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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
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
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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.

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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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LIST OF ABBREVIATIONS

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).

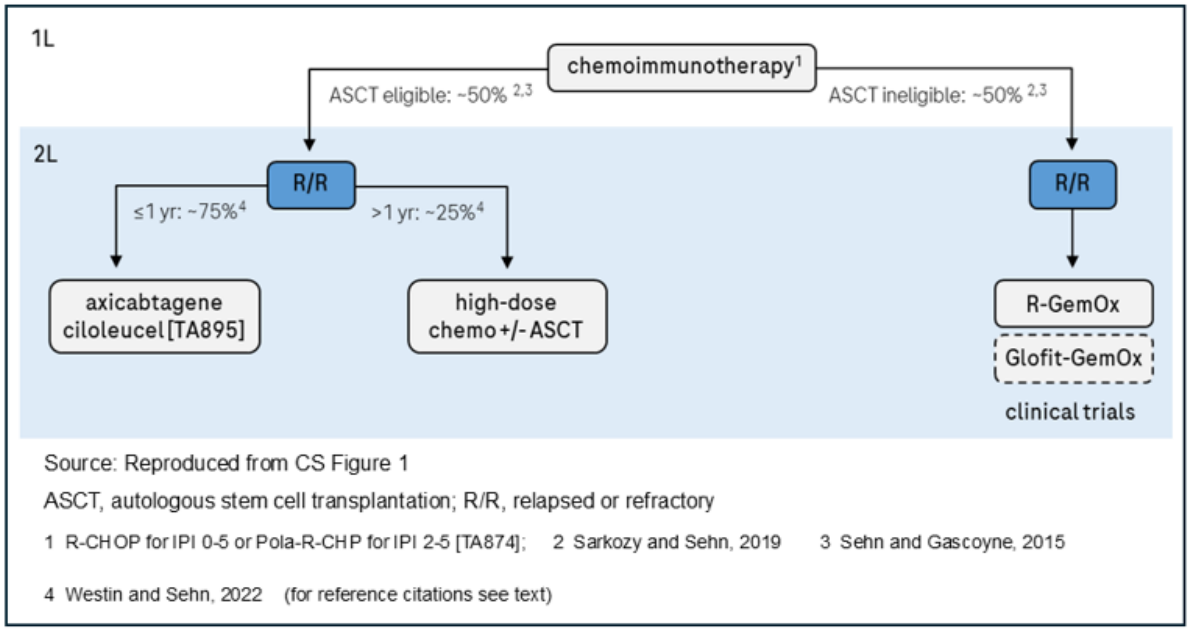

Figure 1 Proposed position of Glofit-GemOx in the treatment pathway

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.

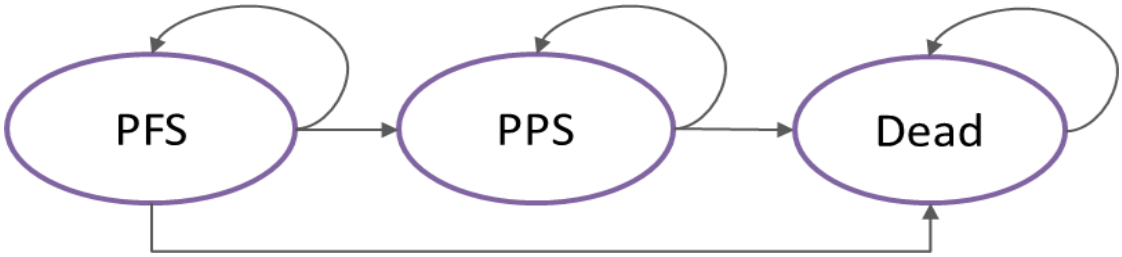

Figure 4 Structure of the economic model

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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