line subpopulation are reported in company Table *t_ae_ctc2_NEUR_SE_2L_16FEB2024_41944*. A [redacted] proportion of patients experienced neurologic adverse events ([redacted] than the R-GemOx arm ([redacted]).

[redacted] neurologic adverse events in both arms were grade 1-2 in severity, but [redacted] proportion in Glofit-GemOx arm were grade 3 ([redacted]). There were [redacted] grade 4 or 5 events in either arm.

One of the EAG's clinical experts commented that neurological adverse events being more common in the Glofit-GemOx arm is consistent with their experience of using glofitamab as a monotherapy, but extended follow-up is needed to determine the longer-term functional and quality of life impact.

3.2.5.7.4 EAG clinical experts' adverse events of special interest

Clinical expert advice to the EAG was that adverse events of special interest to clinicians with respect to Glofit-GemOx are infections of grade ≥ 3 in severity, and hypogammaglobulinaemia. The risk of infection, particularly grade ≥3, is a concern to clinicians because bispecific antibodies, including glofitamab, increase the risk of infection during and long after treatment. One EAG expert commented that events requiring significant intensive and/or prolonged support of a patient, such as infections, can have the biggest economic impact. Hypogammaglobulinaemia is of special interest because it can be very expensive to manage if patients have recurrent infections and require monthly intravenous immunoglobulin infusion.

3.2.5.7.4.1 Grade ≥3 infections

Data relating grade ≥ 3 infections in the second-line subpopulation are reported in CS Appendix D Table 19 and company Table *t_ae_ctc2_GA35_SE_2L_16FEB2024_41944.* A xxxxxxx proportion in the Glofit-GemOx arm compared to the R-GemOx arm experienced a grade ≥3 infection or infestation ([redacted] versus [redacted] respectively). [redacted] infection in the Glofit-GemOx arm was [redacted] ([redacted]), with the proportion [redacted] that compared to the R-GemOx arm ([redacted]).

3.2.5.7.4.2 Hypogammaglobulinaemia

Company Table *t_ae_ctc_bypl_SE_16FEB2024_41944* reports the incidence of hypogammaglobulinaemia. [redacted] patient in the second-line subpopulation experienced this event. [redacted] patient, receiving Glofit-GemOx arm, in the whole population experienced this event.

3.2.6 Pairwise meta-analysis of intervention studies

For the comparison of Glofit-GemOx against R-GemOx, which is the only comparison considered relevant by the company in their decision problem (see section 2.3), the STARGLO trial is the sole source of evidence. A pairwise meta-analysis for this comparison is therefore not possible (CS section 2.9).

The company have excluded Pola-BR as a comparator from their decision problem because, they argue, it is rarely used now in the second-line setting (for full discussion of the decision problem see section 2.3 above). A pairwise meta-analysis of Glofit-GemOx against Pola-BR was therefore not considered necessary by the company (CS section 2.9) (see Key 0). The CS does not discuss whether any individual trials or a pairwise meta-analysis would provide direct comparisons of Glofit-GemOx against Pola-BR, but the EAG and our clinical experts are not aware of any such studies.

3.3 Indirect treatment comparisons

The company have not provided any indirect treatment comparisons (ITC) because they did not deem these to be necessary, either for second-line therapy (see section 3.3.1) or for third and subsequent lines of therapy (see section 3.3.2).

3.3.1 Second-line therapy

The only comparison which the company consider relevant in their decision problem (see section 2.3) is Glofit-GemOx versus R-GemOx. The EAG agree that an ITC for this comparison is unnecessary since this comparison has been made directly in the STARGLO trial. However, as discussed in section 2.3 above, the EAG's clinical experts considered that

another comparison, Glofit-GemOx versus Pola-BR, is also potentially relevant in the second-line setting for this technology appraisal (see Key 0).

The company do not discuss whether an ITC would be feasible for the comparison of Glofit-GemOx against Pola-BR in the second-line setting. Such an ITC would require second-line individual participant data from the Glofit-GemOx arm from the STARGLO trial and a sufficiently similar second-line Pola-BR cohort that could be matched to this in an unanchored comparison. The company provided a Systematic Literature Review and Feasibility Assessment Report for the indirect comparison in Clarification Response A3 (which we refer to henceforth as the "SLR Report"). The review identified 505 articles referring to 304 unique studies eligible for inclusion in the feasibility assessment for ITC (SLR Report section 4.1.1). The SLR included second-line therapies, although the focus of the ITC feasibility assessment was on third-line and later therapies (SLR Report section 4.2) and the second-line studies of Pola-BR among those included are not separately itemised (SLR Report Appendix C). The EAG is uncertain whether any second-line studies on Pola-BR could potentially be included in an unanchored ITC versus Glofit-GemOx. We and our clinical experts are aware of several potential studies for consideration (e.g. an update to the GO29365 study[34] and other studies listed by the company in Appendix C of their SLR Report) but a feasibility assessment would need to be conducted to clarify whether their population characteristics, including treatment history, could be adequately matched to achieve an indirect comparison with a sufficient sample size. If a feasibility assessment for second-line ITC is to be conducted it would be appropriate to also update the searches in the SLR Report to ensure that the latest evidence is considered. Note that an unanchored indirect comparison of Glofit-GemOx against Pola-BR (if feasible) would be equivalent to observational evidence[35] and hence more uncertain than the randomised comparison of Glofit-GemOx against R-GemOx.

3.3.2 Third and subsequent lines of therapy

As explained above (section 2.3), the company is positioning Glofit-GemOx as a second-line therapy, primarily because they argue (and the EAG's clinical experts agree) that second-line treatment has the greatest unmet need and less robust evidence is available for comparing the efficacy and safety of third-line and later therapies (CS sections 1.1, 2.3, and 2.10).

The company conducted feasibility assessments for indirect comparisons comparing Glofit-GemOx against third-line comparators, as reported in CS section 2.10 and their SLR Report.

The CS does not provide any background information on the third-line treatments, as these are not considered in the company's decision problem. Third-line treatments, as specified in the NICE scope, are:

- Rituximab in combination with one or more chemotherapy agents such as:
  - R-GemOx (rituximab, gemcitabine, oxaliplatin)
  - R-Gem (rituximab, gemcitabine)
  - R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine)
  - R-DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine)
  - BR (bendamustine, rituximab)
- Polatuzumab vedotin with rituximab and bendamustine (only when stem cell transplantation is not suitable) [TA649]
- Axicabtagene ciloleucel [TA872]
- Glofitamab [TA927][36]
- Loncastuximab tesirine (only if previously treated with polatuzumab vedotin or if polatuzumab vedotin is contraindicated or not tolerated) [TA947]
- Epcoritamab (only if they have had polatuzumab vedotin, or if polatuzumab vedotin is contraindicated or not tolerated) [TA954]

The company's SLR and feasibility assessment is generally well reported. Figure 3 in the SLR Report provides a flow chart summarising the availability of evidence for each of the third-line comparators. However, there are some uncertainties:

- The number of comparison arms available for each therapy listed in SLR Report section 4.1.2 is larger than the number of arms listed in the feasibility assessment flow chart (SLR Report Figure 3) but the SLR Report does not explain this difference.
- The feasibility assessment does not include any regimens containing rituximab. The SLR Report explains that a third-line indirect comparison of R-GemOx against Glofit-GemOx is unnecessary since this comparison would be available (as a subpopulation analysis) from the STARGLO trial. However, the SLR Report and CS do not explain why no other rituximab-containing therapies were considered in the feasibility assessment (the list of therapies "of interest for the feasibility assessment" in SLR Report section 2.2.2 does not include any of the regimens containing rituximab). The EAG is uncertain whether the company are assuming that the efficacy and safety of R-GemOx when used third-line would sufficiently represent that

of the other rituximab-based therapies, or whether the evidence for these therapies is too sparse for feasibility assessment.

- Polatuzumab vedotin is excluded from the feasibility assessment without a rationale being given. The EAG assumes this is because polatuzumab can only be used once in the treatment pathway (as stated in CS section 1.3.2.1.2).

Having excluded polatuzumab vedotin and the rituximab-containing therapies, the company's feasibility assessment for third-line indirect comparisons included five of the NICE-specified comparators (axicabtagene ciloleucel, loncastuximab tesirine, epcoritamab, and glofitamab monotherapy) (CS section 2.10). The company's feasibility assessment focused on unanchored matching-adjusted indirect comparisons (MAICs), except for the glofitamab monotherapy comparison where individual patient data were available, permitting a propensity score-based indirect comparison.

The company concluded that the unanchored MAICs would be highly uncertain, even after sub-setting data from the Glofit-GemOx arm of the STARGLO trial to improve patient matching, given the poor overlap of population characteristics, especially relating to variation in the DLBCL histology type across studies. The company also concluded that a propensity score analysis for the comparison against glofitamab monotherapy, whilst technically feasible, would be highly uncertain because adjustment for all relevant covariates would result in a substantial reduction in the effective sample size. The EAG requested clarification from the company on whether other analysis approaches such as simulated treatment comparison (STC) might be appropriate, given the limited overlap of the study population characteristics. The company confirmed in clarification responses (without providing any new data) that they did not believe STC would be viable (Clarification Response A4) and that the propensity score analysis for glofitamab monotherapy would be highly uncertain (Clarification Response A5). The company also reiterated in Clarification Response A5 that they do not intend third-line therapy to be within their reimbursement request.

Given that the company do not intend to provide evidence for third-line therapy in this technology appraisal the EAG has not critiqued the company's SLR feasibility assessment for the third-line comparisons in detail. We agree, broadly, that third-line indirect treatment comparisons would likely be highly uncertain due to the heterogeneity of the study populations which is difficult to adjust for satisfactorily. We note that even if an indirect comparison against one of the third-line comparators were feasible this would only address part of the possible comparative evidence base, with uncertainty about the relative

effectiveness and safety of Glofit-GemOx compared to the other third-line comparators unresolved.

3.4 Conclusions on the clinical efficacy and safety evidence

3.4.1 Clinical efficacy conclusions

The company is positioning Glofit-GemOx as a second-line therapy for people who have relapsed or refractory DLBCL NOS and who are unsuitable for autologous stem cell transplant. This indication is relevant to a subset of the population in the company's pivotal STARGLO clinical trial and is narrower than the NICE scope and expected marketing authorisation in four respects:

- The NICE scope and expected marketing authorisation specify that patients should have received a prior line of therapy but do not limit Gofit-GemOx to the second-line setting. The EAG and our clinical experts agree that the company's second-line focus (i.e. excluding third and later lines of therapy from comparison) is appropriate (section 2.3).
- Approximately 10% of people who have DLBCL have subtypes other than DLBCL NOS. These people are not captured in the company's decision problem. The EAG's clinical experts did not consistently agree on whether such patients would receive the same treatment as those with DLBCL NOS (section 2.3). We note that the previous NICE recommendation for glofitamab monotherapy [TA 927] was for patients with any DLBCL subtype.
- The company has excluded Pola-BR as a second-line therapy from comparison (section 2.3). The EAG and our clinical experts question the exclusion of Pola-BR and we have raised this as a Key Issue for further consideration (see Key 0).
- The company has excluded all second-line rituximab-chemotherapy regimens from comparison except R-GemOx because they believe the other regimens are rarely used in practice and R-GemOx sufficiently represents the efficacy and safety of the other regimens. The EAG's clinical experts varied in what they consider as standard second-line therapy but all the experts agreed that the company's approach is appropriate.

The company's systematic literature review was generally well conducted and identified one study, the pivotal ongoing STARGLO trial, comparing Glofit-GemOx against R-GemOx, as relevant to the decision problem. The company did not specifically search for studies that might enable Glofit-GemOx to be compared against Pola-BR via indirect comparison since

they had excluded Pola-BR. The availability and suitability of evidence to support an indirect comparison of Glofit-GemOx against Pola-BR is therefore uncertain (as noted under Key 0).

The company's pivotal STARGLO trial was generally well conducted, but has two key limitations, one of which is inherent to the trial design while the other relates to its application to this technology appraisal:

(i) STARGLO was an open-label trial and so the outcomes could potentially be at high risk of bias.

(ii) The clinical efficacy and safety evidence for the current technology appraisal is from a post hoc second-line subpopulation of the STARGLO trial. This weakens any conclusions on causality since the full randomised (i.e. intention to treat) analysis cannot be applied.

Despite the limitations of the evidence from the STARGLO trial, a clear difference in survival outcomes is evident favouring Glofit-GemOx over standard therapy (i.e. R-GemOx). This difference was generally consistent with the results seen in the full trial ITT population and the EAG's clinical experts all considered the survival outcomes to be clinically meaningful.

3.4.2 Clinical safety conclusions

The most frequent event related to Glofit-GemOx was cytokine release syndrome, with almost [redacted] of the second-line patients in the Glofit-GemOx arm experiencing this. The EAG's clinical experts considered the cytokine release syndrome profile of Glofit-GemOx in the second-line subpopulation of the STARGLO trial consistent with their experience of using glofitamab as a monotherapy in clinical practice and were familiar with how to manage such events. One expert advised that given the less fit (non-transplant eligible) population, care will be needed to ensure that the prophylaxis protocol is maintained, and that clinical vigilance and early intervention is applied regarding cytokine release syndrome management.

Serious adverse events, adverse events of Grade ≥3 (mostly [redacted]) and adverse events leading to discontinuation were notably more frequent in Glofit-GemOx arm, with the most frequent AE leading to treatment discontinuation being [redacted] Deaths were also more frequent in the Glofit-GemOx arm, although numbers were small.

Company-specified adverse events of special interest were Grade ≥ 2 cytokine release syndrome, Grade ≥ 2 neurologic adverse events, tumour lysis syndrome, febrile neutropenia, Grade ≥ 2 AST, ALT or total bilirubin elevation, Grade ≥ 2 tumour flare, pneumonitis or interstitial lung disease, and colitis. These events were [redacted] frequent the Glofit-GemOx

arm apart from tumour lysis syndrome ([redacted] frequent [redacted] number in the R-GemOx arm) and febrile neutropenia ([redacted] in both arms).

Further adverse events of special interest to the EAG's clinical experts were infections of grade ≥ 3 in severity ([redacted] in the glofit-GemOx arm – of interest because bispecific antibodies, including glofitamab, increase the risk of infection during and long after treatment), and hypogammaglobulinaemia (can be very expensive to manage if patients have recurrent infections and require monthly intravenous immunoglobulin infusion, but in the second-line subpopulation was very infrequent).

In summary, the safety profile of Glofit-GemOx in the second-line subpopulation of the STARGLO trial is in line with clinical expectation, with cytokine release syndrome being the key adverse event in terms of its frequency and potential to cause patient morbidity.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company reports details on their systematic literature review (SLR) in CS section B 3.1 and Appendix E. The search was for published health economic evaluations for DLBCL in the second-line and beyond (2L+) and was not restricted to specific therapies. Searches were most recently completed in August 2024. The databases searched were completed in Embase, MEDLINE, EconLit and Evidence Based Medicine [EBM] Reviews.

A total of 54 relevant published economic evaluations were identified, of which 35 were full publications and 19 were previously published HTA submissions. The CS provides more details of the studies in CS Table 37 and 38. Eleven studies were specifically in the second-line setting although none of these were for the intervention or comparator of this appraisal.

Of the studies identified, the EAG considers the two most relevant to this appraisal are the NICE appraisals TA649 (polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory DLBCL in adults who cannot have a haematopoietic stem cell transplant) [17] and TA927 (glofitamab for treating relapsed or refractory DLBCL after 2 or more systemic treatments, in adults).[36]

EAG conclusion on company's review of cost-effectiveness evidence

The company's searches are well constructed and use a comprehensive range of appropriate terms. The company searched a good range of sources.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The EAG considers that the company has met NICE's reference case, as shown in Table 15.

Table 15 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	Appropriate – OS and PFS
Perspective on costs	NHS and PSS	Appropriate – NHS and PSS used

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Appropriate – cost-utility analysis with fully incremental analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Appropriate – Lifetime (60 years). Patients' mean age is 68 years, but the model uses the age distribution of the patient cohort (24 – 88 years), rather than the mean age of the cohort, so a longer time horizon is used
Synthesis of evidence on health effects	Based on systematic review	Yes – company conducted appropriate systematic reviews
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 – company collected EQ-5D-5L data from the STARGLO trial, which were cross-walked to EQ-5D-3L utilities appropriately
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes – company collected EQ-5D-5L data from the STARGLO trial (ITT patient population)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes – EQ-5D uses representative sample from UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – CS discusses equality considerations in CS 1.4; no equality considerations expected for Glofit-GemOx; threshold for severity modifier is not reached and not applied in the model

Element of health technology assessment	Reference case	EAG comment on company's submission
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 - NHS Reference Costs 2023/24; PSSRU 2023 costs used
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes – 3.5% discount rate for both costs and health benefits in the company case; company ran a scenario testing 1.5% discount rate

Source: EAG created table
EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions; 3L, 3 Levels; 5L, 5 Levels; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life year.

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company developed a de novo partitioned survival model in Microsoft Excel. The CS states partitioned survival models are commonly used in oncology, as detailed in TSD 19.[37] The model structure is described in CS B.3.2.3 and illustrated in CS Figure 12, reproduced in Figure 4 below. The model contains three mutually exclusive health states: progression free survival (PFS); post-progression survival (PPS) and death. Patients start in the progression-free survival state, following initiation of one of the included first-line treatments. At disease progression, patients transition to the post-progression survival state, which is irreversible, so patients cannot return from post-progression to progression-free survival health state. Patients in the progression-free survival and post-progression survival states may die from cancer or other causes.

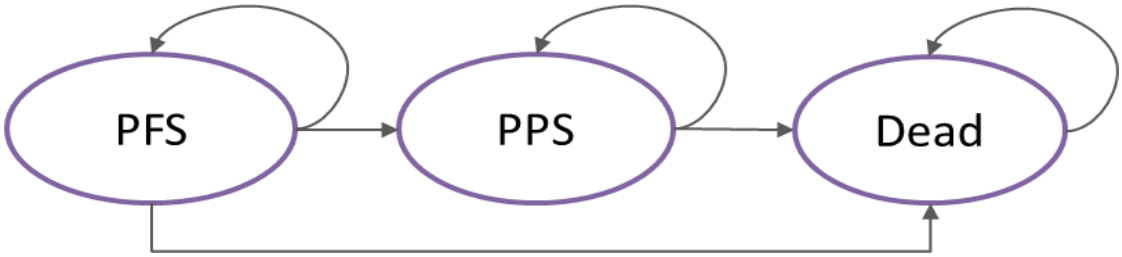

Figure 4 Structure of the economic model

Reproduced from CS B.3.2.3 Figure 12

The proportion of patients in each health state at different time points is based on the progression-free survival and overall survival curves from the STARGLO trial. Logically, the proportion of patients alive at any time is greater than those with progression-free survival. The proportion of patients progressing to the post-progression survival health state is the difference between overall survival and progression-free survival health states (see CS Figure 10).

The model uses weekly cycles as it enables the model to incorporate the different timings in the drug administrations. The model also includes a half-cycle correction to account for the under or over estimations of transitions occurring at the beginning or end of the cycle.

4.2.2.2 EAG critique of model assumptions

4.2.2.2.1 Assumption

Patients who are progression-free and alive at three years are assumed to remain progression-free and do not progress at a later date. The CS states that this assumption was supported by their clinical experts and previous technology appraisals such as TA927 (Glofitamab monotherapy in relapsed and refractory DLBCL).

We consider that mortality for patients who are progression-free should match the general population mortality, but that patients whose disease has progressed should continue to experience disease-related mortality.

In response to Clarification Question B1, the company provided more detail on their decision not to use a mixture cure model. They stated that a mixture cure model may be appropriate for conditions that can be considered to be curative, and where there is sufficient evidence available to support the assumption that a proportion of patients may be cured. In this appraisal, they did not consider that sufficient evidence was available to support the use of a mixture cure model as there was only limited follow-up data. They also noted that in a previous appraisal for relapsed or refractory DBCL (TA649 for polatuzumab plus

bendamustine and rituximab)[17] the committee rejected the use of a mixture cure model due to the uncertainty around the cure fraction and that the company's approach is consistent with the approach taken in other appraisals for relapsed or refractory DBCL such as for glofitamab (TA927)[36] and for epcoritamab (TA954).[38]

The EAG considers that it would have been possible to model this using a mixture cure model and that using a partitioned survival model and assuming that all patients remaining in progression free survival leads to unrealistic survival extrapolations (see section 4.2.6.1 for more discussion on this issue).

EAG conclusion on model structure

The three-state partitioned survival model used in the company's economic evaluation is a standard modelling approach and has been applied in previous NICE appraisals for DLBCL and is commonly used in models for oncology. We consider that the model structure and partitioned survival approach is appropriate. The EAG considers that the cycle length is appropriate, although a half-cycle correction is not needed for such a short cycle length. Our clinical experts also agreed with this assumption. Patients who remain progression-free at three years revert to near general population utility values (assumed 10% lower than general population as in TA927) and do not incur any further costs. In addition, mortality risk for the remaining patients reverts to a near general population level (9% excess versus the general population).

4.2.3 Population

The modelled population is adults with relapsed or refractory DLBCL who are ineligible for autologous stem cell transplant and have received one prior systemic therapy, specifically those in the second-line setting. The company has used a restricted population and does not include treatment later than second-line. The CS states that there is insufficient evidence for these comparators in third-line treatment and beyond to compare them with glofitamab. The EAG agrees with this statement.

The CS states the reason for restricting to the second-line setting is that the comparative evidence of alternative treatments in later lines of treatment is highly uncertain, making conducting an ITC more difficult. Therefore, restricting the comparison to second-line treatment presents the most robust case for cost effectiveness analysis, and the company's clinical experts advised that this was the treatment line with the most unmet need.

Baseline characteristics of the modelled cohort are based on participants in the STARGLO trial, with a mean age of [redacted] years and [redacted] male. The company's clinical experts confirmed that the population of STARGLO was broadly representative of people with relapsed or refractory DLBCL treated in the UK.

EAG conclusion on model population

The EAG notes that the patient population is more restricted than the NICE scope and only includes second-line treatment. The patient population included in the economic model is consistent with the trial population of the STARGLO trial, albeit restricted to the second-line population only.

4.2.4 Interventions and comparators

As already noted, the economic model compares the cost-effectiveness of glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx) to rituximab in combination with gemcitabine and oxaliplatin (R-GemOx).

Glofitamab is administered as an intravenous infusion according to a dose step-up schedule leading to the recommended dose of 30 mg. A course of treatment with glofitamab consists of a maximum of 12 cycles (21-day cycles). Gemcitabine and oxaliplatin are also administered by intravenous infusion for up to eight cycles. All patients receiving Glofit-GemOx must be monitored for at least 24 hours after the first infusion, as specified in the glofitamab SmPC.[25] Thereafter those who experience grade ≥2 CRS in a previous infusion should be monitored for 24 hours after receiving an infusion.

For the comparator treatment, rituximab is also given as an intravenous infusion for a maximum of eight cycles. Details on the dosing of these therapies are given in Table 6.

The only comparator treatment included is R-GemOx, which was used in the STARGLO trial. The NICE scope includes four additional comparators at second-line, including rituximab and polatuzumab vedotin with rituximab and bendamustine (Pola-BR). The CS states that the company's clinical experts considered that R-GemOx is representative of all rituximab-chemotherapy regimens in terms of efficacy and safety outcomes. Clinical advice to the EAG agrees that R-GemOx is representative of the other rituximab-based regimens and that the effectiveness of these regimens could be considered to be similar to each other.

The CS states that polatuzumab vedotin with rituximab and bendamustine is now rarely used for second-line treatment for relapsed or refractory DLBCL, and for this reason has not been included as a comparator. Clinical expert advice to the EAG was that the company's

exclusion of Pola-BR is inappropriate as it is still used in clinical practice, albeit to a reduced extent (discussed in section 2.3).

EAG conclusion on intervention and comparators

We note that the comparators included in the CS and the economic model are not consistent with the NICE scope. We agree that it is reasonable to use R-GemOx to represent all rituximab-based therapies currently used for second-line treatment. However, we consider it inappropriate to exclude Pola-BR, as this is still currently used in clinical practice.

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is the NHS and Personal Social Services (PSS). Costs and QALYs are discounted at 3.5% in the base case, as per the NICE reference case.[39] In the base case, the model has a lifetime horizon of 60 years. The EAG notes that using a time horizon of 60 years results in a patient age of 128 years at the end of the simulation. Generally, it is more standard for the lifetime horizon to end at age 100 years, however as the model results are similar with a time horizon of 40 years or 60 years (CS Table 70) we have kept the same time horizon as the company.

EAG conclusion on perspective, time horizon and discounting

The company adopted the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines[39] and previous NICE appraisals for DLCBL.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Overall survival

4.2.6.1.1 Overall survival - assessment of proportional hazards

CS section B.3.3.4 describes the company's method for assessing proportional hazards for overall survival in the STARGLO second-line subpopulation. The company assessed whether the proportional hazards assumption holds using Schoenfeld residuals plots (CS Figure 15 panel D) and a log-cumulative hazard plot versus log(time) (log-log plot; CS Figure 15 panel C). The CS states that the Schoenfeld test (p=0.1207) suggests that the proportional hazards assumption holds, but that the log-log plot shows convergence at multiple time points. Consequently, the company rejected the proportional hazards assumption for overall survival and fitted survival curves to the Glofit-GemOx and R-GemOx arms independently.

EAG conclusion on assessment of proportional hazards for overall survival

The EAG agree with the company and consider that the assumption of proportional hazards does not hold for overall survival for the STARGLO second-line patients; we consider it appropriate that the company have fitted parametric curves independently.

4.2.6.1.2 Overall survival extrapolation

The company extrapolated time-to-event outcomes using parametric curves over the time horizon of the cost-effectiveness analysis. CS section B.3.3.2 explains that the parametric curves were ranked based on goodness of fit to the Kaplan-Meier data of the STARGLO trial second-line population using Akaike's information criterion (AIC) and Bayesian information criterion (BIC), shown in CS Table 43. The company assessed the hazard plot data to determine if it indicated that a specific distribution was appropriate (a constant hazard suggesting the exponential distribution, for example). In addition, the company visually evaluated the survival plots to determine the most appropriate survival distribution. The company validated their chosen distributions for long-term plausibility with UK clinical experts at their advisory board.

We agree with the company that both the Glofit-GemOx and R-GemOx hazard plots have non-monotonic hazard (i.e. not continuously increasing or decreasing but varies over time) (CS Figure 15 panel B), and that the lognormal, log-logistic and generalised gamma distributions would be appropriate choices in this case. CS 3.3.4 states that the AIC/BIC results indicated that the Gompertz distribution was the best fit for the Glofit-GemOx arm, and the lognormal was the best fit for the R-GemOx arm. However, in the company's judgement the Gompertz curve provided clinically implausible survival estimates (based on a visual inspection of the survival plot). The EAG agrees that the Gompertz curve survival estimates appear to be implausible. The company selected the lognormal curve for the Glofit-GemOx arm instead, because this curve was ranked second according to AIC/BIC analysis. The company tested the generalised gamma and log-logistic curves (the next two highest AIC/BIC ranked distributions) to extrapolate overall survival in scenario analyses. Estimates of long-term overall survival using these different parametric curves are shown in Table 16.

The EAG conducted a targeted literature search for reports of long-term survival outcomes for patients with refractory or relapsed DLBCL receiving R-GemOx. Cazalles et al.(2021; retrospective study, n=196 patients with relapsed or refractory DLBCL treated with R-GemOx, France)[40] reported a two-year overall survival rate of 32% in patients ineligible for

an autologous stem cell transplant. Mounier et al. (2013; single-arm phase II study, n=49 patients with relapsed or refractory DLBCL treated with R-GemOx, France)[16] reported a five-year overall survival rate of 14% in patients who were not candidates for high-dose therapy. We note that both of these studies observed lower overall survival rates than those reported by the company, even when using the parametric curve with the most pessimistic predictions (log-logistic; Table 16). One of our clinical experts considered that the modelled long-term overall survival estimates, for patients unsuitable for transplant and receiving R-GemOx second-line, to be optimistic and would expect 2-year and 5-year overall survival rates to be similar to the predictions of Mournier/Cazalles (Table 16). Our other two clinical experts considered the overall survival predictions used in the company's base case to be plausible.

In response to Clarification Question B1, the company conducted a scenario modelling results using a state transition model where only patients in the progression-free health state have general population mortality and those in the progressed health state have a cancer-related mortality. Based on visual inspection of the overall survival curve produced by this scenario, the EAG considers the results to be unrealistic and lack face validity. Instead, we set the cure point (i.e. when all patients with progressed disease have died and all remaining patients are progression-free) to be at six years, not three. Consequently, we set the mortality for the cohort equal to the general population after six years in our base case, and raise this as a key issue (section 1.4). We note that this produces 5-year overall survival estimates for the R-GemOx arm that align more closely with results observed in the literature (Table 16).

Table 16 Estimates[a] of long-term overall survival (STARGLO 2L subpopulation)

Alive on Glofit-GemOx	**Time point**			
	1 year	2 years	5 years	10 years
STARGLO K-M data	65%	59%	-	-
Lognormal (company base case)[b]	70%	57%	46%	37%
Generalised gamma[b]	70%	58%	47%	38%
Log-logistic[b]	70%	56%	44%	35%
Cure point at 6 years; lognormal (EAG base case)	70%	57%	39%	29%
Alive on R-GemOx				
STARGLO K-M data	61%	40%	-	-
Lognormal (company base case)	60%	39%	26%	21%
Generalised gamma[b]	59%	40%	29%	23%

Log-logistic[b]	60%	38%	25%	20%
Cazalles et al. (2021)[40]	-	32%	-	-
Mournier et al. (2013)[16]	48%	35%	14%	-
Cure point at 6 years; lognormal (EAG base case)	60%	39%	17%	11%

Source: EAG created table, company model
2L, second line; K-M, Kaplan-Meier; Glofit, glofitamab; GemOx, gemcitabine and oxaliplatin; R, rituximab.
[a] Company estimates unless otherwise stated
[b] Assumes cure point is at three years

EAG conclusion on overall survival extrapolation

The EAG agree with company's rationale and consider using the lognormal curve to extrapolate overall survival to be reasonable. Using the same curve for both arms is appropriate, as per NICE Decision Support Unit recommendations.[41]

We note that none of the long-term overall survival estimates in the company's base case for R-GemOx match observed outcomes reported in the literature. Therefore, we prefer to set the cure point (i.e. when all patients with progressed disease have died and all remaining patients are progression-free) to be at six years in our base case. This gives 5-year R-GemOx overall survival estimates similar to results observed by Mournier.[16]

We note that the parametric extrapolations overestimate overall survival for Glofit-GemOx at Year 1. We conduct a scenario analysis using Kaplan-Meier data with a lognormal tail (attached when 20% of patients remain at risk; both arms) (section 6.2).

4.2.6.1.3 Long-term remission/survivorship

The company's economic model assumes that patients who are alive and progression-free at three years enter long-term remission (Figure 5), and this assumption is supported by the company's clinical experts (CS section 3.3.4.1). Furthermore, the NICE committee accepted this assumption in the previous technology appraisal TA927 (Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after two or more systemic treatments).[36]

Two of our clinical experts agreed with the company's assumption. However, another of our clinical experts highlighted that there is currently no evidence that R-GemOx is curative. But, this expert added that clinicians are becoming more comfortable that the risk of relapse at three years, in patients receiving second-line treatment whose disease has not progressed,

is very low. This expert also considered that the risk of relapse is likely to be reduced further with the introduction of new, more effective treatments.

Figure 5 Modelled overall survival and progression-free survival, company base case (A) Glofit-GemOx, (B) R-GemOx

Source: EAG created figure, company model
OS, overall survival; PFS, progression-free survival; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin

The company's model assumes that when patients enter long-term remission, i.e. after three years, the majority of patients whose disease has progressed have died, and the mortality risk for the remaining patients is 9% higher than that of the general population. CS section 3.3.4.1 states that this is in line with the value applied from TA559 (Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies)[42] and TA567(Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies),[43] and is based on a standardised mortality rate identified from Maurer (2014),[44] adjusted to account for potential excess comorbidities.[17, 43] The company assumes the long-term remission to be treatment independent, with the same assumptions applied to both treatment arms.

We note that assuming all patients remain progression-free from three years results in optimistic overall survival extrapolations compared with estimates in the literature (Table 16). In the model, the majority of patients whose disease has progressed have died by six years. We prefer to set this as the cure point in our base case, not three years. Figure 6 shows the effect of this on overall survival predictions.

Figure 6 Modelled overall survival, EAG base case and company base case (A) Glofit-GemOx, (B) R-GemOx

Source: EAG created figure, company model
OS, overall survival; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin

The company conducted scenarios (CS Table 70) for alternative cure rates of two and five years, explored assuming no quality-of-life detriment and no excess mortality in long-term remission, and tested an alternative source for mortality rate from Howlader et al. (2017)[45] (which showed 41% excess mortality in people whose DLBCL had been in remission and progression-free two years after treatment). We note that the NICE committee assessing TA927[36] concluded there was uncertainty concerning the exact mortality risk for people whose disease has been progression-free for three years, but that the company's assumption of 9% increased risk was reasonable.

EAG conclusion on long-term remission/survivorship

We consider that assuming all patients remain progression-free from three years results in optimistic overall survival extrapolations (Figure 6; Table 16), which we discuss in section 4.2.6.1.2. We consider that the majority of patients whose disease has progressed have died by six years and set this as the cure point in our base case, not three years.

4.2.6.1.4 All-cause mortality

CS section 3.3.5 explains the company's approach to calculating the general population mortality using age- and gender-specific all-cause mortality rates by year in the general UK population, using the National Life Tables for England & Wales (2021-2023),[46] including a standardised mortality rate to account for increased mortality risk due to excess comorbidities.

The company model background mortality as a function of the age distribution, rather than the mean age of the cohort, because they consider it better reflects the heterogeneity in mortality given the age range in the STARGLO trial ([redacted]). The CS states that this approach is also more appropriate for potentially curative treatments where survival for cured patients is calculated using general population mortality. We note that using age distribution rather than mean age was not raised as a concern in the technical appraisal for polatuzumab vedotin for untreated DLBCL (TA874).[6] The economic model has the option to calculate the ICER using the average cohort age method to estimate background mortality. The company reports this result in their scenario analyses (CS Table 70).

EAG conclusion on all-cause mortality

The EAG has no concerns regarding using the age distribution method to calculate background mortality and we use this method in our base case. We note that using the average cohort age has a negligible effect on the company's ICER result.

4.2.6.2 Progression-free survival

4.2.6.2.1 Progression-free survival - assessment of proportional hazards

The company used the same method for assessing whether the proportional hazards assumption holds for progression-free survival as for overall survival (CS section B.3.3.3). CS Figure 13 panel C shows the log-log plot, and the Schoenfeld plot is presented in CS Figure 13 panel D.

The company rejected the proportional hazard assumption for progression-free survival because, although the Schoenfeld test (p=0.6658) would accept the proportional hazards assumption holds, the log-log plot shows convergence at an early time point. Consequently, the company fitted curves to the Glofit-GemOx and R-GemOx arms independently.

EAG conclusion on assessment of proportional hazards for progression-free survival

We agree that the assumption of proportional hazards does not hold for progression-free survival for the STARGLO second-line patients; we consider it appropriate that the company have fitted parametric curves independently.

4.2.6.2.2 Progression-free survival extrapolation

CS section 3.3.3 explains the company's method for extrapolating progression-free survival from STARGLO over the time horizon of the model using standard parametric distributions. The company used hazard plot data to determine if a specific distribution was indicated.

They also assessed goodness of fit to the trial Kaplan-Meier data using AIC/BIC criteria (CS Table 41) and visual inspection of the curves; results were validated with clinical experts at the company's UK advisory board.

We agree with the company that the hazard plot for Glofit-GemOx shows a continuously declining hazard rate and that the hazard rate for R-GemOx is non-monotonic (CS Figure 13, panel B). This suggests that the Weibull or Gompertz are appropriate parametric curves to model the Glofit-GemOx arm. But, the company's clinical experts considered the Weibull curve underestimated the long-term progression-free survival for GlofitGemOx (CS 3.3.3).

The Gompertz distribution was the highest ranked curve according to AIC/BIC criteria for Glofit-GemOx. However, the company considered that this curve results in clinically implausible estimates of long-term progression-free survival. The EAG agrees with this. The company's clinical experts considered that the lognormal and log-logistic curves produced the most plausible progression-free survival estimates for both Glofit-GemOx and R-GemOx. Based on this advice, and because the lognormal was the second-highest ranked curve according to the AIC/BIC assessment for both trial arms, the company selected the lognormal curve to extrapolate both Glofit-GemOx and R-GemOx Kaplan-Meier data. The company tested the log-logistic and generalised gamma curves in scenario analyses, because these distributions are the next highest ranked according to the AIC/BIC assessment. Estimates of long-term progression-free survival using these different parametric curves are shown in Table 17.

Cazalles et al. (2021) reported two-year progression-free survival rate of 18% and Mournier et al. (2013) reported five-year progression-free survival rates of 13%, for patients with relapsed or refractory DLBCL receiving R-GemOx. We note that progression-free survival estimates for R-GemOx, produced by the lognormal and log-logistic curves in the company's base case, are similar to the results of Cazalles[40] and Mournier[16] (Table 17). Our clinical experts considered the progression-free survival predictions used in the company's base case to be reasonable.

Table 17 Estimates[a] of long-term progression-free survival (STARGLO 2L subpopulation)

Alive and PF on Glofit-GemOx	Time point			
	1 year	2 years	5 years	10 years
STARGLO K-M data	55%	48%	-	-
Lognormal (company base case)	58%	43%	35%	35%
Generalised gamma	58%	45%	38%	37%
Log-logistic	57%	42%	33%	33%
Alive and PF on R-GemOx				
STARGLO K-M data	33%	28%	-	-
Lognormal (company base case)	31%	16%	10%	10%
Generalised gamma	35%	26%	21%	21%
Log-logistic	29%	15%	10%	10%
Cazalles et al. (2021)[40]	-	18%	-	-
Mournier et al (2013)[16]	27%	18%	13%	-

Source: EAG created table, company model
2L, second line; K-M, Kaplan-Meier; PF, progression-free; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin
[a] Company estimates

EAG conclusion on progression-free survival extrapolation

Based on the company's rationale, advice from our clinical experts and results from the literature, the EAG agree with company's choice of using the lognormal parametric curve to extrapolate progression-free survival. Using the same curve for both arms is appropriate as per NICE Decision Support Unit recommendations.[41]

4.2.6.3 Time on treatment

As the STARGLO trial time on treatment data were complete, time on treatment was modelled using the Kaplan-Meier data and so it was not necessary to fit a distribution curve to the Kaplan-Meier data (CS section 3.3.6).

The EAG consider that the modelled time on treatment estimates fit the corresponding Kaplan-Meier data reasonably closely. However, we noted that there was a discrepancy between the Kaplan-Meier oxaliplatin time on treatment for the R-GemOx arm and the modelled equivalent. In response to Clarification Question B7, the company state that this discrepancy was the result of an error in a formula in the model, which has been corrected

by the company. The model has also been updated to correct errors in time on treatment for gemcitabine and time on treatment for rituximab in the R-GemOx arm.

In addition, the company have corrected the accumulated drug cost of rituximab in the R-GemOx arm of the model, by removing the costs of gemcitabine and oxaliplatin. These costs are accounted for elsewhere in the R-GemOx arm of the model, and so were being double-counted in error.

EAG conclusion on time on treatment

We agree with the company and consider it appropriate to use the Kaplan-Meier data to inform time on treatment in the economic model.

4.2.6.3.1 Treatment effect waning

The company do not apply a treatment effect waning assumption in their base case. Patients receive glofitamab treatment for nine months and the company state that the majority of patients taking glofitamab had completed their regimen within the observed period (CS section 3.2.3.2). As such, the company assume that most patients have been off-treatment long enough that changes in the observed hazards for progression-free survival (declining with no sign of increasing over time, CS Figure 13 panel B, reproduced in Figure 7) are not expected to occur beyond the end of the observed data (CS section 3.2.3.2).

Figure 7 Hazard plot for progression-free survival, Glofit-GemOx versus R-GemOx

Source: Reproduced from CS Figure 13, panel B

EAG conclusion on treatment effect waning

We agree that the observed hazards for glofitamab progression-free survival continue to decline steadily over time. Our clinical experts considered it was

reasonable to assume that most patients have been off treatment long enough that substantial changes in the risk of the disease progressing are not expected to occur beyond the end of the observed data (about 35 months). We consider that not including treatment effect waning in the model is reasonable.

4.2.6.4 Adverse events

The company's economic model includes the treatment-related adverse events with a severity grade ≥3 or more, occurring in ≥1% of patients, in at least one treatment arm in the STARGLO second-line subpopulation (Table 18).

Table 18 Treatment-related adverse events considered in the model – STARGLO 2L subpopulation

Grade 3–5 AEs	Total number of adverse events	
	Glofit-GemOx[a] (n = 112)	R-GemOx (n = 55)
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cytokine Release Syndrome	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Source: Reproduced from CS Table 45
AEs, adverse events; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin
[a] Any treatment exposed

CS Appendix D Table 19 shows that in the second-line subpopulation of STARGLO:

- [redacted] patients in the R-GemOx arm and [redacted] patients in the Glofit-GemOx arm experienced grade 3 tumour lysis syndrome
- [redacted] patients in the Glofit-GemOx arm experienced grade 3 atrial fibrillation
- [redacted] patients in the Glofit-GemOx arm experienced grade 3+ sepsis

These adverse events are not included in the company's base case. In response to Clarification Question B3, the company state that this is because Table 19 in CS Appendix D shows all grade 3–5 adverse events with a frequency of ≥1% in either arm for the second-

line population of STARGLO, regardless of whether the adverse events were considered to be treatment-related or not.

Of the three adverse events listed above, the company consider that only tumour lysis syndrome in the three patients receiving R-GemOx were related to treatment. The economic model has been updated by the company to include this adverse event. The EAG are unclear why tumour lysis syndrome adverse events that occurred in two patients in the Glofit-GemOx arm were also not included. We note further that the company do not explain why the atrial fibrillation and sepsis adverse events were considered treatment-independent in their response to Clarification Question B3.

Our clinical experts considered the incidence of adverse events reported CS Appendix D Table 19 to be broadly reasonable. Two experts highlighted that febrile neutropenia is important, rather than neutropenia, because if a patient develops an infection it can be life-threatening. Another of our experts thought hypogammaglobulinaemia (reduced serum immunoglobulin levels) would also be a concern in this patient group, because it can result in long-term sequelae.

We note that CS Appendix D Table 19 (all grade 3-5 adverse events by preferred term with a frequency of ≥ 1% in either arm (2L subpopulation; STARGLO)) reports that one patient (1.8%) in the R-GemOx arm and two patients (1.9%) in the Glofit-GemOx arm experienced grade 3 febrile neutropenia. Using a cost of £4,810 (SA08G; Non-elective admitted care: Other Haematological or Splenic Disorders, with CC Score 6+)[47] for febrile neutropenia, and applying this cost for one patient in the R-GemOx arm and two patients in the Glofit-GemOx arm, reduces the company's ICER estimate to £3,320 per QALY.

No patient in the second-line subpopulation of STARGLO experienced hypogammaglobulinaemia. Consequently, it is not reported in CS Appendix D Table 19.

EAG conclusion on adverse events

We consider that tumour lysis syndrome adverse events that occurred in two patients in the Glofit-GemOx arm should also have been included in the economic model and we incorporate these costs in our base case.

We are uncertain why the atrial fibrillation and sepsis adverse events were not considered to be related to treatment. However, clinical advice to the EAG was that the adverse events accounted for in the economic model were reasonable. Our clinical experts did not highlight sepsis or atrial fibrillation as adverse events that the economic model should consider. We note that including the febrile

neutropenia adverse events experienced by the second-line subpopulation of STARGLO has a negligible effect on the ICER result.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review for health-related quality of life studies in relapsed or refractory DLBCL, using the methodology described in CS Appendix F. Using Ovid, database searches were carried out in:

- Embase
- MEDLINE (including Epub Ahead of Print, In-Process, Daily)
- Evidence-based Medicines Reviews (including all Cochrane databases, Database for Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, NHS Economic Evaluation Database (EED))

Eligibility criteria are given in CS Appendix F 1.1.1.1. CS section 3.4.1 reports that 14 publications (12 unique studies) were identified that reported health state utility values for patients with DLBCL in the second-line and beyond settings (full publications, n=6; conference abstracts/poster, n=8). Three studies specifically reported results for the second-line setting:

- A full publication reporting utility values for patients with relapsed or refractory DLBCL enrolled in the multicentre, phase 2 single-arm PILOT study for lisocabtagene maraleucel conducted at 18 clinical sites in the US[33]
- A full publication reporting utility values for patients with relapsed or refractory DLBCL enrolled in the international, multicentre phase 3, open-label RCT (ZUMA-7) for treatment with axicabtagene ciloleucel [48]
- Poster reporting a health state elicitation study employing the UK general population[49]

In response to Clarification Question B9, the company confirmed that they are not aware of published cost effectiveness studies or HTA studies for relapsed or refractory DLBCL that have been published since the 19th August 2024 update of the systematic literature review. The EAG conducted a brief PubMed search (on 20th March 2025) for articles reporting utilities in patients with second-line DLBCL published after 19th August 2024. We found one paper, published in September 2024:

- Li et al. (2024). EQ-5D-5L and SF-6Dv2 health utilities scores of diffuse large B-cell lymphoma patients in China.[50]

We note that the utilities are for patients with DLBCL in China, rather than the UK, and that the article is not specific to patients with second-line relapsed or refractory DLBCL. Consequently, we do not consider that these utility results provide additional information to this current submission.

CS Appendix E Table 45 lists seven previous NICE Technology Appraisals associated with relapsed or refractory DLBCL.

The company conducted a scenario analysis using the health state utility values from TA649 (CS Table 70). The CS does not explain why utilities from this particular Technology Appraisal were used, while utilities from the other Technology Appraisals were not.

EAG conclusion on the systematic literature review for utilities

The EAG has no concerns with the company's systematic review methodology. The company employed a broad search strategy, all relevant sources were searched, and the results were clearly reported. We consider that the systematic literature review would likely have found all relevant studies at the time of the most recent search (19th August 2024). We conducted a brief search in PubMed for articles reporting utilities in patients with second-line DLBCL published after 19th August 2024 but found no new relevant studies.

4.2.7.2 Study-based health related quality of life

CS section B.3.4.2 states that health-related quality of life data were collected from patients in the STARGLO trial using the EQ-5D-5L questionnaire. Data were collected at baseline, on Day 1 of Cycles 2 to 7, and every three months during long-term follow-up to Month 21 (company Table *t_qs_cb2_ITT_EQ_2L_16FEB2024_41944*). The EQ-5D-5L data were then cross-walked to EQ-5D-3L using the method of Hernández Alava et al.[51]

4.2.7.3 Utility values applied in the model

The company use utilities from the full intention-to-treat (ITT) population of STARGLO in their base case, explaining that the sample size is larger and that they assume utilities do not differ between patients receiving second-line treatment, and those receiving treatment beyond second-line (CS section 3.4.2). The company conducted a scenario analysis using utilities from STARGLO patients receiving second-line treatment only.

The company used the EQ-5D-3L values to estimate utilities for three health states (Table 19):

- Progression-free on-treatment
- Progression-free off-treatment
- Post-progression survival

The company distinguished between on- and off-treatment for the progression-free health state, to account for the potential impact of treatment related factors (such as toxicities, burden of administration, etc.) on utility (CS section 3.4.2). The CS states the health state utilities were adjusted using the method of Ara and Brazier[52] to account for sex- and age-related changes in general population utility (coefficients shown in CS Table 47). Lastly, when patients enter long-term remission in the economic model, the model assumes that they do not continue to progress, and have utility values 10% lower than those of the general population (as per TA927).[36]

Table 19 Utility values and scenario utility values, company base case

Scenario	State	Utility values	Standard error
Base case: STARGLO (ITT)	PFS – on treatment	0.758	0.011
	PFS – off treatment	0.751	0.012
	PPS	0.685	0.016
Scenario: STARGLO (2L only)	PFS – on treatment	0.757	0.012
	PFS – off treatment	0.757	0.013
	PPS	0.691	0.021

Source: Partly reproduced from CS Table 46
PFS, progression-free survival; PPS, post progression survival; 2L second-line; ITT, intention to treat.

Clinical advice to the EAG was that patients who were progression-free and not receiving treatment would be expected to have a better health-related quality of life compared with patients who are progression-free but are on treatment. In response to Clarification Question B8. the company provided a figure showing the mean pre-progression utility estimates for the STARGLO second-line sub-population (Figure 8), which supports our experts' expectations.

Figure 8 Mean pre-progression utility estimates (STARGLO second-line subpopulation)

Source: Company figure; response to Clarification Question B8 (Figure 4)

We note that for the utilities used in the company's base case (STARGLO ITT population; Table 19), the utility value is higher for patients who are progression-free and 'on treatment' compared with patients who are progression-free and 'off treatment', which appears to be counterintuitive.

Our clinical experts also commented that patients achieving long-term remission after three years would likely have reduced quality of life compared with the general population, because they have already received two lines of treatment, with the associated sequelae of that treatment (e.g. toxicity effects), and risk from the disease itself (increased risk of secondary cancer and cardiovascular disease). Lastly, one expert highlighted that long-term follow-up of the effect of treatment with bispecifics is not yet available, so there may be further detrimental effects that are currently unknown.

EAG conclusion on utility values used in the model

We prefer to use utility scores specific to second-line patients in our base case, because this is the population of interest for this appraisal.

We consider the company's approach to long-term remission i.e. patients experience utilities 10% lower than the general population, to be reasonable. We note that this methodology was also accepted by the EAG assessing TA927.[36]

4.2.7.4 Disutilities for adverse events

The company assume that any disutility arising from adverse events has been accounted for in the health state utilities derived from the STARGLO EQ-5D results. CS section 3.4.4 states disutilities specific to adverse events are not included in the model to avoid double counting. The EAG considers the company's approach to be reasonable.

4.2.8 Resources and costs

Costs in the model include drug costs (acquisition and administration) for glofitamab, comparator treatments, subsequent treatment costs, health care resource use and adverse event costs. These are discussed in the following sections.

4.2.8.1 Drug acquisition

4.2.8.1.1 Glofit-GemOx costs

Glofitamab costs per model cycle are shown in Table 20, with and without applying the PAS discount of [redacted] Glofitamab is administered via intravenous infusion using the step-up dosing schedule from the STARGLO trial:

- Cycle 1: 2.5mg on Day 8, 10mg on Day 15
- Cycles 2−12: 30mg on Day 1
- Maximum of twelve 21-day cycles (treatment period of about 8 months)

The model does not assume any vial sharing, because the glofitamab regimen does not require the 2.5 mg or 10 mg vials to be split. The glofitamab step-up dosing schedule also requires pre-treatment with a single dose of obinutuzumab on Day 1 of Cycle 1 (1000 mg, at a cost of [redacted] with a PAS discount of [redacted]), to deplete circulating B-cells and reduce the likelihood of experiencing cytokine release syndrome.

Gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) were administered intravenously on Day 2 of Cycle 1, and Day 1 or 2 (per local practice) of subsequent 21-day cycles, up to Cycle 8 (treatment period of about 5.5 months; posology as per the STARGLO trial). Details of gemcitabine and oxaliplatin dosing and acquisition are given in CS Table 49; costs per model cycle are shown in Table 22. The economic model uses an algorithm that calculates the combination of small and large vials required to minimise the overall cost of treatment with GemOx.

Table 20 Acquisition costs of glofitamab – cost per model cycle

Vial size	Without PAS	With PAS
2.5mg (first cycle, Day 1)	£687	[redacted]
10mg (first cycle, Day 8)	£2,748	[redacted]
30mg (cycle 2 onwards)	£8,244	[redacted] every 3 weeks (i.e. [redacted] per week)
Source: Adapted from CS Table 52 PAS, patient access scheme, mg milligram.		

4.2.8.1.1.1 Glofitamab monitoring costs

CS 3.5.2.1 states that all patients must be monitored for at least 24 hours after completing their first glofitamab infusion. For subsequent infusions, patients who experience Grade ≥2 cytokine release syndrome should be monitored for 22 hours after completing the infusion (i.e. they experience two monitoring periods in total). The additional costs for glofitamab monitoring are shown in Table 21. Our clinical experts considered that the company's monitoring assumptions (24 hours post first infusion and 22 hours after subsequent infusions) were reasonable. Our experts confirmed that no monitoring is required for R-GemOx.

Table 21 Monitoring costs for glofitamab

Component	Percent of patients	Cycles applied for	National NHS cost collection	Cost	Inflated costs
Monitoring (24 hours after first glofitamab infusion)	100%	1	Average of malignant lymphoma (currency codes SA31A-F): day case	£488.57	NHS Reference Costs 2023 to 2024[47]
Monitoring (22 hours for patients experiencing Grade ≥2 CRS after first glofitamab infusion)	12.79%	2	2 x average of malignant lymphoma (currency codes SA31A-F): day case	£977.14	NHS Reference Costs 2023 to 2024[47]
Source: Reproduced from CS Table 51 CRS, cytokine release syndrome					

4.2.8.1.2 R-GemOx costs

In line with the rituximab SmPC,[53] in the R-GemOx regimen, rituximab was given at 375 mg/m^2 every 21 days. Patients received gemcitabine and oxaliplatin as per the Glofit-

GemOx arm. This comparator regimen was given up to a maximum of 8 cycles (treatment period of about 5.5 months). Costs per model cycle are shown in Table 22. Our clinical experts commented that GemOx is usually given for 6 cycles in the NHS, because the extra two cycles do not provide any extra clinical advantage.

The model estimated treatment dosing and schedule according to the British National Formulary[54] and the electronic market information tool (eMIT) database[55] and assumed no vial sharing. CS 3.5.2.3 states that dosing for some treatments depends on weight or body surface area (BSA); consequently, drug wastage may occur. The economic model uses an algorithm that calculates the combination of small and large vials required to minimise the overall comparator treatment cost.

Table 22 Comparator treatment costs

Comparator	Unit cost	Cost per model cycle
Rituximab (100 mg)	£314.33	£1,098.23
Rituximab (500 mg)	£785.84	
Gemcitabine (200 mg)	£3.51	£20.09
Gemcitabine (1000 mg)	£9.86	
Oxaliplatin (50 mg)	£6.47	£25.84
Oxaliplatin (100 mg)	£17.47	
Source: Adapted from CS Table 53 and CS table 54		

4.2.8.2 Drug administration

The CS reports the drug administration costs for intravenous chemotherapy:

- The first administration is assumed to take place under supervision at hospital, costed as a prolonged infusion
- Subsequent administrations are assumed to take place in an outpatient setting, costed as subsequent elements of the chemotherapy cycle

Unit costs are taken from the NHS reference costs 2023-2024[47] shown in CS Table 50. Administration costs for R-GemOx were assumed to be the same as for Glofit-GemOx. The EAG agrees with drug administration costs used in the economic model. We note that the administration cost of administering three treatments (for Glofit-GemOx and R-GemOx) has been costed as three separate administration costs. However, administering these drugs together on the same day incurs a single administration cost. We prefer to apply one administration cost that covers the three treatments in our base case.

4.2.8.3 Treatment costs at subsequent lines of therapy

The company apply the post-discontinuation therapy cost to the proportion of patients who move into the post-progression survival health state each cycle (CS section 3.5.3). CS Table 55 shows the proportion of patients receiving each third-line treatment in the company's base case. Our experts highlighted that bendamustine with rituximab (BR) treatment is permitted in the UK, but it is rarely used in the NHS.

The proportion of patients receiving the different subsequent treatments upon progression, and the mean duration of treatment are shown in CS Table 55. The CS states these estimates are based on data from the STARGLO trial, and UK clinical expert opinion obtained at the company's advisory board meeting (CS section 3.5.3). The weekly costs associated with each subsequent treatment (including administration) are given in CS Table 56. The weekly cost of subsequent treatment in the model is the proportion of progressed patients receiving each treatment multiplied by the appropriate treatment cost per cycle multiplied by the associated mean treatment duration. Thus, the total cost of post-discontinuation treatment is the cost of one course of subsequent treatment.

The model assumes that subsequent treatment costs do not apply to the proportion of patients in long-term remission (i.e. progression-free after 30 months). Different proportions of patients are assumed to be in long-term remission in each treatment arm, so the company's estimated post-discontinuation costs are different for each modelled treatment: £52,700 for Glofit-GemOx and £66,066 for R-GemOx (reported in the economic model).

Clinical advice to the EAG was that the distribution of subsequent treatments shown in CS Table 55 was broadly reasonable for the patients who go on to receive third-line therapy. However, our experts considered that a significant proportion of patients (range: 20% - 50%) would be too frail to receive third-line therapy and would receive palliative care instead. One expert highlighted that effective new treatments, such as glofitamab and epcoritamab, are now available providing more third-line options. Consequently, fewer patients (20 – 25%) now move from second-line therapy to full palliation.

Consequently, we have assumed that 30% of patients receive palliative care third-line, rather than all patients receiving third-line treatment, as assumed by the company. This change results in post-discontinuation costs of £36,898 for Glofit-GemOx and £44,203 for R-GemOx when applied to the company's base case, and we raise this as a key issue (section 1.4). We conduct scenario analyses with 20% and 50% of patients receiving third-line palliative care in (section 6.1).

4.2.8.3.1 CAR-T cell therapies

The model includes a cost of £48,353 for administering CAR-T cell therapies (CS section 3.5.3). This is the CAR-T tariff cost of £58,964 minus the costs associated with adverse events (estimated to be £10,611), which was the preferred approach of the EAG assessing Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable (GID-TA10778).[56] The company assumes CAR-T administration costs are the same as for glofitamab (CS Table 50). We agree with the company's approach for costing CAR-T therapies in the model.

4.2.8.4 Health care resource use

The model applies resource use costs to each model cycle that a patient is alive. These costs depend on health state (progression-free or progressed disease) and are not influenced by the treatment a patient received. The weekly resource use costs used in the economic model are shown in CS Table 58. CS section 3.5.4 explains that these data were taken from the appraisal of Pola-BR for relapsed or refractory DLBCL (TA649)[17] and validated by the company's clinical experts, who modified the resource use estimates based on their clinical experience. The company costed each resource using current NHS reference costs,[47] or inflated costs using the NHS Cost Inflation Index (NHSCII) from the Personal Social Services Research Unit (PSSRU).[57] Our clinical experts considered these estimates of healthcare resource use to be reasonable.

CS Table 59 shows the one-off cost of disease progression, which is applied in the cycle that disease progression occurs. The proportion of patients requiring each resource is shown in Table 23. Our clinical experts explained that nearly all patients would undergo a PET-CT, because this is used to assess disease progression, but added that there may be practical reasons why it is not possible for 100% of patients to receive a PET-CT.

Our clinical experts commented that MUGA scans are done very rarely now and that echocardiograms are the clinicians' preferred scan of choice. An echocardiogram is used to assess heart function and to determine if a patient can tolerate grade 3-4 cytokine release syndrome and/or sepsis i.e. to determine if a patient is fit enough to tolerate the potential side effects of some treatments. There was a range in our experts' estimates of the proportions of patients receiving an echocardiogram, possibly reflecting variation in clinical practice around the country. Two of our experts thought that most patients would have an echocardiogram, whilst one thought that 10-20% of patients receiving R-GemOx in the second-line setting who are transplant ineligible would have an echocardiogram. This same expert highlighted that patients receiving Glofit-GemOx are at greater risk of cytokine release

syndrome and consequently would undergo more echocardiograms than patients receiving R-GemOx.

Clinical advice to the EAG was that an ECG is straightforward to perform, and that more patients than modelled in the company's base case would likely undergo one on disease progression. However, we do not have an estimate of the proportion of patients receiving an ECG to use in our base case, so we also use the company's proportion.

We consider that the company have used a suitable costing source and inflated costs appropriately. In response to Clarification Question B4, the cost of an MRI has been corrected from £246, given in CS Table 59 (one-off progression costs), to £156, based on 2023/24 NHS Reference Costs (Diagnostic Imaging, RD01A, outpatient costs). Based on clinical advice to the EAG and the company's Clarification Question response, our preferred proportions of patients using each one-off progression resource, and the associated costs, are shown in Table 23, which we use in our base case.

Table 23 One-off progression resource use

Unit	Company base case		EAG base case	
	Proportion of patients	Unit cost (£)	Proportion of patients	Unit cost (£)
ECG	15.9%	£142	15.9%	£142
MUGA	7.9%	£378	0.0%	£378
MRI	20.0%	£156	20.0%	£156
PET-CT	85.0%	£638	85.0%	£638
Echocardiogram	-	-	50.0%	£108

Source: Adapted from CS Table 59; costs for echocardiogram sourced by EAG from the 2023/24 NHS Reference Costs (RD51A simple echocardiogram, 19+ years, outpatient setting)
ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PET-CT, positron emission tomography – computed tomography

4.2.8.5 Adverse event costs

CS 3.4.4 states that only treatment-related adverse events with a severity grade of 3 and higher were costed in the model (shown in Table 18) The probability of each event in each treatment arm was multiplied by the associated unit cost (shown in CS Table 60). These costs were then applied in the model to the proportion who remain on treatment in each cycle. The adverse event costs per model cycle (weekly) are £180.41 for Glofit-GemOx and £113.78 for R-GemOx (CS Table 62).

In response to Clarification Question B3, the company explain that the economic model has been updated to include the cost of tumour lysis syndrome (£1,324) for patients receiving R-GemOx. The cost was calculated from TA796[58] (£1,233) and inflated to 2023 costs using the NHS inflation indices reported in the current Unit Costs of Health and Social Care manual.[57]

Total costs for cytokine release syndrome management are £11,707 (updated by the company in response to Clarification Question B5). In line with TA872 (Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies),[59] the company assume that everyone experiencing cytokine release syndrome as a treatment-related adverse event with a severity of grade 3 or higher would require two doses of tocilizumab, and that these patients would also require a four day stay in the intensive care unit. Two of our clinical experts agreed that patients experiencing cytokine release syndrome would need two doses of tocilizumab. One of our experts considered that 10-20% of patients may need a third injection of tocilizumab to manage cytokine release syndrome. Two of our experts thought that four days in the intensive care unit might be slightly long.

We note that the company in TA872 originally costed a one day stay in the intensive care unit for managing cytokine release syndrome as a treatment-related adverse event, and we test this in a scenario analysis (section 6.2).

In response to Clarification Question B6, the company updated the cost for a pharmacist's time (original cost shown in CS Table 61). The company's calculation assumes that preparing an infusion takes 39 minutes. Using an hourly rate of £48 for a hospital pharmacist (PSSRU 2018 unit costs manual) results in a cost of £31.20.[17] Inflating this cost to 2023 values gives an hourly rate of £53.87, and thus a cost of £35.02 per infusion preparation.

4.2.8.5.1 End of life costs

The company do not model end of life costs separately. The company assume these costs to be zero and that the cost of terminal care is incorporated in the weekly resource use costs used in the model (CS Table 58, taken from TA649[17]). We are unsure how the costs of residential care, day care, home care and hospice care were calculated in TA649, nor are we certain if these costs are specific to cancer patients. Furthermore, one of our clinical experts commented that in the UK many inpatient bed days are used in last year of life, which is applicable to many patients with DCLBL receiving treatment at second-line and beyond. Our expert noted that this inpatient bed day cost is not accounted for in the modelled weekly resource use costs.

Consequently, we prefer to set the weekly resource use costs for residential care, day care, home care and hospice care to zero, and model end of life costs separately using the one-off full terminal care costs specifically for cancer patients, as presented by Georghiou and Bardsley (2014).[60] After adjusting for inflation using the most current PSSRU inflation indices[57]), total end of life costs are £10,403 (Table 24).

Table 24 Terminal care costs (one-off costs based on the last 3 months of life), inflated to 2022/23 costs

Cost	Patients with a cancer diagnosis
GP visits	£453
District nurse	£729
Nursing and residential care	£567
Hospital care – inpatient	£682
Hospital care – final 3 months of life	£7,301
Marie Curie nursing service	£672
Total	£10,403

EAG conclusion on resources and costs

The EAG consider that the resources and costs for drug acquisition and administration are reasonable. The doses used in the model are consistent with those used in the STARGLO trial, but we note that GemOx is given for only six cycles in the NHS and so we use this timing in both arms in our base case. In addition, we also prefer to apply one administration cost that covers the three treatments (for Glofit-GemOx and R-GemOx), rather than three separate administration costs, because these drugs are given together on the same day.

Our clinical experts considered that a significant proportion of patients (30-50%) would be too frail to receive third-line therapy and would only receive palliative care instead. We assume 30% of patients receive palliative care third-line and use our preferred distribution of subsequent treatment in our base case. We highlight this as a key issue in section 1.4. We test 20% and 50% of patients receiving palliative care third-line in scenario analyses.

Following advice from our clinical experts, and the company's response to Clarification Question B4, we have adapted the one-off resource use costs used in our base case (Table 23).

The EAG consider that the costs for tumour lysis syndrome are from an appropriate source and have been inflated correctly. However, we consider that the costs for tumour lysis syndrome that occurred in the two patients in the Glofit-GemOx arm should also been included in the economic model.

Based on clinical advice to the EAG, we agree with the company's approach to cytokine release syndrome management, and test patients staying one day in the ICU rather than four in a scenario analysis.

We confirmed the pharmacy cost in TA649 and agree that this has been inflated appropriately. We consider the corrected cost for pharmacist time to be reasonable. We are uncertain how the end-of-life costs have been calculated within the supportive care resource use costs in the company's base case. We prefer to apply a separate one-off terminal care cost of £10,403 (breakdown of costs shown in Table 24) in our base case.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

In response to clarification questions, the company made several changes to their base case model, as follows:

- The cost of grade 3 tumour lysis syndrome has been included for R-GemOx (Clarification Question B3),
- The cost of MRI has been changed to £156 (Clarification Question B4),
- The cost of ICU hospitalisation has been changed to £2,444 (Clarification Question B5),
- The cost of pharmacist time is £35.02 per infusion preparation (Clarification Question B6),
- The time on treatment for oxaliplatin has been corrected (Clarification Question B7),
- The costs for gemcitabine and oxaliplatin have been corrected (Clarification Question B7).

The updated results are shown in Clarification response Appendix Table 1 for Glofit-GemOx versus R-GemOx. The results show that Glofit-GemOx has additional costs of [redacted] and has an incremental QALY gain of [redacted] compared with R-GemOx, resulting in an ICER of £3,412 per QALY. The cost-effectiveness results presented include a confidential Patient Access Scheme (PAS) discount price for glofitamab and obinutuzumab. However, they do not include existing discounts for the other anti-lymphoma therapies in the model (these will be included in a separate confidential addendum to this report). Therefore, the ICERs do not reflect the actual prices that would be paid by the NHS.

Table 25 Deterministic base-case cost-effectiveness results (glofitamab PAS price, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Glofit-GemOx	[redacted]	6.73	[redacted]				
R-GemOx	[redacted]	4.31	[redacted]	[redacted]	2.42	[redacted]	£3,412

Source: Clarification Response Appendix Table 1
Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; R-GemOx, rituximab with gemcitabine and oxaliplatin.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

Clarification Response Appendix section 2.2 reports the deterministic sensitivity analysis results for Glofit-GemOx versus R-GemOx. There is limited detail in the CS on the parameters included in the deterministic sensitivity analysis. The analysis includes the following input parameters:

- Treatment costs for intervention and comparator
- Total subsequent treatment costs by treatment arm
- Administration costs (first and subsequent cycles)
- Utility values – progression-free survival (on and off treatment) and progressed disease
- Adverse event management costs per patient for both arms
- Monitoring costs for patients with cytokine release syndrome

Patient characteristics, such as average patient age at baseline, have not been included. The survival curves for progression-free survival, overall survival and time to treatment discontinuation have not been varied in the deterministic sensitivity analyses.

The upper and lower bounds of the parameters were varied by +/- 20% of the mean value, which the EAG considers is reasonable.

The results of the deterministic sensitivity analyses are presented as tornado plots in Clarification Response Appendix Figure 3 and 4 for net monetary benefit (NMB) and cost per QALY respectively. The parameter that had the largest impact on the results was the cost of subsequent therapies. The CS states that this is expected due to the high cost of some of these therapies. However, the company considers there is a low level of uncertainty around the cost effectiveness results.

5.2.2 Scenario analysis

The company explored a range of scenarios to test structural and methodological uncertainty (Clarification Response Appendix Table 3). Generally, the company tested scenarios using data that were not used in the base case. We consider the following parameters explored by the company to be reasonable.

- Time horizon (30, 40 and 50 years)
- Using cohort age (Average age [redacted] years with a 35-year age time horizon)

- Survival modelling (alternative distributions and assumptions for progression-free survival and overall survival)
- Alternative utility values (STARGLO second-line, TA649)
- Discounting (1.5% for costs and outcomes)
- Subsequent treatment PAS discount estimates

The results are presented for ICER and NMB (using a willingness to pay threshold of £20,000). The results range from dominant (cure point of two years) to £19,877 per QALY (using the generalised gamma distribution to model progression-free survival). The results are most sensitive to changes in the progression-free survival distribution, the time to the cure point and the comparator and subsequent treatment PAS discounts.

5.2.3 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis (PSA) results were estimated for 1000 simulations and are summarised in scatterplots and cost effectiveness acceptability curves (CEACs) (Clarification Response Figures 1 and 2). Clarification Response Appendix Table 2 shows the company's mean probabilistic base case results.

All the variables that were included in this analysis are summarised in CS Table 66, with the distributions used. The EAG considers the choice of distributions to be appropriate and the parameters included in the PSA to be reasonable.

The probabilistic results are stable and consistent with the deterministic results. The results show that Glofit-GemOx is a cost-effective treatment option with a probability of [redacted] and [redacted] at a willingness to pay threshold of £20,000 and £30,000 respectively.

5.3 Model validation and face validity check

5.3.1 Company model validation

The company briefly describes their approach to model validation in CS section B.3.14. The CS states that they have designed the model to align with NICE's preferred methods, e.g. model structure, health states, perspective, time horizon and discount rates. Clinical experts from the UK validated some of the company's key assumptions, including the natural history of DLBCL and standard clinical practice in the UK.

The CS states that the model was subject to an external quality assurance procedure, which included technical validation of key model inputs and calculations. The company has not provided detailed information about the technical validation or about the external validation

of the model parameters; therefore, we conducted some additional comparisons as part of the EAG's model validation (see section 5.3.2).

EAG conclusion on company model validation

The company state that they conducted a technical validation. We believe that the company could have provided external validity checks. Moreover, the company did not report any comparison of the model results against results from models included in previous NICE technology appraisals of DLBCL in refractory / relapsed populations (TA649).

5.3.2 EAG model validation

The EAG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources;
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses;
- Checking the individual equations within the model;
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses;
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

5.3.2.1 Comparison with other studies

We compared the progression-free survival and overall survival data for R-GemOx from the second-line subpopulation from the STARGLO trial and extrapolations in the company model with data from Mounier et al.,[16] who conducted a phase 2 study involving 49 patients with refractory or relapsing DLBCL (median age 69 years). The progression-free survival and overall survival data from the two trials are shown in Table 26. We note that the results are reasonably similar for the first two years. The progression-free survival and overall survival for Mounier et al. are similar at five years, whereas overall survival remains significantly higher than progression-free survival for STARGLO.

Table 26 Modelled overall survival (OS) and progression-free survival (PFS)

Time (years)	R-GemOx (STARGLO)		R-GemOx (Mounier et al.) [16]	
	PFS	OS	PFS	OS
1 (trial data)	[redacted]	[redacted]	27%	48%
2 (trial data)	[redacted]	[redacted]	18%	35%
5 (extrapolation)	[redacted]	[redacted]	13%	14%
Source: EAG created table R-GemOx, rituximab with gemcitabine and oxaliplatin				

5.3.3 EAG corrections to the company model

We have not made any corrections to the company model.

5.3.4 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 27. We investigate uncertainties through additional scenario analysis in section 6.2.

Table 27 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Model structure			
Model structure	Section 4.2.2	We agree	No change
Population	Section 4.2.3	We agree	No change
Comparators	Section 2.3 and section 4.2.4	We agree, but Pola-BR may also be an appropriate comparator	No change
Perspective	Section 4.2.5	We agree	No change
Time horizon	Section 4.2.5	We agree	No change
Discounting	Section 4.2.5	We agree	No change
Survival curves			
OS	Section 4.2.6.1	We disagree with setting the cure point at 3 years, as we consider the OS extrapolation is unrealistic.	We consider the cure point to be 6 years
PFS	Section 4.2.6.2	We agree	No change
ToT	Section 4.2.6.3	We agree	No change
Adverse events			
Frequency of adverse events	Section 4.2.6.4	We disagree with only including TLS in the R-GemOx arm	For consistency, TLS should also be included in the Glofit-GemOx arm

Parameter	Company base case	EAG comment	EAG base case
Utilities			
Patient utilities	Section 4.2.7.3	We disagree with using utility values from the STARGLO ITT population	We use utility scores specific to 2L patients, as this is the subpopulation of interest.
AEs disutilities	Section 4.2.7.4	We agree	No change
Severity modifier	Section 7	We agree	No change
Resource use and costs			
Drug acquisition and administration	Section 4.2.8.1 and 4.2.8.2	We disagree with applying GemOx costs for 8 cycles, based on clinical advice. We disagree with applying three separate administration costs for administering three treatments (for Glofit-GemOx and R-GemOx)	We apply GemOx costs for 6 cycles. We apply one administration cost that covers the three treatments, as is standard costing in NICE appraisals.
Healthcare resource use	Section 4.2.8.4	We disagree with the company's one-off progression costs, based on clinical advice.	We use the one-off progression resource use shown in Table 23; We separate end-of-life costs (Table 24) out from the weekly healthcare resource use costs (CS Table 58)
Adverse event costs	Section 4.2.8.5	We agree	We agree with AE costs
Subsequent treatment	Section 4.2.8.3	We disagree with the company's distribution of 3L treatment, based on clinical advice.	30% of patients receive palliative care 3L

Source: EAG created table
2L, second-line; 3L, third-line; AE, adverse event; AIC, Akaike's information criterion; BIC Bayesian information criterion; EQ-5D, EuroQol five dimensions; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; R-GemOx, rituximab with gemcitabine and oxaliplatin; TLS, tumour lysis syndrome; ToT, time-on-treatment.

6 EAG'S ADDITIONAL ANALYSES

6.1 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 27, we have identified several key aspects of the company base case with which we disagree. The results are shown with a PAS discount for glofitamab and obinutuzumab and list price for the other treatments. We provide a separate EAG confidential addendum with all treatments costed with their confidential price discounts.

Our preferred model assumptions are the following:

- Mortality (for patients who are progression-free or whose disease has progressed) assumed to be same as general population after six years, instead of three years (section 4.2.6.1.3)
- Proportion of patients not receiving third-line treatment: 30% (section 4.2.8.3)
- Utility scores specific to second-line patients, rather than from the ITT population (section 4.2.7.3
- GemOx given for 6 cycles in both arms, rather than 8 cycles (section 4.2.8.1.2)
- Use the one-off progression resource use shown in Table 23 (section 4.2.8.4)
- Terminal end-of-life costs (Table 24) used, rather than the weekly healthcare resource use costs (section 4.2.8.4)
- Administration cost applied once for each combination of treatments, rather than for each treatment (section 4.2.8.1)
- Adverse event costs included for tumour lysis syndrome included in Glofit-GemOx arm (section 4.2.8.5)

The EAG base case results are shown in Table 28 using the EAG's preferred assumptions. When using these assumptions, the ICER increases to £12,257 per QALY for Glofit-GemOx versus R-GemOx. The model results are most sensitive to using mortality that is the same as the general population after six years, and 30% of patients not receiving third-line treatment. All other changes have only minimal effects on the model results.

Table 28 EAG's preferred model assumptions, cumulative results, PAS for glofitamab and obinutuzumab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY.
Company base-case	Glofit-GemOx	[redacted]	[redacted]	£3,412
	R-GemOx	[redacted]	[redacted]	
+ Mortality same as for general population after six years	Glofit-GemOx	[redacted]	[redacted]	£9,851
	R-GemOx	[redacted]	[redacted]	
+ 30% of patients not receiving 3L treatment	Glofit-GemOx	[redacted]	[redacted]	£13,396
	R-GemOx	[redacted]	[redacted]	
+ Utility scores specific to 2L patients	Glofit-GemOx	[redacted]	[redacted]	£13,398
	R-GemOx	[redacted]	[redacted]	
+ GemOx given for 6 cycles in both arms	Glofit-GemOx	[redacted]	[redacted]	£13,123
	R-GemOx	[redacted]	[redacted]	
+ Use revised progression resource use	Glofit-GemOx	[redacted]	[redacted]	£13,122
	R-GemOx	[redacted]	[redacted]	
+ Use terminal costs, rather than weekly healthcare resource use costs	Glofit-GemOx	[redacted]	[redacted]	£12,708
	R-GemOx	[redacted]	[redacted]	
+ Administration cost applied once for each combination of treatments	Glofit-GemOx	[redacted]	[redacted]	£12,181
	R-GemOx	[redacted]	[redacted]	
+ Adverse event: Grade 3 Tumour lysis syndrome in Glofit-GemOx arm	Glofit-GemOx	[redacted]	[redacted]	£12,257
	R-GemOx	[redacted]	[redacted]	
EAG base case	Glofit-GemOx	[redacted]	[redacted]	£12,257
	R-GemOx	[redacted]	[redacted]	

Source: EAG created table
EAG, evidence assessment group; OS, overall survival; PFS, progression-free survival; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost effectiveness ratio; R-GemOx, rituximab with gemcitabine and oxaliplatin.

6.2 EAG scenarios

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some model assumptions on the final cost-effectiveness results. Table 29 below summarises the results of the scenario analyses on the EAG base case. In addition to a selection of the scenarios previously conducted in the CS, we also conducted the following scenarios:

- OS: Kaplan-Meier data with a lognormal tail (attached when 20% of patients remain at risk; both arms) in a scenario analysis
- OS: loglogistic (most pessimistic survival estimates)
- Cytokine release syndrome: 1 day in ICU, not 4 days (Total cost: £4,375.42)
- Subsequent treatment: 20% of patients receive third-line palliative care; 50% palliative care of patients receive third-line palliative care

The results were most sensitive to changes in the cure point and the distribution used for overall survival. The ICERs for the scenarios varied between £6,078 per QALY (Cure point at 2 years) and £16,808 per QALY (using the generalised gamma distribution to extrapolate progression-free survival).

Table 29 EAG's scenario analyses with PAS for glofitamab and obinutuzumab

Scenario	Inc. Costs	Inc. QALYs	ICER (£/QALY)
EAG base case	[redacted]	[redacted]	£12,257
Selected company scenarios			
PFS distribution – generalised gamma	[redacted]	[redacted]	£16,808
PFS distribution – log-logistic	[redacted]	[redacted]	£13,437
OS distribution – generalised gamma	[redacted]	[redacted]	£11,102
OS distribution – log-logistic	[redacted]	[redacted]	£13,421
Cure point (PFS and OS) – 2 years	[redacted]	[redacted]	£6,078
Cure point (PFS and OS) – 5 years	[redacted]	[redacted]	£13,288
No QoL adjustment in long term remission	[redacted]	[redacted]	£11,143
No excess mortality in long-remission	[redacted]	[redacted]	£11,838
Standard mortality rate source (Howlader et al. 2017)	[redacted]	[redacted]	£13,586
Utilities from TA649	[redacted]	[redacted]	£12,294
EAG additional scenarios			

Scenario	Inc. Costs	Inc. QALYs	ICER (£/QALY)
OS: Kaplan-Meier data with a lognormal tail (attached when 20% of patients remain at risk; both arms)	[redacted]	[redacted]	£12,594
Cytokine release syndrome: 1 day in ICU, not 4 days (Total costs: £4,375.42)	[redacted]	[redacted]	£11,632
Subsequent Treatment: 20% palliative care	[redacted]	[redacted]	£11,105
Subsequent Treatment: 50% palliative care	[redacted]	[redacted]	£14,561

Source: EAG created table
EAG, evidence assessment group; ICU, intensive care unit; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; ICER, incremental cost effectiveness ratio; QoL, quality of life.

6.3 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of glofitamab with gemcitabine and oxaliplatin compared to rituximab with gemcitabine and oxaliplatin for patients with refractory / relapsed DLBCL. The EAG considers the structure of the model to be reasonable, appropriate and consistent with previous cost-effectiveness models for DLBCL. In general, the EAG considers that the model is well constructed and coded and the parameters have been selected according to best practice as described in the NICE process and methods manual.[39]

However, in contrast to the NICE scope, the company do not consider Pola-BR to be relevant in this setting and do not include this comparison in the model. Clinical advice to the EAG was that Pola-BR is still used to a sufficient extent that it could be a relevant second-line comparator for this appraisal.

The EAG disagrees with several of the assumptions in the company's model. Our preferred model assumptions are the following:

- Mortality (for patients who are progression-free or whose disease has progressed) assumed to be same as general population after six years, instead of three years
- Proportion of patients not receiving third-line treatment: 30%
- Utility scores specific to second-line patients, rather than from the ITT population
- GemOx given for 6 cycles in both arms, rather than 8 cycles
- Use the one-off progression resource use shown in Table 23
- Terminal end-of-life costs (Table 24) used, rather than the weekly healthcare resource use costs

- Administration cost applied once for each combination of treatments, rather than for each treatment
- Adverse event costs included for tumour lysis syndrome included in Glofit-GemOx arm
- Incorporating the EAG preferred assumptions, the ICER increases to £12,457 per QALY for Glofit-GemOx versus R-GemOx. The model results are most sensitive to assuming that the mortality (for patients who are progression-free and whose disease has progressed) is the same as the general population after six years, and that the proportion of patients not receiving third-line treatment is 30%.

7 SEVERITY

The company calculated the QALY shortfall for patients with relapsed or refractory DLBCL by using the QALY shortfall calculator by McNamara et al.[61] The company used the gender proportion ([redacted] male) and starting age ([redacted] years) from the STARGLO trial population (CS Table 63). The QALYs for patients with second line DLBCL are taken from the R-GemOx arm of the company model. The proportional QALY shortfall is [redacted] (see Table 30 below). As such, the company concludes that no severity modifier should be included.

We also calculated the absolute and proportional QALY shortfall using the EAG base case (Table 28) and obtained similar results to the company's revised base case (Table 30). We agree that no severity modifier should be included.

Table 30 QALY shortfall analysis

	Expected total QALYs for the general population	**Total QALYs that people living with a condition would be expected to have current treatment**	**Absolute QALY shortfall**	**Proportionate QALY shortfall**
Company's revised base case	9.86	R-GemOx: [redacted]	[redacted]	[redacted]
EAG base case	9.86	R-GemOx: [redacted]	[redacted]	[redacted]

Source: CS Table 65 and company model
QALY, quality adjusted life-year; R-GemOx; rituximab with gemcitabine and oxaliplatin.

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CONFIDENTIAL

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Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

Addendum 1 to the EAG report: EAG critique of company scenario analyses of comparison to Pola-BR

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Contents

1 INTRODUCTION

This document is the External Assessment Group (EAG)'s critique of a scenario analysis submitted by the company, Roche, to NICE in response to Key Issue 1 of the EAG Report dated 15 April 2025 for the technology appraisal of Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma (ID6202).

Polatuzumab vedotin in combination with bendamustine and rituximab (Pola-BR) is a relevant second-line comparator in the NICE scope. However, the company excluded this comparator from its decision problem stating that according to clinical expert opinion, Pola-BR is "very rarely used" ("0-10% estimated") as a second-line treatment today (company submission (CS) Table 1 and CS section 1.3.2.1.2). The EAG's three clinical experts agreed that its use has declined due to the availability of polatuzumab vedotin in combination with rituximab, doxorubicin, cyclophosphamide and prednisolone (Pola-R-CHP) as a first-line treatment (NICE TA874).[1] However, the estimated range of use of Pola-BR provided by the EAG's clinical experts suggested that it may currently be used for up to 10-20% for transplant ineligible patients. The EAG therefore questioned the appropriateness of excluding Pola-BR from the company's decision problem.

The EAG suggested the following might help to resolve this key issue:

- An indirect treatment comparison (ITC), if feasible, to compare glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx) against Pola-BR. The EAG is aware that potentially relevant Pola-BR studies exist, for example the GO29365 trial comparing Pola-BR against bendamustine plus rituximab which informed NICE TA649.[2]
- Additional clinical expert opinion to clarify the extent to which Pola-BR is used as a second-line treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in clinical practice and whether this use would be expected to change given that Pola-R-CHP is now available for first-line treatment.

In response to Key Issue 1, the company submitted new evidence in a document which henceforth we refer to as the Scenario Analysis Document. This includes:

1. Additional evidence (the recent British Society of Haematology (BSH) guidelines,[3] which were published after the submission of the EAG Report to NICE, and company's discussions with NHS England) which the company state support its position that Pola-BR is not a relevant comparator for this appraisal.

2. An indirect treatment comparison (propensity score analysis) comparing the second-line patients from the STARGLO trial (Glofit-GemOx) with second-line patients from the GO29365 trial (Pola-BR).
3. Economic analysis for Glofit-GemOx versus Pola-BR.

The EAG has critiqued the above in this addendum as follows: additional evidence the company state support its position that Pola-BR is not a relevant comparator for this appraisal in section 2.1; the ITC in section 2.2; the company's economic model in section 3; and cost-effectiveness results in section 4.

2 CLINICAL EFFECTIVENESS

2.1 Evidence from clinical guidelines and NHS England on the use of Pola-BR

In section 1 of the Scenario Analysis Document, the company describe information relating to current use of Pola-BR as second-line treatment in: a) BSH treatment guidelines for relapsed or refractory DLBCL published on 19th May 2025,[3] and b) company discussions with NHS England.

2.1.1 BSH guidelines

The company state these guidelines, specifically the section concerning the second-line management of patients who are ineligible for high dose chemotherapy and autologous stem cell transplant (HDT-ASCT) on page 3,[3] provide the following information to support avoidance of Pola-BR:

- There are currently no data on the activity of Pola-BR for relapsed or refractory large B cell lymphoma in patients who received polatuzumab in first-line therapy.
- Where possible, Pola-BR should be avoided for patients who may be suitable for third-line chimeric antigen receptor (CAR) T-cell therapy given that bendamustine exposure prior to apheresis is associated with increased risk of CAR T-cell manufacturing failure and inferior outcomes after CAR T-cell therapy.
- Although definitive data are not yet available and current literature is conflicting, there is concern that prior bendamustine exposure may adversely impact the efficacy of subsequent CD3xCD20 bispecific antibody therapy (glofitamab and epcoritamab) especially if the interval between these therapies is short.

2.1.2 NHS England

The company sought opinion from NHS England regarding the use of Pola-BR in the second-line setting. NHS England confirmed the use of Pola-BR in clinical practice was

sufficient (40%) to justify its inclusion as a comparator in the appraisal. However, NHS England also stated that clinical experts it consulted were surprised that the use of this regimen is still so high and believed this could be driven by use in regional hospitals, possibly due to a lower uptake of Pola-RCHP and the concerns on bendamustine use in the second line setting not filtering down from specialist treatment centres.

2.1.3 EAG comment on the evidence from the new BSH guidelines and NHS England

The EAG sought the opinion of the three clinical experts who advised the EAG Report as to whether they consider Pola-BR remains a relevant comparator for this appraisal, after considering the recommendations in the new BSH guidelines. At the time of this critique, only one of the three experts had responded.

This expert acknowledged that they would not recommend Pola-BR when planning CAR T-cell therapy or bispecific antibody therapy at third-line for a transplant ineligible second-line patient. However, in light of the new BSH guidelines, they considered that Pola-BR may be even more relevant as a comparator for this appraisal for the following reasons:

1. Figure 1 in the new BSH guidelines lists Pola-BR as a second-line treatment option for patients who are transplant ineligible.

2. Not all patients will receive Pola-R-CHP as a first-line treatment, and they would therefore be eligible for Pola-BR as a second-line treatment.

3. Clinicians may prefer to use epcoritamab as third-line treatment, because either the patient would not be fit enough to receive glofitamab (e.g. if performance status is 2) or the hospital delivering treatment and the patient prefer continuous subcutaneous epcoritamab over fixed duration intravenous glofitamab. However, due to blueteq criteria, the use of epcoritamab as third-line treatment would only be possible if the patient had received Pola-BR as second-line treatment.

4. Some patients would not be fit enough to receive CAR T-cell therapy or bispecific antibody therapy, so their third-line treatment would likely be loncastuximab tesirine or palliation. For second-line treatment these patients would probably not be fit enough to receive rituximab in combination with gemcitabine and oxaliplatin (R-GemOx), but may tolerate Pola-BR, which has broadly similar efficacy. For example, a frailer patient who received rituximab in combination with gemcitabine, cyclophosphamide, vincristine and prednisolone (RGCVP) or rituximab in

combination with reduced dose cyclophosphamide, doxorubicin, vincristine and prednisolone (R-miniCHOP) as first-line treatment could have a performance status of 2-3 and be relapsed or refractory. Such a patient may not be fit for third-line treatment, and probably not fit to receive R-GemOx as second-line treatment, but may tolerate Pola-BR.

Overall, our clinical expert concluded that although the use of Pola-BR second-line will be in a small percentage of patients, it will continue to be relevant as a second-line treatment for some patients who are transplant ineligible.

2.2 Indirect treatment comparison (propensity score analysis)

The company describe the methods, results and limitations of their indirect treatment comparison, comparing the second-line patients from the STARGLO trial (Glofit-GemOx) with second-line only patients from the GO29365 trial (Pola-BR), in the Scenario Analysis Document (sections 2.1, 2.2 and 2.3 respectively).

2.2.1 Methods

The methods are briefly reported in the Scenario Analysis Document, and some aspects either lack detail (ITC methods used e.g. “Full matching”) or are not reported (rationale for choice of covariates in analyses, quantity of missing data, and distribution of weights).

To ensure that the patient cohorts used for the analysis were as homogeneous as possible before attempting any comparisons, the populations from the STARGLO and GO29365 trials were subsetted to remove differences in trial enrolment criteria. The population was further subsetted to limit it to the second-line (i.e. 1 prior line of therapy) setting. This resulted in xxx patients in the Glofit-GemOx arm, and xx patients in the Pola-BR arm.

The company performed four analyses:

- **Unadjusted**
- **Inverse probability of treatment weighting** (**IPTW**) to adjust for imbalances in patient characteristics, but without adjustment for cell type of origin and bone marrow involvement. The missing values of the adjusted covariates were set to be equal to the mean or mode of each covariate, so that patients were not dropped from the analysis. This was the company’s main analysis and is henceforth referred to as the “main analysis”.

- **IPTW with multiple imputation** (the same as the main analysis, but included cell type or origin and bone marrow as covariates and used multiple imputation for any missing values of covariates)
- **Full matching** (without adjustments for cell type of origin and bone marrow involvement. Missing values of other covariates were set to be equal to the mean or mode of each covariate, so that patients were not dropped from the analysis)

The following 11 covariates were included in the main analysis and full matching analysis:

- Age, years
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1, %
- Eastern Cooperative Oncology Group (ECOG) PS 2, %
- Ann Arbor Stage III/IV, %
- High Lactate dehydrogenase (LDH), %
- Extranodal disease, %
- International Prognostic Index (IPI) 3–5, %
- Refractory first-line, %
- Bulky disease
- Time since last treatment to first study treatment, months
- Male sex, %

The company reports on the balance of these covariates for the unadjusted analysis (Table 1 and Figure 1 in its Scenario Analysis Document) and the company main analysis (IPTW) only (Table 2 and Figure 1 in its Scenario Analysis Document)

The unadjusted analyses were unbalanced on 8 covariates (absolute standardised mean difference (SMD) > 0.1). Covariate balance improved after fitting the IPTW model for all covariates, but three covariates remained unbalanced (age, ECOG PS=1, high LDH). Matching resulted in the effective sample size (ESS) for the Pola-BR group reducing from [redacted] to [redacted]

2.2.1.1 EAG comment on the indirect treatment comparison methods

The EAG agree with the company's subsetting of trial populations, which resulted in [redacted] patients in the Glofit-GemOx arm, and [redacted] patients in the Pola-BR arm.

The company's reporting of the different ITC methods used lacked detail but overall appears appropriate.

The rationale for the choice of covariates is not reported in the Scenario Analysis Document. The EAG note that these covariates are listed as high or medium priority variables in CS section B.2.10 which reports on indirect comparisons for the third-line setting for this appraisal. The EAG also found further information explaining the prioritisation of these variables and their validation as prognostic factors/treatment effect modifiers in the committee papers for TA927.[4] The EAG therefore consider that key prognostic factors/treatment effect modifiers were adequately considered for the analyses, except that there is ambiguity around how the bulky disease covariate was analysed. The first paragraph of section 2.1 of the Scenario Analysis Document states that "the size of the largest node lesion was used instead of bulky disease ≥10 cm as bulky disease was not available in the data. The size of the large node lesion in both studies was used to match." However, for both the Glofit-GemOx and Pola-BR groups, Table 1 and Table 2 in the Scenario Analysis Document report mean and SD for bulky disease but not "size of largest node lesion". It is therefore unclear to the EAG whether bulky disease (listed as a medium priority variable in CS section B.2.10) or size of the largest node lesion were used in the analyses.

Given that cell type of origin and bone marrow involvement were low priority prognostic factors/ treatment effect modifiers (CS section B.2.10) the EAG do not consider the lack of adjustment for these two variables from the company's main analysis or full matching would result in significant bias.

The EAG consider the handling of missing values for covariates in the main analysis and in the full matching analysis, i.e. missing values of other covariates were set to be equal to the mean or mode of each covariate, to be a rather crude approach. Furthermore, the quantity of missing data was not reported. The EAG is therefore uncertain of the impact of missing data on the results for these two analyses. We consider IPTW with multiple imputation to be the most robust analysis.

The EAG agree with the company, and its use of the threshold of 0.1 for absolute SMD, that covariate balance was improved after IPTW, but not all variables achieved balance. The EAG consider that Love plots, which were provided in Scenario Analysis Document Figure 1, show that matching was not wholly successful (e.g. for age, ECOG PS=1, high LDH), suggesting lack of overlap of populations. The EAG note that these 3 covariates were all considered high priority variables for indirect comparisons in the CS (section B.2.10). The EAG is uncertain of the impact of the remaining imbalances of these 3 covariates on the results of the main analysis. The company state that as imbalances still existed after

matching, all baseline covariates were adjusted in the outcome regression after the IPTW and full matching was performed. The EAG consider this an appropriate approach.

Scenario Analysis Document section 2.3 states that the effective sample size for Pola-BR was reduced from [redacted] which indicates that "data for this comparison has significant uncertainties". The EAG, however, consider this a relatively minor limitation compared to the uncertainties around the covariate adjustments and missing data noted above.

2.2.2 Results

Results for overall survival and progression-free survival are reported in Scenario Analysis Document section 2.2. Hazard ratios and 95% confidence intervals are reported for overall survival and progression-free survival for all four analyses in Table 3 and Table 4 of the Scenario Analysis Document respectively. These tables are also reproduced below in Table 1 and Table 2.

Kaplan-Meier (KM) curves for overall survival and progression-free survival are provided in the Scenario Analysis Document for the unadjusted, IPTW, and full matched analyses only (i.e. not for IPTW with multiple imputation).

Table 1 Summary of indirect treatment comparison results for OS

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]
IPTW	[redacted]
IPTW with multiple imputation	[redacted]
Full matching	[redacted]

Source: Reproduced from Scenario Analysis Document Table 3
Abbreviations: CI, confidence interval; Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab
HRs presented for the comparison of Glofit-GemOx versus Pola-BR.
HRs <1 favour Glofit-GemOx.

The company state that the hazard ratio for overall survival [redacted]

Results from the IPTW with multiple imputation and full matching showed similar estimates.

Table 2 Summary of indirect treatment comparison results for PFS

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]
IPTW	[redacted]
IPTW with multiple imputation	[redacted]
Full matching	[redacted]

Source: Reproduced from Scenario Analysis Document Table 4
Abbreviations: CI, confidence interval; Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PFS, progression free survival
HRs are presented for the comparison of Glofit-GemOx versus Pola-BR.
HRs <1 favour Glofit-GemOx.

As with the results for overall survival the company state that the hazard ratio for progression-free survival [redacted] Results from the IPTW analysis with multiple imputation and full matching showed similar estimates.

2.2.2.1 EAG comment on the indirect treatment comparison results

The company's main analysis is IPTW, whereas the EAG prefer IPTW with multiple imputation. However, hazard ratios and their 95% confidence intervals for overall survival, and for progression-free survival, are similar and consistent across all four analyses (and none of the results are statistically significant). This would suggest that the issues of missing data, and omission of cell type of origin and bone marrow involvement from some analyses, are probably unimportant.

2.3 Real world evidence

Scenario Analysis Document section 2.3 states that real world evidence from UK patients with relapsed or refractory DLBCL demonstrate that median progression-free survival and overall survival for Pola-BR was 4.8 and 8.2 months respectively, compared to 9.2 months and 12 months in GO29365, citing a study by Northend et al. 2022.[5]

2.3.1 EAG comment on the real world evidence

The EAG note that the median progression-free survival and overall survival figures in the Northend et al. study cited in the Scenario Analysis Document are for the whole analysis population, which included patients receiving Pola-BR with treatment intent for bridging to CAR T-cell therapy, re-induction therapy with planned stem cell consolidation, and stand-alone treatment (no planned CAR T-cell therapy or SCT).[5] The EAG, however, consider that the results for the standalone population, which are reported in Figure 1 panel C of the paper

by Northend et al.,[5] to be more relevant for this appraisal. Median progression-free survival and overall survival for Pola-BR for the standalone population were 5.4 months and 10.2 months respectively.

The Scenario Analysis Document does not mention a process for identifying and selecting real world evidence or whether the Northend et al. study[5] is the only relevant source of real-world evidence for Pola-BR.

3 COST EFFECTIVENESS

The company's economic model used for the Pola-BR scenario analysis has the same partitioned survival structure as the model used in the company's submission comparing Glofit-GemOx with R-GemOx, which the EAG considers to be appropriate.

3.1 Survival analysis

The company describe its method for fitting parametric curves to the Glofit-GemOx and Pola-BR progression-free survival and overall survival Kaplan-Meier data in its Scenario Analysis Document (sections 3.1.1 and 3.1.2, respectively). The curves chosen by the company are shown in Table 3.

Table 3 Parametric distributions used in the company's Pola-BR scenario survival analysis, company model (dated 05 06 2025)

Survival outcome	Glofit-GemOx	Pola-BR
Progression-free survival	KM with lognormal tail (fitted at 20 months when [redacted] of patients remain at risk).	KM with lognormal tail (fitted at 20 months when [redacted] of patients remain at risk).
Overall survival	KM with lognormal tail (fitted at 20 months when [redacted] of patients remain at risk).	KM with lognormal tail (fitted at 20 months when [redacted] of patients remain at risk).

Source: EAG-created table.
Abbreviations: Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; KM, Kaplan-Meier; Pola-BR, polatuzumab with bendamustine and rituximab

The EAG agrees with the company that the proportional hazards assumption does not hold for progression-free survival or overall survival data and so fitting survival curves independently is reasonable. Based on the hazard plots and AIC/BIC rankings, we consider the company's choice of the lognormal curve for both Glofit-GemOx progression-free and

overall survival to be suitable. The company has fitted the same parametric distribution to the Pola-BR arm for both progression-free and overall survival, in line with NICE DSU TSD 14 recommendations.[6]

However, the company considers that all distributions fit the observed Glofit-GemOx and Pola-BR Kaplan-Meier data poorly (Scenario Analysis Document Figure 9 and Figure 11) and so the company fitted the lognormal curve from 20 months for both progression-free and overall survival in both arms. The EAG agrees with this approach and considers the parametric curves have been fitted when a reasonable proportion of patients remain at risk.

3.2 Long-term remission

The company's model sets mortality for the cohort (both for patients who are progression-free and those with progressed disease) near equal to that of the general population after three years (with 9% excess vs. the general population [in line with value applied from TA559 and TA567,[7, 8] based on a standardised mortality rate (SMR) identified from Maurer 2014[9]]). The EAG notes that, in the model, there are remaining patients with progressed disease and the company set the mortality rate of these progressed patients to the general population mortality. As discussed in the EAG Report, we prefer to set the cure point to six years and we maintain this in this Pola-BR scenario. The overall survival estimates using different assumptions are shown in Table 4.

Table 4 Modelled overall survival for Glofit-GemOx (Pola-BR comparison population) and Pola-BR

Scenario	Time			
	Proportion alive at 1 year	Proportion alive at 2 years	Proportion alive at 5 years	Proportion alive at 10 years
Glofit-GemOx (Pola-BR comparison subpopulation); KM+lognormal; company base case[a]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit-GemOx (Pola-BR comparison subpopulation); KM+lognormal; cure point at 6 years; EAG base case	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Time			
	Proportion alive at 1 year	Proportion alive at 2 years	Proportion alive at 5 years	Proportion alive at 10 years
Glofit-GemOx (Pola-BR comparison subpopulation); KM+lognormal; cure point at 8 years	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR; KM+lognormal; company base case[a]	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR; KM+lognormal; cure point at 6 years; EAG base case	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR; KM+lognormal; cure point at 8 years	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG-created table
Abbreviations: Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; KM, Kaplan-Meier; Pola-BR, polatuzumab with bendamustine and rituximab
[a] Assumes a cure point of 3 years

3.3 Additional inputs and assumptions

The company's inputs and assumptions in their Glofit-GemOx versus Pola-BR scenario analysis are the same as in their base case submission for Glofit-GemOx compared with R-GemOx. The company also conducted a scenario analysis using the EAG's preferred assumptions from the original submission; results are reproduced in section 4 below.

3.3.1 Adverse events

The Scenario Analysis Document section 3.2 describes inputs specific to the Pola-BR arm; Table 7 in that document shows the Pola-BR treatment-related adverse events considered in the model. The EAG was not provided with the reference for the GO29365 study, consequently we were unable to confirm the proportions of patients experiencing the adverse events listed in the Scenario Analysis Document Table 7. We note that the number of patients in GO29365 reported in the model (n = [redacted]) does not match the number of patients in GO29365 reported in CS Table 32 for TA649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma);[2] n = 45. Nor does it match the safety population reported in Sehn et al. (2020);[10] n = 39. Furthermore, the breakdown of adverse events reported in the model does not match TA649 CS Table 32 nor Sehn et al. (2020).[2, 10] The cost per patient to manage adverse events is similar in both arms of the model: £185 for Glofit-GemOx and £196 for Pola-BR. The EAG notes that making the

cost per patient of managing adverse events the same in both arms has a negligible effect on the ICER.

3.3.2 Subsequent treatments

Scenario Analysis Document Table 8 shows the proportion of patients receiving subsequent third-line treatment in the company's analysis. As per clinical experts' advice in the EAG Report on the main company submission, we assume that 30% of patients receive palliative care third-line, rather than all patients receiving third-line treatment, resulting in post discontinuation costs of £35,816 for Glofit-GemOx and £33,341 for Pola-BR in the company's analysis.

3.3.3 Severity modifier

Comparing Glofit-GemOx with Pola-BR results in a proportional QALY shortfall of [redacted] and an absolute QALY shortfall of [redacted]. The EAG agrees with the company that a severity modifier is not warranted.

4 COST-EFFECTIVENESS RESULTS

The cost-effectiveness results presented include confidential Patient Access Scheme (PAS) discount prices for glofitamab, polatuzumab and obinutuzumab. However, they do not include existing discounts for subsequent therapies in the model. These have been provided by the EAG as a scenario within an updated version of the confidential comparator PAS addendum to the EAG Report (see section 4 within the updated comparator PAS addendum).

To compare Glofit-GemOx with Pola-BR, the company has used a subpopulation of the STARGLO trial participants that differs from the STARGLO ITT population used in their main submission. Consequently, a fully incremental analysis including Gloft-GemOx, R-GemOx and Pola-BR cannot be made, only a pairwise comparison between Glofit-GemOx and Pola-BR. Table 5 shows the results of the analyses for the company's base case and when using the EAG's preferred assumptions.

We were unable to reproduce the company's analysis using the EAG's preferred assumptions in the model provided by the company (dated 05/06/2025), because the company had not programmed these options into their version of the model. We programmed our preferred assumptions into the model and note a slight discrepancy in the ICER. The company's model, set to the EAG preferred assumptions, produces an ICER of

£22,745 per QALY (Scenario Analysis Document Table 11), but we calculate an ICER of £23,044 per QALY (Table 5). The difference between the ICERs is caused by alternative approaches to coding the administration costs (i.e. once per combination not per treatment).

Table 5: Glofit-GemOx compared with Pola-BR; EAG model, EAG preferred assumptions, cumulative results

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY.
Company base-case	Glofit-GemOx	[redacted]	[redacted]	£25,462
	Pola-BR	[redacted]	[redacted]	
+ Mortality same as for general population after six years	Glofit-GemOx	[redacted]	[redacted]	£25,745
	Pola-BR	[redacted]	[redacted]	
+ 30% of patients not receiving 3L treatment	Glofit-GemOx	[redacted]	[redacted]	£26,749
	Pola-BR	[redacted]	[redacted]	
+ Utility scores specific to 2L patients	Glofit-GemOx	[redacted]	[redacted]	£26,754
	Pola-BR	[redacted]	[redacted]	
+ GemOx given for 6 cycles in both arms	Glofit-GemOx	[redacted]	[redacted]	£26,069
	Pola-BR	[redacted]	[redacted]	
+ Use revised progression resource use	Glofit-GemOx	[redacted]	[redacted]	£26,067
	Pola-BR	[redacted]	[redacted]	
+ Use terminal costs, rather than weekly healthcare resource use costs	Glofit-GemOx	[redacted]	[redacted]	£23,307
	Pola-BR	[redacted]	[redacted]	
+ Administration cost applied once for each combination of treatments	Glofit-GemOx	[redacted]	[redacted]	£22,913
	Pola-BR	[redacted]	[redacted]	
+ Adverse event: Grade 3 Tumour lysis syndrome in Glofit-GemOx arm	Glofit-GemOx	[redacted]	[redacted]	£23,044
	Pola-BR	[redacted]	[redacted]	
EAG preferred base case assumptions	Glofit-GemOx	[redacted]	[redacted]	£23,044
	Pola-BR	[redacted]	[redacted]	

Source: Adapted from Scenario Analysis Document Table 11
Abbreviations: 2L, second-line; 3L, third-line; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; Pola-BR, polatuzumab with bendamustine and rituximab; QALY, quality-adjusted life-year

5 EAG CONCLUSION

- Uncertainty remains regarding the appropriateness of excluding Pola-BR given the company opinion and BHS guidelines on the one hand versus the opinions of NHS England and our clinical expert on the other.
- Overall, the ITC methods appear appropriate, except for ambiguity around how bulky disease was handled. However, whilst hazard ratios from the indirect treatment comparisons for overall survival and progression-free survival directionally favour Glofit-GemOx, the benefits are not statistically significant.
- As a different population is used for the comparison of Glofit-GenOX with Pola-BR to that used for Glofit-GemOx vs R-Gem-Ox, it is not possible to present an incremental analysis and instead pairwise results have been presented.

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ID6202 Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse B-cell lymphoma – additional analyses requested by NICE

24th June 2025

Overall survival graphs

NICE requested the EAG provide graphs overlaying the estimates of long-term overall survival using parametric curves with the Kaplan-Meier data for:

- Glofit-GemOx compared with R-GemOx
- Glofit-GemOx compared with Pola-BR

These comparisons are shown in Figure 1 and Figure 2 below. Please note: the Kaplan-Meier data cannot be overlaid in the Pola-BR scenario graphs, because the overall survival estimates use the Kaplan-Meier data with a lognormal tail.

Figure 1 Overall survival estimates for (A) Glofit-GemOx and (B) R-GemOx, company base case
Source: Company model (EAG analyses version)

Figure 2 Overall survival estimates for (A) Glofit-GemOx and (B) Pola-BR; Pola-BR scenario
Source: Company model (dated 05062025; EAG analyses version)

Cure assumption survival estimates

The EAG were asked to clarify their position regarding the cure assumption survival estimates described in EAR Section 4.2.6.1.2, which we do here:

- In clarification question B1, we asked the company to conduct a scenario using a mixture cure model (i.e. patients in the progression-free health state have general population mortality and those in the progressed health state have a cancer-related mortality).
- The company provided this analysis, but this scenario changed the model structure from a partitioned survival model (PSM) to a state transition model (STM), with state transition probabilities derived from the STARGLO trial.
- The EAG considers the results from this STM scenario to be unrealistic and lack face validity (Figure 3).
- Consequently, in our base case we prefer to use the company's original PSM, but we set the cure point (i.e. when all patients with progressed disease have died and all remaining patients are progression-free) to be at six years, not three. This means the mortality for the patient cohort is equal to the general population after six years in our base case and is our best approximation to a mixture cure model.
- We appreciate the company endeavouring to provide the analysis we requested in clarification question B1, but recognise that this was extremely challenging given the short time available.

Figure 3 Overall survival estimates using the company state transition model (Glofit-GemOx vs R-GemOx)
Source: Company model (dated 19032025)

Single Technology Appraisal

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

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 Thursday 1 May 2025** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as [redacted] in pink.

Please note that page numbers in the EAG's response refer to the track changes version of the EAG Report

Issue 1 Use of obinutuzumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 1] "The company's revised deterministic base case cost-effectiveness results are shown in Table 2 with a confidential patient access scheme (PAS) discount applied for glofitamab and obinutuzumab (a subsequent treatment made by the same company)."	"The company's revised deterministic base case cost-effectiveness results are shown in Table 2 with a confidential patient access scheme (PAS) discount applied for glofitamab and obinutuzumab (administered as a pre-treatment prior to cycle 1 and is made by the same company)."	Obinutuzumab is not a subsequent treatment in this context, it is administered as a pre-treatment to lower the circulating and lymphoid B cells to reduce the risk of cytokine release syndrome	We have made the suggested changes to the text (page 1).

Issue 2 Over-estimation of survival estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 3] "The company set the cure point to three years. After this time all patients are assumed to have the same mortality as the general population."	"The company set the cure point to three years. After this time, the mortality risk for the remaining patients reverts to a near general population level (9% excess vs. the general population based on a standardised mortality rate (SMR)	The current wording does not reflect that the mortality risk is adjusted to account for potential excess comorbidities.	Thank you for highlighting this issue, we have changed the text as suggested (page 3).

	identified from Maurer 2014), adjusted to account for potential excess comorbidities.		

Issue 3 Update to reflect lisocabtagene maraleucel NICE guidance

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 9] "The current CAR-T therapy available for this indication in the NHS is axicabtagene ciloleucel (TA895), under the managed access agreement under the Cancer Drugs Fund."	""The current CAR-T therapies available for this indication in the NHS are axicabtagene ciloleucel (TA895), under the managed access agreement under the Cancer Drugs Fund, and lisocabtagene maraleucel (TA1048) (routine commissioning)."	Final guidance for lisocabtagene maraleucel was published on the NICE website on 26th March 2025	Thank you for highlighting this. We have added the proposed text and the following sentence to the report: "It should be noted that final guidance for lisocabtagene maraleucel was published by NICE on 26 March 2025 and therefore this therapy is not included in the NICE scope" (page 9)

Issue 4 Update to expected marketing authorisation date for Glofit-GemOx

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 12] "UK marketing authorisation for glofitamab in combination with GemOx is expected in [redacted]	"UK marketing authorisation for glofitamab in combination with GemOx is expected in [redacted]	Update to reflect current anticipated marketing authorisation approval date	Thank you for providing an updated anticipated date for UK marketing authorisation for glofitamab in combination with GemOx. We have changed the marketing authorization date to this new date in our report (page 12).

Issue 5 Incorrect details of administration days

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 12] "Glofitamab is administered as an intravenous (IV) infusion. It must be administered according to a dose step-up schedule in cycle 1 (2.5mg on Day 8 and 10mg on Day 10)"	"Glofitamab is administered as an intravenous (IV) infusion. It must be administered according to a dose step-up schedule in cycle 1 (2.5mg on Day 8 and 10mg on Day 15)"	The report states that the cycle 1 step up dosing for glofitamab is '2.5mg on Day 8 and 10mg on Day 10'. This is incorrect as the 10mg dose was given on Cycle 1 Day 15 in the STARGLO trial and this is represented in the SmPC too.	Thank you for highlighting this error. We have corrected this in our report (page 12).
[Page 25, Table 6] "Rituximab: 375 mg/m^2 administered IV on Day 1 of	"Rituximab: 375 mg/m2 administered IV on Day 1 of cycles 1-8. Administered before gemcitabine and oxaliplatin"	This was an error in the CS that has been carried across to the EAG report	Not a factual inaccuracy, but thank you for highlighting this

cycles 2-8. Administered before gemcitabine and oxaliplatin”			typographical error in the CS which we have corrected in our report (page 25, Table 6)

Issue 6 Clarification on analyses conducted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 36, Table 9] “Three analyses were conducted”	Propose this states that two analyses were conducted	Details are only provided for the interim analysis (which became the primary analysis) and the updated analysis. Should this state two analyses were conducted, or are the EAG making reference to the 2L population analysis, hence why it mentions three analyses being conducted.	Thank you for highlighting this ambiguity. We have updated the text in Table 9 as suggested.
[Page 41, Table 11 footnote] “CS section B.2.6.2.1 also reports the p-value as [redacted]	“Note, the unstratified HR is [redacted]	Clarification that the HR of [redacted] is referring to the unstratified analysis to avoid confusion on the correct value reported in the table	Thank you for clarifying this. The inconsistency arose because in CS section B.2.6.2.1 this p-value is given alongside the stratified HR. For consistency across the

			tables we have removed footnote b which contains this p-value from Table 11.

Issue 7 Incorrect data presented

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 40, Table 10] Median OS, months (95% CI)	This column is currently presenting hazard ratios, not medians. An updated table is provided below for accuracy, complete with correct confidential marking for your reference	Presentation of correct data	Thank you for highlighting this error. We have corrected Table 10 as suggested.
[Page 43, Table 13] N numbers	N numbers for the updated analysis and 2L subpopulation are incorrect. An updated table is provided below for accuracy, complete with correct confidential marking for your reference		Thank you for highlighting this error. We have corrected Table 13 as suggested.

Issue 8 Clarity on population being referred to

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 41] "The secondary outcome of IRC-assessed PFS met the criterion for statistical significance at the primary analysis according to the pre-	"The secondary outcome of IRC-assessed PFS in the ITT population met the criterion for statistical significance at the primary analysis according to the pre-specified hierarchical testing procedure	Clarity that this is referring to the ITT population, not the 2L population	Thank you for highlighting this omission. We have amended the text as suggested to address this (page 41).

specified hierarchical testing procedure”			
[Page 42] “The secondary outcome of IRC-assessed complete response met the criterion for statistical significance at the primary analysis…”	“The secondary outcome of IRC-assessed complete response for the ITT population met the criterion for statistical significance at the primary analysis…”		Thank you for highlighting this omission. We have amended the text as suggested to address this (page 43).
[Page 43] “Data for this IRC-assessed secondary outcome were immature at the primary analysis…”	“Data for this IRC-assessed secondary outcome were immature at the primary analysis for the ITT population…”		Thank you for highlighting this omission. We have amended the text as suggested to address this (page 43).

Issue 9 Inclusion of tumour lysis syndrome (TLS) adverse events in the Glofit-GemOx arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 76] “We consider that tumour lysis syndrome adverse events that occurred in two patients in the Glofit-GemOx arm should also have been included in the economic model and we	The company believes that this consideration is based on a factual error, therefore the incorporation of TLS adverse events in the Glofit-GemOx arm is inappropriate and these costs should not be incorporated in the EAG’s base case analysis, and as such not be cited in the report.	As mentioned in section 2.3.7 of the CS, only treatment-related AEs with a severity grade of 3 or higher were considered in the model, so that those events that are most likely to impact cost-effectiveness are reflected in the analysis.	The EAG considers that the tumour lysis syndrome (TLS) adverse events should be included in both arms of the model for consistency, even though the STARGLO study investigators determined that these adverse events

incorporate these costs in our base case”		Assessment of the causality of adverse events was made by investigators in the STARGLO trial based on their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event was considered to be related to the study treatment. TLS was defined as an adverse event of special interest in STARGLO. While Table 19 in Appendix D of the CS reports that 2 patients in the Glofit-GemOx arm reported a Grade 3 TLS event, neither of these events were considered to be related to Glofit-GemOx following assessment by the study investigators. Conversely, the three TLS events that occurred in the R-GemOx arm	are not treatment-related in the Glofit-GemOx arm. The effect of removing the TLS adverse events in the Glofit-GemOx arm is shown in EAG Report Table 28. We note that this change has a negligible effect on the ICER.

		were concluded by investigators to be related to study treatment. Therefore, based on the definition of adverse events that were included in the economic evaluation, the company included the TLS events in the R-GemOx arm only as these were the only events related to treatment. As such, costs for TLS in the Glofit-GemOx arm should be excluded from the EAG's analysis.	
[Page 76] "The EAG are unclear why tumour lysis syndrome adverse events that occurred in two patients in the Glofit-GemOx arm were also not included	If the explanation provided above is satisfactory and the EAG is in agreement with the Company, these mentions should be removed from the report	TLS events in the Glofit-GemOx arm were determined by study investigators to not be related to study treatment and therefore should not be included in the EAG model. Model results should also be updated to reflect the removal of this assumption if the EAG is in agreement (EAG base case ICER reverts to £12,181)	For all cases listed here, the text has not been removed, and the model results have not been updated, because the EAG considers the TLS adverse events should be included in both arms of the model for consistency.
[Page 89] "The EAG consider that the costs for tumour lysis syndrome are from an appropriate source and have been inflated correctly.			

However, we consider that the costs for tumour lysis syndrome that occurred in the two patients in the Glofit-GemOx arm should also been included in the economic model.”			
[Page 95, Table 27] Row: Frequency of adverse events “We disagree with only including TLS in the R-GemOx arm” “For consistency, TLS should also be included in the Glofit-GemOx arm”			
[Page 97] “Adverse event costs included for tumour lysis syndrome included in Glofit-GemOx arm (section 4.2.8.5)”			
[Page 98 – Table 28]			

+ Adverse event: Grade 3 Tumour lysis syndrome in Glofit-GemOx arm row			

Issue 10 Drug administration costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 83] "Administration costs for R-GemOx were assumed to be the same as for Glofit-GemOx. The EAG agrees with drug administration costs used in the economic model. We note that the administration cost of administering three treatments (for Glofit-GemOx and R-GemOx) has been costed as three separate administration costs. However, administering these drugs together on the same day incurs a single administration cost. We prefer to apply one administration cost that covers the three treatments in our base case.	Provide further information as to how administration costs for cycle 1 are applied in the EAG model	The company would like to query if the EAG needs to consider the administration costs in cycle 1, where glofitamab is administered separately from GemOx on Day 8 and Day 15, and rituximab which is administered one day earlier than GemOx in cycle 1, or if this has been accounted for in its model already? This section of the report should be amended to reflect how cycle 1 administration costs are addressed in the model.	Thank you for this comment. We have checked the model and we note that we have only included one administration cost for cycle 1 week 1 whereas in fact glofitimab is administered on a separate day from GemOx and rituximab is administered on a separate day from GemOx. We have not corrected the model as this correction is likely to have a minor impact on the model results as it applies to both arms in cycle 1 (page 84).

Issue 11 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 3] "The EAG is aware that potentially relevant Pola-BR studies exist, for example the GO29365 trial comparing Pola-BR against polatuzamab plus rituximab which informed NICE TA649."	"The EAG is aware that potentially relevant Pola-BR studies exist, for example the GO29365 trial comparing Pola-BR against bendamustine plus rituximab which informed NICE TA649."	GO29365 compared polatuzumab with bendamustine and rituximab against bendamustine and rituximab, not polatuzumab and rituximab	Thank you for highlighting this typo. We have made the suggested correction (page 3).
[Page 7] "CS section 3.1 provides key background information on diffuse large B-cell lymphoma"	"CS section 1.2 provides key background information on diffuse large B-cell lymphoma"	Reference to incorrect section of CS	Thank you for highlighting this typo. We have amended this to CS section 1.3 rather than the proposed CS section 1.2. The reason for this is CS section 1.2 provides a description of the technology being evaluated whereas CS section 1.3 provides a description of the health condition (page 7).

[Page 37] "For PFS, as indicated in CS Figures 5 and 6, patients who received any new anti-leukaemia therapy (NALT)	"For PFS, as indicated in CS Figures 5 and 6, patients who received any new anti-lymphoma therapy (NALT)"	Typographical error	Thank you for highlighting this typo. We have made the suggested correction (page 37).
[Page 50] "Conversely, the proportion of patients experiencing tumour lysis syndrome in the R-GemOx arm was greater in the Glofit-GemOx arm (5.5% versus 1.9% respectively) (CS Table 29)."	"Conversely, the proportion of patients experiencing tumour lysis syndrome in the R-GemOx arm was [redacted] **than** in the Glofit-GemOx arm ([redacted] versus [redacted] respectively) (CS Table 29).	Missing "than", the context of the sentence changes without this	Thank you for highlighting this typo. We have made the suggested correction (page 51).
[Page 84] "Consequently, we have assumed that 30% of patients receive palliative care third-line, rather than all patients receiving third-line treatment, as assumed by the company. This results in post-discontinuation costs of £36,898 for Glofit-GemOx and £44,203 for R-GemOx, and raise this as a key issue"	"Consequently, we have assumed that 30% of patients receive palliative care third-line, rather than all patients receiving third-line treatment, as assumed by the company. This results in post-discontinuation costs of £36,898 for Glofit-GemOx and £43,760 for R-GemOx, and raise this as a key issue	Correcting report to value stated in the EAG model	Thank you for the comment. These values refer to 30% of patients receiving palliative care third-line in the company's base case, which we have clarified in the EAG report (page 85).