Single Technology Appraisal

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

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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

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   a. Lymphoma Action

3. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Tuesday 19 August 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche Products Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[redacted]
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** The company would like to thank the evaluation committee for reviewing the submitted evidence and for providing the opportunity to address the outstanding issues highlighted in the Draft Guidance consultation. In summary: • The company asserts that the results from the STARGLO study are generalisable to the UK NHS population. While some inconsistencies were observed in regional subgroups, these were determined to be non-biological and attributed to confounding factors, such as imbalances in subsequent therapies and the impact of COVID-19. Post-hoc analyses, including event-free survival (EFS) and inverse probability of censoring weighting (IPCW), confirmed the applicability of the overall study findings. This conclusion is supported by the positive opinions from both the EMA and the MHRA, which granted marketing authorisation for Glofit-GemOx, as well as by recent guidelines from the European Society of Medical Oncology (ESMO) (1) and BSH (2) recommending the treatment. • The updated analyses provided in this response include an additional 14.5 months' clinical data from the STARGLO study. This data addresses a key concern from the Draft Guidance by demonstrating a significant and clinically meaningful overall survival (OS) benefit for Glofit-GemOx in the second-line (2L) subpopulation. In this group of patients, Glofit-GemOx led to a 42% reduction in the risk of death and a robust and sustained progression-free survival (PFS) benefit. Moreover, a landmark OS analysis indicates the potential for long-term remission following treatment with Glofit-GemOx in 2L patients who had a complete response at the prior analysis. • The company continues to hold significant reservations regarding the relevance of Pola-BR as a comparator. These concerns are supported by an analysis of UK real-world data presented at the 2025 British Society of Haematology (BSH) annual conference, which demonstrated that prior bendamustine treatment was associated with an inferior clinical response to subsequent bispecific antibody therapies (glofitamab and epcoritamab) in third-line patients with large B-cell lymphoma (3). This finding aligns with recently published BSH guidance advising against the use of Pola-BR for patients who may be eligible for later therapies

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	such as CAR T-cell therapy due to a negative impact on outcomes. The company also notes that the NHS England clinical lead for the Cancer Drugs Fund highlighted that the use of Pola-BR is continuing to decline, further diminishing its long-term relevance as a comparator. • The company updated its propensity score analysis for Glofit-GemOx versus Pola-BR using the most recent STARGLO data. This new analysis shows a clear separation in the PFS and OS curves favouring Glofit-GemOx although [redacted]; This updated analysis has been incorporated into the updated cost-effectiveness model. However, the company emphasises that the propensity score analysis results must be interpreted with caution due to several limitations: remaining imbalances in covariates, a small effective sample size for Pola-BR, and clinical expert opinion suggesting that the Pola-BR study data from GO29365 overestimates real-world clinical effectiveness. Despite these uncertainties, the company considers this robust analysis to be the best available evidence for this comparison to support NICE's decision-making process. • The economic analysis has been updated with the latest STARGLO data and the committee's preferred assumptions. The deterministic base-case results demonstrate that Glofit-GemOx is cost-effective at a £20,000 threshold when compared with both R-GemOx and Pola-BR. The ICER for Glofit-GemOx vs R-GemOx is £6,862 per QALY, while the ICER vs Pola-BR is £15,612 per QALY (PAS discount applied). The company has provided a fully incremental analysis as requested by the Committee but strongly advocates for a pairwise comparison against both R-GemOx and Pola-BR in the decision-making process. This is because R-GemOx is considered the standard of care by clinical experts, who have raised significant concerns about the long-term suitability of Pola-BR, particularly its negative impact on subsequent CAR T-cell therapy, as acknowledged in the new BSH guidelines. The company strongly advocates for NICE to reimburse Glofit-GemOx, underscored by robust clinical and economic evidence, regulatory approvals, clinical opinion and alignment with recent clinical guidelines. This therapy addresses the unmet need for patients with 2L R/R DLBCL, delivering a highly effective treatment that enhances survival outcomes and offers the possibility of long-term remission.
2	**Generalisability of STARGLO population to UK NHS population**

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	The STARGLO study was powered to assess OS benefit of Glofit-GemOx versus R-GemOx in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not candidates for transplant. At the primary analysis (CCOD1), Glofit-GemOx demonstrated a statistically significant and clinically meaningful improvement in OS, PFS and CR rate versus R-GemOx. This benefit was consistent at the updated analysis (CCOD2) and the recent analysis (CCOD3) with a median of 3 years' follow-up. The treatment effect of Glofit-GemOx was consistent across most subgroups, including the clinically relevant subgroup of patients who had one or more prior lines of therapy (the second-line [2L] subpopulation). In this subpopulation, the OS hazard ratio (HR) was 0.67 (95% CI: 0.41, 1.07; p=0.092) at the updated analysis and 0.58 (95% CI: 0.38, 0.89; p=[redacted]) at CCOD3. While some inconsistencies were noted in exploratory subgroups based on race and enrolment region, interpretation is confounded by small subgroups, a 2:1 randomisation ratio and wide HR confidence intervals. Additionally, since race and enrolment region were not stratification factors for randomisation, there are some imbalances in baseline characteristics between the study arms in these subgroups. A strong association was found between race and region, with European and North American patients being predominantly White and patients from the rest of the world (RoW) being mainly Asian. However, given the mechanism of action of glofitamab, and since pharmacological analysis showed no significant difference in glofitamab exposure based on race, it is likely that the observed differences in OS HR were regional rather than biological. Several post-hoc statistical analyses were supplied to the EMA to explain the potential differences in the regional subgroups and support generalisability of outcomes in the ITT population of STARGLO to the European population. In STARGLO, the European subgroup and overall ITT population were broadly comparable in terms of baseline demographic and disease characteristics, with some difference noted. Specifically, these were related to age (slightly more advanced in the European subgroup), race (mostly White in the European subgroup vs. a mix of White and Asian in the ITT population), Ann Arbor Stage (slightly higher percentage of patients with Stage III/IV disease in the European subgroup), prior CAR-T therapy (slightly higher proportion in the European subgroup) and refractory status (lower proportion refractory to prior therapies in the European subgroup).

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	The baseline demographic and disease characteristics of STARGLO were found to be similar to those of the ITT population of the Niveau study (4), which is another recently conducted phase III study in which R-GemOx is the control arm. Moreover, the 1-year and 2-year event-free rates for PFS and OS are comparable across the R-GemOx arms of both studies. Post-hoc analyses identified two main confounding factors in the European subgroup: imbalances in the use of subsequent therapies (new anti-lymphoma therapies; NALTs) and the impact of COVID-19. In the European R-GemOx arm, more patients received effective NALTs like CAR-T therapy, which may have biased the results. To correct for this, additional analyses for event-free survival (EFS) and inverse probability of censoring weighting (IPCW) were performed. These analyses adjusted for NALT use and showed that the European subgroup's results were comparable to the overall population. Similarly, sensitivity analyses censoring for COVID-19-related deaths resulted in more favourable OS HRs for the European subgroup. Based on these results, and with no biological reason to expect a smaller effect in the European population, the findings of STARGLO were deemed applicable to Europe. The CHMP issued a positive opinion, and the European Commission approved this indication for Glofit-GemOx on 14 April 2025. Alongside the new approval, conditions to convert the conditional marketing authorisation to a full marketing authorisation were fulfilled. Subsequently, the MHRA approved an extension of marketing authorisation to include the new indication for Glofit-GemOx on 16 July 2025, thus accepting that the results from the ITT population in STARGLO are applicable to the UK NHS population. In addition, the European Society of Medical Oncology (ESMO) and BSH have recently published guidelines recommending Glofit-GemOx as the preferred 2L treatment for transplant-ineligible DLBCL patients, based on the STARGLO study results (1, 2). Therefore, European and UK lymphoma experts accept that the STARGLO results are applicable to the European and UK populations, respectively. Based on the views of the European and UK regulators, together with guidelines published by European and UK lymphoma experts, it should be accepted in this Technology Appraisal that the STARGLO results are generalisable to the UK population. Refer to the Appendix to this response for a more detailed discussion on this topic.
3	**Uncertainty of clinical effectiveness of Glofit-GemOx in 2L transplant-ineligible DLBCL**

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	The Appendix to this response includes updated clinical data from the STARGLO study, with a clinical cut-off date (CCOD) of 1 May 2025. This provides an extra 14.5 months of follow-up data compared to the 16 February 2024 data in the original submission. Firstly, it should be noted that subgroup analyses, including the 2L subgroup, were pre-specified in STARGLO and prior number of therapies (1 vs ≥2), defining this subgroup was a stratification factor for randomisation, resulting in similar balance of baseline characteristics between treatment arms in the 2L subgroup compared to the whole ITT study population. This was not a post-hoc subgroup as stated in the Draft Guidance Document. The extended follow-up shows a hazard ratio for overall survival (OS) in the 2L subpopulation that has a 95% CI <1.0. Specifically, there is a 42% reduction in the risk of death with Glofit-GemOx compared with R-GemOx (stratified HR=0.58; 95% CI: 0.38, 0.89; nominal p-value of [redacted]). This more mature data directly addresses the committee's previous concern about the confidence interval for the OS hazard ratio crossing 1, thereby reducing the uncertainty in the estimates. Notably, a landmark analysis of OS by EOT response in the 2L Glofit-GemOx-treated subpopulation estimated that [redacted]% of patients who had a complete response (CR) at EOT would be alive 24 months after EOT, indicating potential for long-term remission in this subset of responders. Furthermore, the updated data reinforces the sustained PFS benefit of Glofit-GemOx seen in the earlier analyses. At the latest CCOD, the risk of a PFS event was consistently reduced by 59% in the Glofit-GemOx arm relative to the R-GemOx arm in both the whole population and the 2L subpopulation (stratified HR=[redacted]; 95% CI: [redacted], [redacted]; p-value = [redacted]). The median PFS in the 2L subpopulation treated with Glofit-GemOx was 20.4 months, compared with 5.5 months with R-GemOx. This robust and substantial PFS benefit, maintained with longer follow-up, further strengthens the clinical effectiveness profile of Glofit-GemOx as a 2L treatment regimen for patients who are ineligible for ASCT. Importantly, the safety data in the extended analysis confirms that the AE profiles for both Glofit-GemOx and R-GemOx remained consistent with those observed at the prior CCOD when all patients had completed study treatment. No new safety signals were identified in either the whole population or the 2L subpopulation, providing reassurance regarding the long-term safety of Glofit-GemOx. In summary, the latest data cut resolves uncertainty over the OS benefit of Glofit-GemOx in the 2L subpopulation and demonstrates the potential for long-term remission in these

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	patients. Given the urgent need for effective treatments in the 2L transplant-ineligible setting, Glofit-GemOx should be reimbursed for patients who are ineligible for transplant when their disease relapses after 1L therapy.
4	**Inclusion of Pola-BR as a comparator** Although the committee concludes that Pola-BR is a relevant comparator for the current appraisal, the company still has significant reservations about the inclusion of this regimen and how the results of this comparison are considered in decision making. The Draft Guidance highlights the company rationale for excluding this regimen in our base case submission; in addition to these points, the company would like to highlight the results of a retrospective analysis of UK real-world data for the bispecific antibodies (BsAb), glofitamab and epcoritamab, as 3L+ treatments for large B-cell lymphoma presented at the 2025 British Society of Haematology annual conference (3). This provided results for a multivariate analysis on the BsAb-treated evaluable patients (n=312) for progression-free survival (PFS) with several variables, including prior bendamustine treatment. This variable was statistically significantly associated with reduced PFS for the BsAbs with a hazard ratio of 1.68 (95% CI: 1.18-2.39; p=0.004). These data support the concerns highlighted in the British Society for Haematology (BSH) guidance that prior bendamustine exposure may adversely impact the efficacy of subsequent CD3xCD20 bispecific antibody (BsAb) therapy (2). The Draft Guidance also notes that clinical experts believed that “some people may have polatuzumab vedotin alone for a short time as a bridging option to third-line treatment such as CAR T-cell therapy”. The company wishes to clarify that when discussing the current use of this regimen with NHS England it was informed that there was no indication that Pola-BR was being used as a bridging therapy to CAR T-cell therapy, therefore this does not represent how this regimen is used in clinical practice. The company also acknowledges that the NHSE clinical lead for the Cancer Drugs Fund highlighted the use of Pola-BR is continuing to decrease. This is expected to continue as the uptake of Pola-R-CHP in the first line increases and advice from the BSH guidelines to avoid Pola-BR are disseminated to more loco-regional hospitals, where NHS clinical experts hypothesise where this regimen is still being used. As such, the relevance of Pola-BR as a comparator will continue to fall over time. Therefore, the company feels that these factors should be taken into account when considering the importance of Pola-BR and when interpreting the cost-effectiveness

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	analysis of Glofit-GemOx vs this regimen, in particular as part of a fully incremental analysis (see response row 6).
5	**Indirect treatment comparison for Pola-BR** The propensity score analysis of Glofit-GemOx vs Pola-BR provided prior to the first committee meeting has been updated to incorporate the updated data cut (CCOD3) from STARGLO. These analyses and curves from the IPTW analysis are included in the updated cost-effectiveness model and can be found in the supporting Appendix. The updated analysis shows a clear separation in the PFS and OS curves for Glofit-GemOx and Pola-BR at approximately 12 months, with the tail on the Glofit-GemOx plateauing further with longer follow-up, although [redacted]; This updated analysis has been incorporated into the updated cost-effectiveness model. It is important that these results are continued to be interpreted in context of the limitations of this analysis previously highlighted, namely: • Remaining imbalances between covariates of interest remain after subsetting the trial populations and further matching to align the 2L only populations of STARGLO and GO29365 • The small effective sample size for Pola-BR ([redacted]) indicates the data for this comparison has significant uncertainties. • Clinical expert opinion, which states that evidence from GO29365 study outperforms the experience of Pola-BR in clinical practice (real world evidence from UK patients with R/R DLBCL demonstrate that median PFS and OS for Pola-BR was 4.8 and 8.2 months respectively, compared to 9.2 months and 12 months in GO29365 (5)). The company notes that comparisons to Pola-BR in prior appraisals of R/R DLBCL were limited to matching-adjusted indirect treatment comparisons (5, 6), whereas the availability of individual patient data from the GO29365 means the company was able to conduct a more robust propensity score analysis for the current appraisal. Despite the limitations and uncertainties associated with this ITC, these results represent the best available evidence for the comparison of Glofit-GemOx vs Pola-BR. This should therefore be taken into account when considering the acceptable ICER for this comparison.
6	**Updated cost-effectiveness results**

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The economic analysis has been updated to reflect the most recent data cut (CCOD3) from STARGLO and to include the committee's preferred assumptions as highlighted in Section 3.14 of the Draft Guidance, specifically:

- Mortality reverts to the near general population (standardised mortality ratio of 1.09) after 6 years
- 15% of people in the Glofit-GemOx arm receive subsequent palliative care
- One-off end of life healthcare cost is applied

In addition, the company base case has been updated to align with the majority of the EAG's preferred assumptions for additional inputs given that these have a negligible impact on the ICER. This includes reducing the number of GemOx cycles to 6 from 8 in the original base case, applying progression resource costs as per the EAG model, and applying administration costs once per combination, not once per treatment.

The cost-effectiveness results for Glofit-GemOx vs R-GemOx and Pola-BR with the current approved PAS discount for both glofitamab and polatuzumab are presented in Table 1. Glofit-GemOx is shown to be cost-effective at a £20,000 threshold versus both comparators.

Table 1: Deterministic base-case cost-effectiveness results (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)	NMB at £20,000
Glofit-GemOx vs R-GemOx								
Glofit-GemOx	[redacted]	6.48	[redacted]					
R-GemOx	[redacted]	3.19	[redacted]	[redacted]	3.29	[redacted]	£6,862	[redacted]
Glofit-GemOx vs Pola-BR								
Glofit-GemOx	[redacted]	5.74	[redacted]					
Pola-BR	[redacted]	3.82	[redacted]	[redacted]	1.92	[redacted]	£15,612	[redacted]

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

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	The results from the probabilistic sensitivity analysis are consistent with the deterministic results, demonstrating that the base case results are robust and are likely to represent the average experience per person treated with Glofit-GemOx. As requested in the Draft Guidance, a fully incremental analysis is provided (see Appendix); however, the company has significant reservations with this approach and does not consider it to be appropriate for decision making. Based on the results of the fully incremental analysis, R-GemOx should be excluded as a comparator as it is dominated by Pola-BR, leaving Pola-BR as the sole comparator for consideration in this appraisal. The company feels strongly that the cost-effectiveness of Glofit-GemOx in comparison to this R-GemOx must be considered in decision making since clinical experts have confirmed this regimen represents the standard of care for the 2L treatment of transplant-ineligible R/R DLBCL patients due to concerns associated with the suitability of Pola-BR as a treatment in this setting. The relevance of Pola-BR has been debated not only in the current appraisal but in other R/R DLBCL appraisals (TA954, TA947) (6),(7). The company acknowledges that the use of Pola-BR in NHS clinical practice today is sufficient for the committee to consider it a relevant comparator for the current appraisal, however it should be noted that clinical experts consulted by NHS England stated they were surprised the usage of this regimen was so high, suggesting that this may be reflective of use in loco-regional hospitals rather than expert centres. Clinical experts from expert treatment centres consulted by the company concur with this view, stating that Pola-BR is not used in these settings due to: • Restrictions on prior exposure to polatuzumab vedotin following the approval of Pola-R-CHP in the first-line setting, and • Concerns regarding the negative impact that bendamustine has on subsequent CAR T-cell therapy and bispecific antibodies. ○ This concern is now acknowledged in the BSH guidelines for R/R DLBCL, published in May 2025, which states that “Pola-BR should be avoided for patients who may be suitable for third-line CAR T-cell therapy given that bendamustine exposure prior to apheresis is associated with increased risk of CAR T-cell manufacturing failure and inferior outcomes after CAR T-cell therapy” (2). The company also acknowledges that the NHS England representative stated that the use of Pola-BR has declined in the first four months of 2025. The company expects this

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	trend to continue as the uptake of Pola-R-CHP increases across the country and the recommendations in the BSH guidelines around the avoidance of Pola-BR are followed at a loco-regional level. As such, the company feels that a pairwise comparison for both R-GemOx and Pola-BR should be considered in decision making rather than the fully incremental analysis as this would factor in the most-relevant comparator for this population.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, and all information submitted as '[redacted]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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2. Chaganti S, Fox CP, Maybury BD, Burton C, Barrington SF, Illidge T, et al. Management of relapsed or refractory large B-cell lymphoma: A British Society for Haematology Guideline. British journal of haematology. 2025.
3. Haynes E TW, Wilson, W et al.,, editor Real World Experience of Glofitamab and Epcoritamab: A Retrospective U.K. Multicentre Analysis. BSH 65th AGM; 2025.
4. Held G, Houot R, Avigdor A, André M, Dabrowska-Iwanicka A, Jaeger U, et al. Niveau, a Phase 3 Study for Pts with B- or T-Cell Aggressive Non-Hodgkin Lymphoma in First Relapse or Progression Not Eligible for High-Dose Chemotherapy (HDT), Testing Nivolumab in Combination with Gemcitabine, Oxaliplatin (GemOx), Plus Rituximab (R) in Case of B-Cell Lymphoma. Blood. 2019;134:5311.
5. National Institute for Health and Care Excellence. TA954: Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [TA954] 2024 [updated 6 March 2024. Available from: https://www.nice.org.uk/guidance/ta954.
6. National Institute for Health and Care Excellence. TA947: Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic treatments. 2024.
7. National Institute for Health and Care Excellence. TA954: Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments. 2024.

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Appendix to Draft Guidance Response

August 2025

File name	Version	Contains confidential information	Date
ID6202_GlofitGemOx_RR DLBCL_DG Response Appendix_[CON]	1.0	Yes	19 August 2025

Contents

Tables and Figures

Draft Guidance Response Appendix

1. Generalisability of STARGLO to the European population

As a multiregional, centrally randomised, controlled phase III trial, the STARGLO study was adequately powered to assess the overall survival (OS) benefit of Glofit-GemOx versus R-GemOx in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not candidates for transplant. At the primary analysis with data from the first clinical cut-off date (CCOD1: 29 March 2023), Glofit-GemOx demonstrated statistically significant and clinically meaningful improvement over R-GemOx on the basis of OS, as well as progression-free survival (PFS) and complete response (CR) rate assessed by an Independent Review Committee (IRC). This robust benefit in primary and key secondary endpoints continued to be observed at the time of the updated analysis (CCOD2: 16 February 2024) and the recent analysis with a median of 3 years' follow-up (CCOD3: 1 May 2025) (See Section 2).

A directionally consistent treatment effect for Glofit-GemOx for OS and PFS was observed in the majority of the subgroups, including clinically relevant stratified subgroups. Relevant to the current Technology Appraisal, the subgroup based on the stratification factor, number of prior lines of therapy (1 vs. ≥2) was reflective of the outcomes in the intention-to-treat (ITT) population; at the updated analysis (CCOD2), the OS hazard ratio (HR) in the second line (2L) subpopulation was 0.67 (95% CI: 0.41, 1.07; p=0.092) and 0.58 (95% CI: 0.38, 0.89; p=[redacted]) at CCOD3.

However, potential inconsistencies were observed in the unstratified subgroups of race and enrolment region when compared to the overall ITT population. Interpretation of exploratory subgroup analysis results is limited given the small sample sizes of some of the subgroups relative to the ITT population, the 2:1 randomisation and the wide HR confidence intervals reflecting a high uncertainty in the HR estimates. In addition, race and enrolment region were not stratification factors for randomisation and, as a result, there are imbalances in baseline characteristics that confound the comparison of Glofit-GemOx with R-GemOx within these subgroup analyses.

A high association between pre-specified subgroups by race and geographic region was observed (Update CSR GO41944, Report No. 1130634, Table 45). In the Europe and North America subgroups, the majority of patients enrolled were of the White race, while in the rest of the world (RoW) subgroup (China, Korea, Australia, Taiwan), the majority of patients enrolled were of the Asian race. In addition, PK analyses for glofitamab exposure and exposure-response data did not vary significantly by patient race, and there was high

consistency between the results of the additional exploratory post-hoc analysis by race and region (Update CSR GO41944, Report No. 1130634, Section 5.1.5). Importantly, given the mechanism of action of glofitamab, the similarity in glofitamab pharmacology across racial groups, and data on glofitamab monotherapy across race subgroups, there does not appear to be a biological reason that outcomes to glofitamab-based therapy would differ by race. At an advisory board organised by the company, UK lymphoma experts agreed with this position (1). Therefore, it is likely that the potential inconsistencies observed in the OS HR by race were driven by potential inconsistencies in geographic region rather than by the race itself.

There has been extensive discussion with the EMA regarding the generalisability of the STARGLO study results to the European population. Several post-hoc statistical analyses were supplied to the agency to explain the potential differences in the regional subgroups and support generalisability of outcomes in the ITT population of STARGLO to the European population. The full response to the EMA is provided with the Draft Guidance Response.

The application for variation of the UK Marketing Authorisation was submitted on 31 March to the MHRA via the International Recognition Procedure with the EMA as reference regulator. Extension of the Marketing Authorisation to include the new indication for Glofit-GemOx was approved by the MHRA on 16 July 2025, thus accepting that the results from the ITT population in STARGLO are applicable to the UK NHS population.

In addition to this endorsement by the MHRA, the British Society for Haematology (BSH) has already recommended the use of Glofit-GemOx in for the treatment of LBCL after first relapse in patients who are ineligible for HDT-Auto based on the level 1A evidence from the ITT population in the STARGLO trial (2). This highlights that key lymphoma experts recognise the results from the ITT population in the STARGLO study as generalisable to the NHS population, with endorsement from the BSH.

1.1 Study population

Baseline demographic and disease characteristics between the European subgroup and the overall ITT population in STARGLO were broadly comparable, although some differences were noted

- **Age**: Patients in the European subgroup were slightly older, with a median age of 71 years, compared to 68 years in the overall ITT population. This difference in age did not appear to translate into a difference in OS benefits, as all age subgroups in the ITT population showed an OS benefit for Glofit-GemOx over R-GemOx.

- **Race**: The European subgroup was predominantly White (76.1%), whereas the overall ITT population was a mix of White (42%) and Asian (50%) patients.
- **Ann Arbor Stage**: The European subgroup had a slightly higher percentage of patients with Ann Arbor Stage III/IV disease (75%) compared to the overall ITT population (58.4%).
- **Prior CAR-T Therapy**: A slightly higher proportion of patients in the European subgroup had received prior CAR-T therapy (13.6%) compared to the overall ITT population (7.7%).
- **Refractory Status**: Conversely, the ITT population (excluding the European subgroup) generally had a higher percentage of patients who were refractory to prior therapies than the European subgroup, including:
    - Refractory to last therapy (64.5% vs. 52.3% in Europe).
    - Primary refractory disease or relapse within 12 months after first-line therapy (75.8% vs. 63.6% in Europe).
    - Double refractory disease to any prior anti-CD20 and anthracycline-based regimen (58.6% vs. 48.9% in Europe).

Additionally, the baseline demographic and disease characteristics, as well as treatment outcomes of STARGLO, were compared with those from the **Niveau study** (3), a recent phase III study conducted almost exclusively in European countries within the same patient population with R-GemOx as a control arm.

- The baseline demographic and disease characteristics of the ITT population of STARGLO were similar to the study population of the Niveau study.
- Comparison of the 1-year and 2-year event-free rates for PFS and OS from both studies showed overall comparable results across the Niveau R-GemOx arm and the GO41944 R-GemOx arm (ITT and European subgroup).

1.2 ITT results

The company performed thorough post-hoc exploratory subgroup evaluation using multiple methods to examine confounding factors. In the European subgroup, NALTs and COVID-19 were identified as the primary potential confounding factors that may have led to a higher OS HR compared to the ITT population.

In the European subgroup, NALT was administered more frequently in the R-GemOx arm compared to the Glofit-GemOx arm, with 57.7% of patients in the R-GemOx arm receiving at least one NALT, compared to 29.0% in the Glofit-GemOx arm. This pattern was consistently observed across all regional subgroups. However, regional differences in the type of NALT administered were observed. Notably, the European subgroup had a higher number of patients receiving chimeric antigen receptor T-cell (CAR-T) therapy as NALT, particularly in the R-GemOx arm:

- In the R-GemOx arm in Europe, the most frequently used NALT was CAR-T therapy, followed by CD20-CD3 bispecifics and other immunotherapies. Efficacious NALTs (CAR-T, CD19 immunotherapy, CD20-CD3 bispecifics) accounted for 46.3% of all administered NALTs in this arm.
- In contrast, in the Glofit-GemOx arm in Europe, the most frequently used NALT was chemotherapy, and the usage of efficacious NALTs was lower (16.2% of total NALTs) compared to the R-GemOx arm.

To adjust for the confounding effect of the imbalance in effective NALT use, two specific post-hoc exploratory analyses were performed.

- An event-free survival (EFS; time to progression, death, or initiation of NALT) analysis was conducted which showed improved HRs favouring Glofit-GemOx compared to R-GemOx. This pattern was observed in the ITT population and the European subgroup. This improvement in HRs for EFS suggests that when treatment failures, including the need for subsequent NALT, were considered as an event, Glofit-GemOx demonstrated a more consistent benefit over R-GemOx. This indicates a potential bias in favor of R-GemOx in the original PFS analysis due to informative censoring, as earlier and more frequent NALT utilisation disproportionately affected the R-GemOx arm.
- An inverse probability of censoring weighting (IPCW) method was utilised to estimate the treatment effect on both OS and PFS after adjusting for the impact of NALT. The IPCW-adjusted OS and PFS HRs for the European subgroup were numerically lower compared to the original unadjusted HRs and results in the European subgroup were comparable to the findings in the overall ITT population.

The STARGLO study was conducted during the COVID-19 pandemic, prior to the widespread usage of effective COVID-19 anti-viral therapies and during varying preventive COVID-19 restrictions across countries. Three pre-planned sensitivity analyses were performed including censoring in the OS analysis for patients who died from COVID-19 or

had a COVID-19 adverse event. These analyses resulted in lower OS HRs compared to the naïve comparison in the European subgroup, whilst OS in the Rest of World and North American regional subgroups remained unchanged.

Post-hoc multivariate analyses were conducted for OS. Variables adjusted for in this model, based on univariate analyses, included the two study stratification factors (number of previous lines of systemic therapy (1 vs. ≥2) and outcome of last systemic therapy (relapsed vs. refractory)), sex, IPI score, bulky disease of ≥ 10 cm, sum of products of diameters (SPD) and enrolment region. The OS HR for the ITT population after adjusting for these variables remained consistent with that observed at CCOD2, with the adjusted OS HR 0.63 (95% CI: 0.44, 0.90) compared with the unstratified HR in the updated analysis was 0.62 (95% CI: 0.44, 0.89).

With the overall positive and statistically persuasive primary results and the lack of a pharmacological / biological rationale why the effect should be smaller in the European population, the observed effects in the ITT population should be applicable to Europe.

Taking also into account the results of multivariate analyses to account for the contribution of multiple potentially prognostic factors the CHMP concluded that a benefit in a European context was satisfactorily substantiated. As a result, on 27 February 2025, the CHMP issued positive opinion recommending the variation of the marketing authorisation to include the use of Glofit-GemOx for the treatment of adult patients with R/R DLBCL NOS who are ineligible for autologous transplant. The European Commission approved this indication for Glofit-GemOx on 14 April 2025. Subsequently, the European Society for Medical Oncology (ESMO) has published guidelines on the treatment of lymphomas, which includes recommendation of Glofit-GemOx for this indication, based on the Level 1A evidence from the STARGLO study (4).

2. Updated clinical effectiveness data from STARGLO

The data presented in this section is based on the latest clinical cut-off date (CCOD3), representing an additional 14.5 months of clinical follow-up from CCOD2 presented in the Company submission. For ease of comparison, data derived from CCOD2 is tabulated alongside data from CCOD3.

2.1 Efficacy

2.1.1 Primary efficacy endpoint

2.1.1.1 Overall survival

The OS benefit in the Glofit-GemOx arm for the whole ITT population was maintained at CCOD3 (median follow-up of 35.1 months), with a 40% reduction in the risk of death in patients treated with Glofit-GemOx compared with patients treated with R-GemOx: stratified HR=0.60 (95% CI: 0.43, 0.83; log-rank p-value of [redacted]) (Table 1; Figure 1). Median OS in the Glofit-GemOx and R-GemOx arms was 25.5 months (95% CI: 17.0, NE) and 12.5 months (95% CI: 7.9, 16.5), respectively.

In the 2L subpopulation, the OS benefit of Glofit-GemOx improved in magnitude with median follow-up of 34.9 months compared to CCOD2, with a 42% reduction in the risk of death compared with R-GemOx and 95% CI <1.00 (stratified HR=0.58; 95% CI: 0.38, 0.89; log-rank nominal p-value of [redacted]). Median OS was not reached (95% CI (months): 22.8, NE) in the Glofit-GemOx arm and was 14.4 months (95% CI: 10.3, 26.8) in the R-GemOx arm (Table 1; Figure 2). At 24 months, estimated OS rates were 57.0% (95% CI: 47.7%, 66.2%) in the Glofit-GemOx arm and 37.9% (95% CI: 24.6%, 51.3%) in the R-GemOx arm. At 36 months, estimated OS rates were 54.6% (95% CI: 45.2%, 64.0%) in the Glofit-GemOx arm and 30.8% (95% CI: 17.7%, 44.0%) in the R-GemOx arm, albeit with low numbers at risk at this stage in the Kaplan-Meier analysis.

Table 1: Summary of OS data (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
CCOD2 (16 Feb 2024) (median follow-up: 20.7 months)		
Median, months (95% CI)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
Stratified HR (95% CI)	0.62 (0.43, 0.88)	
p-value* (log-rank)	0.006	
CCOD3 (1 May 2025) (median follow-up: 35.1 months)		
Median, months (95% CI)	12.5 (7.9, 16.5)	25.5 (17.0, NE)
Stratified HR (95% CI)	0.60 (0.43, 0.83)	
p-value* (log-rank)	[redacted]	
2L subpopulation	**n=57**	**n=115**
CCOD2 (16 Feb 2024) (median follow-up: 20.2 months)		

Median, months (95% CI)	15.7 (10.3, NE)	NE (20.4, NE)
Stratified HR (95% CI)	0.67 (0.41, 1.07)	
p-value* (log-rank)	0.092	
CCOD3 (1 May 2025) (median follow-up: 34.9 months)		
Median, months (95% CI)	14.4 (10.3, 26.8)	NE (22.8, NE)
Stratified HR (95% CI)	0.58 (0.38, 0.89)	
p-value* (log-rank)	[redacted]	

*p-values are descriptive.
Source: STARGLO_updated_CSR and data on file

Figure 1: Kaplan-Meier plot of OS, whole population (STARGLO; CCOD3)

[redacted]Source: Data on file

Figure 2: Kaplan-Meier plot of OS, 2L subpopulation (STARGLO; CCOD3)[redacted]

[redacted]Source: Data on file

2.1.2 Key secondary efficacy endpoints

2.1.2.1 Progression-free survival

At CCOD3 (median follow-up of 26.3 months), the PFS benefit of Glofit-GemOx in the whole (ITT) population was maintained, with a 59% decrease in risk of progression or death compared with R-GemOx (stratified HR=0.41; 95% CI: 0.29, 0.57; log-rank p-value [redacted]). Median PFS was 14.4 months (95% CI: 8.8, 27.4) in the Glofit-GemOx arm and 3.3 months (95% CI: 2.3, 5.6) in the R-GemOx arm (Table 2; Figure 3).

In the 2L subpopulation (median follow-up of 26.3 months), the risk of a PFS event was [redacted] in the Glofit-GemOx arm relative to the R-GemOx arm (stratified HR=[redacted]; 95% CI: [redacted], [redacted]; log-rank p-value = [redacted]), consistent with the whole population. Median PFS was 20.4 months (95% CI: 9.2, NE) in the Glofit-GemOx arm and 5.5 months (95% CI: 2.6, 9.7) in the R-GemOx arm (Table 2; Figure 4) and the 12-month PFS rates were [redacted] (95% CI: [redacted]) in the Glofit-GemOx arm and [redacted] (95% CI: [redacted]) in the R-GemOx arm. Estimated 24-month PFS rates were [redacted]% (95% CI: [redacted]%, [redacted]%) in the Glofit-GemOx arm and [redacted]% (95% CI: [redacted]%, [redacted]%) in the R-GemOx arm.

Table 2: Summary of IRC-assessed PFS data (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
CCOD2 (16 Feb 2024) (median follow-up: 15.7 months)		
Median, months (95% CI)	3.6 (2.5, 7.1)	13.8 (8.7, 20.5)
Stratified HR (95% CI)	0.40 (0.28, 0.57)	
p-value* (log-rank)	<0.000001	
CCOD3 (1 May 2025) (median follow-up: 26.3 months)		
Median, months (95% CI)	3.3 (2.3, 5.6)	14.4 (8.8, 27.4)
Stratified HR (95% CI)	0.41 (0.29, 0.57)	
p-value* (log-rank)	[redacted]	

2L subpopulation	n=57	n=115
CCOD2 (16 Feb 2024) (median follow-up: 15.5 months)		
Median, months (95% CI)	5.6 (3.0, 13.1)	20.4 (9.2, NE)
Stratified HR (95% CI)	0.41 (0.25, 0.67)	
p-value* (log-rank)	0.0002	
CCOD3 (1 May 2025) (median follow-up: 26.3 months)		
Median, months (95% CI)	5.5 (2.6, 9.7)	20.4 (9.2, NE)
Stratified HR (95% CI)	[redacted]	
p-value* (log-rank)	[redacted]	

*p-values are descriptive.
Source: STARGLO_updated_CSR and data on file

Figure 3: Kaplan-Meier plot of IRC-assessed PFS*, whole population (STARGLO; CCOD3)

[redacted]

*censored before NALT
Source: **Data on file**

Figure 4: Kaplan-Meier plot of IRC-assessed PFS*, 2L subpopulation (STARGLO; CCOD3)[redacted]

[redacted]

*censored before NALT
Source: Data on file

2.1.2.2 Complete response rate

At CCOD3, the number of patients who achieved a complete response in each treatment arm remained the same as at CCOD2. This is to be expected as all patients had completed study treatment at CCOD2.

2.1.2.3 Duration of complete response

At CCOD3, with median follow-up of [redacted] months, median DOCR was [redacted] in the Glofit-GemOx treated patients with CR (n= [redacted]; 95% CI: [redacted], [redacted]) and was [redacted] (95% CI: [redacted], [redacted]), in the R-GemOx treated patients with a CR (n= [redacted]), with an HR of [redacted] (95% CI: [redacted], [redacted]) and an unstratified log-rank p-value of [redacted] (Table 3; Figure 5).

In the 2L subpopulation, median DOCR was [redacted] in the Glofit-GemOx treated patients with CR (n=[redacted]; 95% CI: [redacted], [redacted]) [redacted] in R-GemOx treated patients with CR (n=[redacted]; 95% CI: [redacted], [redacted]), with an HR of [redacted] (95% CI: [redacted], [redacted]) and an unstratified log-rank p-value of [redacted] (Table 3; Figure 6).

Table 3: Summary of IRC-assessed DOCR (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population (No. of patients with CR)	**n=23**	**n=107**

CCOD2 (16 Feb 2024)		
Median, months (95% CI)	24.2 (6.9, NE)	NE (NE, NE)
Unstratified HR (95% CI)	0.59 (0.25, 1.35)	
p-value* (log-rank)	0.2040	
CCOD3 ([redacted])		
Median, months (95% CI)	[redacted]	[redacted]
Unstratified HR (95% CI)	[redacted]	
p-value* (log-rank)	[redacted]	
2L subpopulation	**n=16**	**n=73**
CCOD2 (16 Feb 2024)		
Median, months (95% CI)	NE (6.5, NE)	NE (NE, NE)
Unstratified HR (95% CI)	0.57 (0.21, 1.54)	
p-value* (log-rank)	0.2574	
CCOD3 ([redacted])		
Median, months (95% CI)	[redacted]	[redacted]
Unstratified HR (95% CI)	[redacted]	
p-value* (log-rank)	[redacted]	

*p-values are descriptive.
Source: STARGLO_updated_CSR and data on file

Figure 5: Kaplan-Meier plot of IRC-assessed DOCR, whole population (STARGLO; CCOD3)

[redacted]Source: Data on file

Figure 6: Kaplan-Meier plot of IRC-assessed DOCR, 2L subpopulation (STARGLO; CCOD3)

[redacted]Source: Data on file

2.1.3 Overall survival by end-of-treatment response

A landmark survival analysis was conducted for Glofit-GemOx-treated patients in the 2L subpopulation based on their end-of-treatment (EOT) response at CCOD3. In the Glofit-GemOx arm, [redacted] patients had a complete response, [redacted] patients had no response and [redacted] patients had a partial response at EOT. Of the [redacted] patients who had a complete response at EOT, the estimated 24-month OS rate was [redacted]% (95% CI: [redacted]%, [redacted]%) (Figure 7).

Figure 7: Kaplan-Meier plot of OS by end-of-treatment response, 2L Glofit-GemOx-treated subpopulation (STARGLO; CCOD3)[redacted]

[redacted]

Source: Data on file

2.2 Subsequent treatments

At CCOD3, the proportion of patients receiving at least one NALT [redacted]

(Table 4).

In the 2L subpopulation, the total number of patients receiving NALT (new anti-lymphoma therapy) continued to be lower in the Glofit-GemOx arm ([redacted]/115 patients [[redacted]%]) compared to the R-GemOx arm ([redacted]/57 [[redacted]%]) (Table 4).

The most frequently administered NALTs in the Glofit-GemOx and R-GemOx arms for the 2L subpopulation, respectively, were:

- CAR T-cell therapy: [redacted]% vs. [redacted]%
- Chemotherapy (non-intensive): [redacted]% vs. [redacted]%
- Chemotherapy (intensive): [redacted]% vs. [redacted]%
- CD19 immunotherapy: [redacted]% vs. [redacted]%
- CD20-CD3 bispecific antibody: [redacted]% vs. [redacted]%
- Immunotherapy (other): [redacted].0% vs. [redacted]%
- Other (systemic): [redacted]% vs. [redacted]%
- PD-1 inhibitor: [redacted]% vs. [redacted]%
- Stem cell transplant: [redacted]% vs. [redacted]%

Table 4: Overview of NALT (STARGLO)

	R-GemOx	Glofit-GemOx
Whole population	**n=91**	**n=183**
CCOD2 (16 Feb 2024)		
Patients with ≥1 NALT, n (%)	52 (57.1)	46 (25.1)
Total patients (n [%]) with ≥ of:		
CAR T-cell therapy	12 (13.2)	8 (4.4)
CD19 immunotherapy	6 (6.6)	9 (4.9)
CD20-CD3 bispecific antibody	15 (16.5)	2 (1.1)
Chemotherapy (non-intensive)	15 (16.5)	16 (8.7)
Chemotherapy (intensive)	10 (11.0)	7 (3.8)
Immunotherapy (other)	9 (9.9)	13 (7.1)
Other (procedure)	14 (15.4)	6 (3.3)
Other (systemic)	6 (6.6)	3 (1.6)
PD-1 inhibitor	4 (4.4)	4 (2.2)
Stem cell transplant	1 (1.1)	2 (1.1)
CCOD3 ([redacted])		
Patients with ≥1 NALT, n (%)	[redacted]	[redacted]

Total patients (n [%]) with ≥ of:		
CAR T-cell therapy	[redacted]	[redacted]
CD19 immunotherapy	[redacted]	[redacted]
CD20-CD3 bispecific antibody	[redacted]	[redacted]
Chemotherapy (non-intensive)	[redacted]	[redacted]
Chemotherapy (intensive)	[redacted]	[redacted]
Immunotherapy (other)	[redacted]	[redacted]
Other (procedure)	[redacted]	[redacted]
Other (systemic)	[redacted]	[redacted]
PD-1 inhibitor	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]
2L subpopulation	**n=57**	**n=115**
CCOD2 (16 Feb 2024)		
Patients with ≥1 NALT, n (%)	[redacted]	[redacted]
Total patients (n [%]) with ≥ of:		
CAR T-cell therapy	[redacted]	[redacted]
CD19 immunotherapy	[redacted]	[redacted]
CD20-CD3 bispecific antibody	[redacted]	[redacted]
Chemotherapy (non-intensive)	[redacted]	[redacted]
Chemotherapy (intensive)	[redacted]	[redacted]
Immunotherapy (other)	[redacted]	[redacted]
Other (procedure)	[redacted]	[redacted]
Other (systemic)	[redacted]	[redacted]
PD-1 inhibitor	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]
CCOD3 ([redacted])		
Patients with ≥1 NALT, n (%)	[redacted]	[redacted]
Total patients (n [%]) with ≥ of:		
CAR T-cell therapy	[redacted]	[redacted]
CD19 immunotherapy	[redacted]	[redacted]
CD20-CD3 bispecific antibody	[redacted]	[redacted]
Chemotherapy (non-intensive)	[redacted]	[redacted]
Chemotherapy (intensive)	[redacted]	[redacted]
Immunotherapy (other)	[redacted]	[redacted]
Other (procedure)	[redacted]	[redacted]
Other (systemic)	[redacted]	[redacted]
PD-1 inhibitor	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]

Source: Updated CSR, data on file

2.3 Safety

The adverse event profiles of Glofit-GemOx and R-GemOx at CCOD3 [redacted] CCOD2 for both the whole population and the 2L subpopulation (Table 5).

Table 5: Overview of adverse events (safety evaluable population; STARGLO)

	R-GemOx	Glofit-GemOx (any treatment exposed)	Glofit-GemOx (glofitamab-exposed)
Whole population	**n=88**	**n=180**	**n=172**

CCOD (16 Feb 2024)			
Any AE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	84 (95.5%) 58 (65.9%)	180 (100%) 149 (82.8%)	
SAE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	15 (17.0%) 7 (8.0%)	98 (54.4%) 62 (34.4%)	
Grade 3+ AEs, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	36 (40.9%) 20 (22.7%)	140 (77.8%) 85 (47.2%)	
Grade 5 AEs, n (%)	4 (4.5%)	15 (8.3%)	
AE leading to treatment withdrawal, n (%)	11 (12.5%)	48 (26.7%)	
AE related to rituximab/glofitamab leading to withdrawal from rituximab/glofitamab	3 (3.4%)	13 (7.2%)	
AE related to rituximab/glofitamab leading to dose interruption of rituximab/glofitamab	9 (10.2%)	43 (23.9%)	
CCOD ( )			
Any AE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin			
SAE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin			
Grade 3+ AEs, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin			
Grade 5 AEs, n (%)			
AE leading to treatment withdrawal, n (%)			
AE related to rituximab/glofitamab leading to withdrawal from rituximab/glofitamab			
AE related to rituximab/glofitamab leading to dose interruption of rituximab/glofitamab			
2L subpopulation	**n=55**	**n=112**	**n=108**
CCOD (16 Feb 2024)			
Any AE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	54 (98.2%)	112 (100%)	
SAE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin			
Grade 3+ AEs, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	23 (41.8%)	85 (75.9%)	
Grade 5 AEs, n (%)	1 (1.8%)	9 (8.0%)	
AE leading to treatment withdrawal, n (%)			

AE related to rituximab/glofitamab leading to withdrawal from rituximab/glofitamab	[redacted]	[redacted]	[redacted]
AE related to rituximab/glofitamab leading to dose interruption of rituximab/glofitamab	[redacted]	[redacted]	[redacted]
CCOD ([redacted])			
Any AE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	[redacted]	[redacted]	[redacted]
SAE, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	[redacted]	[redacted]	[redacted]
Grade 3+ AEs, n (%) related to rituximab/glofitamab related to obinutuzumab related to gemcitabine related to oxaliplatin	[redacted]	[redacted]	[redacted]
Grade 5 AEs, n (%)	[redacted]	[redacted]	[redacted]
AE leading to treatment withdrawal, n (%)	[redacted]	[redacted]	[redacted]
AE related to rituximab/glofitamab leading to withdrawal from rituximab/glofitamab	[redacted]	[redacted]	[redacted]
AE related to rituximab/glofitamab leading to dose interruption of rituximab/glofitamab	[redacted]	[redacted]	[redacted]

Source: STARGLO_updated_CSR and data on file

2.4 Discussion

The updated clinical effectiveness data from the STARGLO study, with a later CCOD of 1 May 2025, directly addresses uncertainties in the clinical data highlighted in the Draft Guidance. It should first be noted that subgroup analyses, including the 2L subgroup, were pre-specified in STARGLO, and prior number of therapies (1 vs ≥2), defining this subgroup was a stratification factor for randomisation. This resulted in a similar balance of baseline characteristics between treatment arms in the 2L subgroup compared to the whole ITT study population. This was not a post-hoc subgroup as stated in the Draft Guidance Document. The extended follow-up, representing an additional 14.5 months of data, shows a hazard ratio for OS in the 2L subpopulation that has a 95% CI <1.0. Specifically, there is a 42% reduction in the risk of death with Glofit-GemOx compared with R-GemOx (stratified HR=0.58; 95% CI: 0.38, 0.89; nominal p-value of [redacted]). This more mature data directly addresses the committee's previous concern about the confidence interval for the OS hazard ratio crossing 1, thereby reducing the uncertainty in the estimates. Notably, a landmark analysis of OS by EOT response in the 2L Glofit-GemOx-treated subpopulation estimated that [redacted]% of patients who had a complete response at EOT would be alive 24 months after EOT, indicating potential for long-term remission in this subset of responders.

Furthermore, the updated data reinforces the sustained PFS benefit of Glofit-GemOx seen in the earlier analyses. At CCOD3, the risk of a PFS event was consistently reduced by [redacted]% in

the Glofit-GemOx arm relative to the R-GemOx arm in both the whole population and the 2L subpopulation (stratified HR=[redacted]; 95% CI: [redacted], [redacted]; p-value = [redacted]). The median PFS in the 2L subpopulation treated with Glofit-GemOx was 20.4 months, compared with 5.5 months with R-GemOx. This robust and substantial PFS benefit, maintained with longer follow-up, further strengthens the clinical effectiveness profile of Glofit-GemOx as a 2L treatment regimen for patients who are ineligible for ASCT.

Importantly, the safety data from CCOD3 confirms that the AE profiles for both Glofit-GemOx and R-GemOx remained consistent with those observed at the prior CCOD when all patients had completed study treatment. No new safety signals were identified in either the whole population or the 2L subpopulation, providing reassurance regarding the long-term safety of Glofit-GemOx.

3. Updated Pola-BR indirect treatment comparison

The company acknowledges that the use of Pola-BR in NHS clinical practice today is sufficient for the committee to consider it a relevant comparator for the current appraisal; however, the company reiterates its position that the dwindling use of this regimen and concerns regarding bendamustine prior exposure on the effectiveness of subsequent treatments (as highlighted in clinical guidelines) should be taken into account when interpreting the results versus Pola-BR.

Nevertheless, the propensity score analysis of Glofit-GemOx vs Pola-BR provided prior to the first committee meeting has been updated to incorporate the updated data cut (CCOD3) from STARGLO. These analyses and curves from the IPTW analysis are included in the updated cost-effectiveness model.

3.1 Overall survival

A summary of the PSA results for OS is provided in Table 6, and the Kaplan-Meier curves are provided for the unadjusted, IPTW, and full matched samples in Figure 8, Figure 9, and Figure 10, respectively. Note that the risk tables in the adjusted Kaplan-Meier curves show the sum of weights, which is different from ESS and should not be interpreted.

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

Table 6: Summary of PSA results for OS

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]

IPTW	[redacted]
IPTW with multiple imputation	[redacted]
Full matching	[redacted]

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

Figure 8: Kaplan-Meier plot of OS for the unadjusted sample

[redacted]

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

Figure 9: Kaplan-Meier plot of OS for the IPTW sample

[redacted]

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IPT, inverse probability of treatment; IPTW, inverse probability of treatment weighting; OS, overall survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.
Note: The risk table shows sum of weights which is different from ESS and should not be interpreted.

Figure 10: Kaplan-Meier plot of OS for the full matched sample

[redacted]

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

3.2 Progression-free survival

A summary of the PSA results for PFS IRC-assessed is provided in Table 7, and the Kaplan-Meier curves are provided for the unadjusted, IPTW, and full matched samples in Figure 11, Figure 12, and Figure 13, respectively. The PFS definition that censors for NALT in both trials was used.

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

Table 7: Summary of PSA results for (IRC-assessed) PFS

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

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

HRs presented for the comparison of Glofit-GemOx versus Pola-BR.
HRs <1 favour Glofit-GemOx.

Figure 11: Kaplan-Meier plot of PFS for the unadjusted sample

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

Figure 12: Kaplan-Meier plot of PFS for IPTW sample

Abbreviations: Glofit-GemOx, glofitamab + gemcitabine + oxaliplatin; IPT, inverse probability of treatment; IPTW, inverse probability of treatment weighting; PFS, progression-free survival; Pola-BR, polatuzumab vedotin + bendamustine + rituximab.
Note: The risk table shows sum of weights which is different from ESS and should not be interpreted. estimand is ATE.

Figure 13: Kaplan-Meier plot of PFS for the full matched sample

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

3.3 Propensity score analysis: conclusions and limitations

The updated analysis with data from CCOD3 shows a clear separation in the PFS and OS curves for Glofit-GemOx and Pola-BR at approximately 12 months, with the tail on the Glofit-GemOx plateauing further with longer follow-up.

It is important that these results are continued to be interpreted in context of the limitations of this analysis previously highlighted, namely:

- Remaining imbalances between covariates of interest remain after subsetting the trial populations and further matching to align the 2L only populations of STARGLO and GO29365,
- The small effective sample size for Pola-BR indicates the data for this comparison has significant uncertainties.
- Clinical expert opinion, which states that evidence from GO29365 study outperforms the experience of Pola-BR in clinical practice (real world evidence from UK patients with R/R DLBCL demonstrate that median PFS and OS for Pola-BR was 4.8 and 8.2 months respectively, compared to 9.2 months and 12 months in GO29365 (5)).

The company notes that comparisons to Pola-BR in prior appraisals of R/R DLBCL were limited to matching-adjusted indirect treatment comparisons, whereas the availability of individual patient data from the GO29365 means the company was able to conduct a more robust propensity score analysis for the current appraisal. Despite the limitations and uncertainties associated with this ITC, these results represent the best available evidence for the comparison of Glofit-GemOx vs Pola-BR. This should therefore be taken into account when considering the acceptable ICER for this comparison.

4. Updated cost-effectiveness results

4.1 Model assumptions and inputs

The economic analysis has been updated to consider the committee's preferred assumptions as highlighted in Section 3.14 of the draft guidance, specifically:

- Mortality reverts to the near general population (standardised mortality ratio of 1.09) after 6 years
- 15% of people in the Glofit-GemOx arm receive subsequent palliative care
- One-off end of life healthcare cost is applied

In addition, the company base case has been updated to align with the majority of the EAG's preferred assumptions for additional inputs given that these have a negligible impact on the ICER. A summary of the updated model base case assumptions is provided in Table 8.

As was the case with the analysis comparing Glofit-GemOx with Pola-BR based on CCOD2, all statistical distributions continue to demonstrate a poor fit to the updated Kaplan-Meier data. As such, the log-normal distribution continues to be applied to tail of the Kaplan-Meier curves to reflect estimates of PFS and OS from the ITC at the early stages of the model. However, with further follow up and more robust data for the Glofit-GemOx arm, the PFS and OS curves for this arm plateau later, therefore in the updated analysis the log-normal distribution is applied at 25 months for both PFS and OS, with approximately 30% and 50% of patients remaining at risk, respectively. A scenario in which the distribution is applied at 20 months as per the original submitted analysis is provided.

Table 8: Summary of variables applied in the economic model

Variable	Original company model base case	Updated company model base case	Rationale
Cure point for background mortality to revert to general population	3 years	6 years	Committee preference
Proportion of pts in Glofit-GemOx arm receiving palliative care	15%	15%	Committee preference
End-of-life care costs	Included in weekly healthcare resource-use costs	One-off cost	Committee preference
Number of cycles of GemOx	8	6	Align with EAG model as negligible impact on ICER and corresponds to mean number of cycles received in STARGLO
Utilities	ITT population from STARGLO	2L population from STARGLO	Align with EAG model as negligible impact on ICER
Progression resource use costs	7.9% receiving MUGA, no echocardiogram use	50% receive echocardiogram; 0% MUGA	Align with EAG model as negligible impact on ICER; clinical experts agree this is reasonable
Administration costs	Applied for each treatment	Applied once for each combination	Align with EAG model as negligible impact on ICER; EAG notes this is the standard method for costing
TLS events in Glofit-GemOx arm	Not included	Not included	The two TLS events in the Glofit-GemOx arm were not considered to be treatment-related (the model includes treatment-related events only)
Time point on PFS and OS KM curves to extrapolate from for Glofit-GemOx arm	20 months	25 months	With further follow up data, the tail on the PFS and OS KM curves plateau later. Extrapolating after 20 months is provided as a scenario

MUGA, multigated acquisition scan; OS, overall survival; PFS, progression-free survival; TLS, tumour lysis syndrome

4.2 Severity modifier

As with the original analysis, no adjustment to the value of Glofit-GemOx QALYs applies for the comparison vs Pola-BR following QALY shortfall analysis based on the updated data.

The proportional QALY shortfall vs. Pola-BR is [redacted] and the absolute QALY shortfall is [redacted].

Table 9: QALY shortfall analysis

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

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

4.3 Cost-effectiveness results

4.3.1 Base case results

The cost-effectiveness results for Glofit-GemOx vs R-GemOx and Pola-BR with the current approved PAS discount for both glofitamab and polatuzumab are presented in Table 10. Glofit-GemOx is shown to be cost-effective at a £20,000 threshold versus both comparators.

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

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)	NMB at £20,000
Glofit-GemOx vs R-GemOx								
Glofit-GemOx	[redacted]	6.48	[redacted]					
R-GemOx	[redacted]	3.19	[redacted]	[redacted]	3.29	[redacted]	£6,862	[redacted]
Glofit-GemOx vs Pola-BR								
Glofit-GemOx	[redacted]	5.74	[redacted]					
Pola-BR	[redacted]	3.82	[redacted]	[redacted]	1.92	[redacted]	£15,612	[redacted]

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

4.3.2 Probabilistic sensitivity analysis

The median probabilistic incremental costs and QALYs gained from Glofit-GemOx vs. R-GemOx and Pola-BR with the PAS discounts considered for 1,000 iterations are given in Table 11. The pairwise cost-effectiveness acceptability curves are presented in Figure 14.

Assuming a willingness-to-pay (WTP) threshold of £20,000 and £30,000 per QALY gained, the probability of Glofit-GemOx being the most cost-effective treatment vs. R-GemOx was [redacted] and [redacted], respectively, and [redacted] and [redacted] vs Pola-BR, respectively. The incremental results of each iteration in the PSA are displayed in Figure 15. The results from the probabilistic analysis are in line with those of the deterministic analysis in terms of the estimated QALY and LY gains and the estimated incremental costs. This demonstrates that the deterministic base case results are robust as they are likely to represent the average experience per person treated with Glofit-GemOx.

Table 11: Probabilistic base-case cost-effectiveness results (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)	NMB at £20,000
Glofit-GemOx vs R-GemOx								
Glofit-GemOx	[redacted]	6.47	[redacted]					
R-GemOx	[redacted]	3.17	[redacted]	[redacted]	3.30	[redacted]	£6,681	[redacted]
Glofit-GemOx vs Pola-BR								
Glofit-GemOx	[redacted]	5.71	[redacted]					
Pola-BR	[redacted]	3.66	[redacted]	[redacted]	2.05	[redacted]	£14,375	[redacted]

Figure 14: Cost-effectiveness acceptability curve (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

[redacted]

Figure 15: Incremental cost-effectiveness plane (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

[redacted]

4.3.3 Deterministic sensitivity analysis

The ten most influential parameters on cost-effectiveness with descending sensitivity when Glofit-GemOx is compared with R-GemOx and Pola-BR are presented below.

The parameter that had the largest impact on the results for the comparison vs R-GemOx was the cost of subsequent therapy post Glofit-GemOx; however, for all parameters presented in the tornado plot, none were shown to an exert a significant impact compared to

the deterministic base case with respect to NMB at a WTP of £20,000, thereby indicating a low level of uncertainty around the cost-effectiveness conclusion vs R-GemOx.

Similarly, the parameter that had the largest impact on the results for the comparison vs Pola-BR was also the cost of subsequent therapy post Glofit-GemOx (NMB of [redacted] at a WTP of £20,000). All other parameters presented in the tornado plot did not exert a significant impact compared to the deterministic base case with respect to NMB at a WTP of £20,000.

Figure 16: Tornado diagram showing OWSA results on NMB – Glofit-GemOx vs. R-GemOx (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

[redacted]

Figure 17: Tornado diagram showing OWSA results on cost per QALY – Glofit-GemOx vs. R-GemOx (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

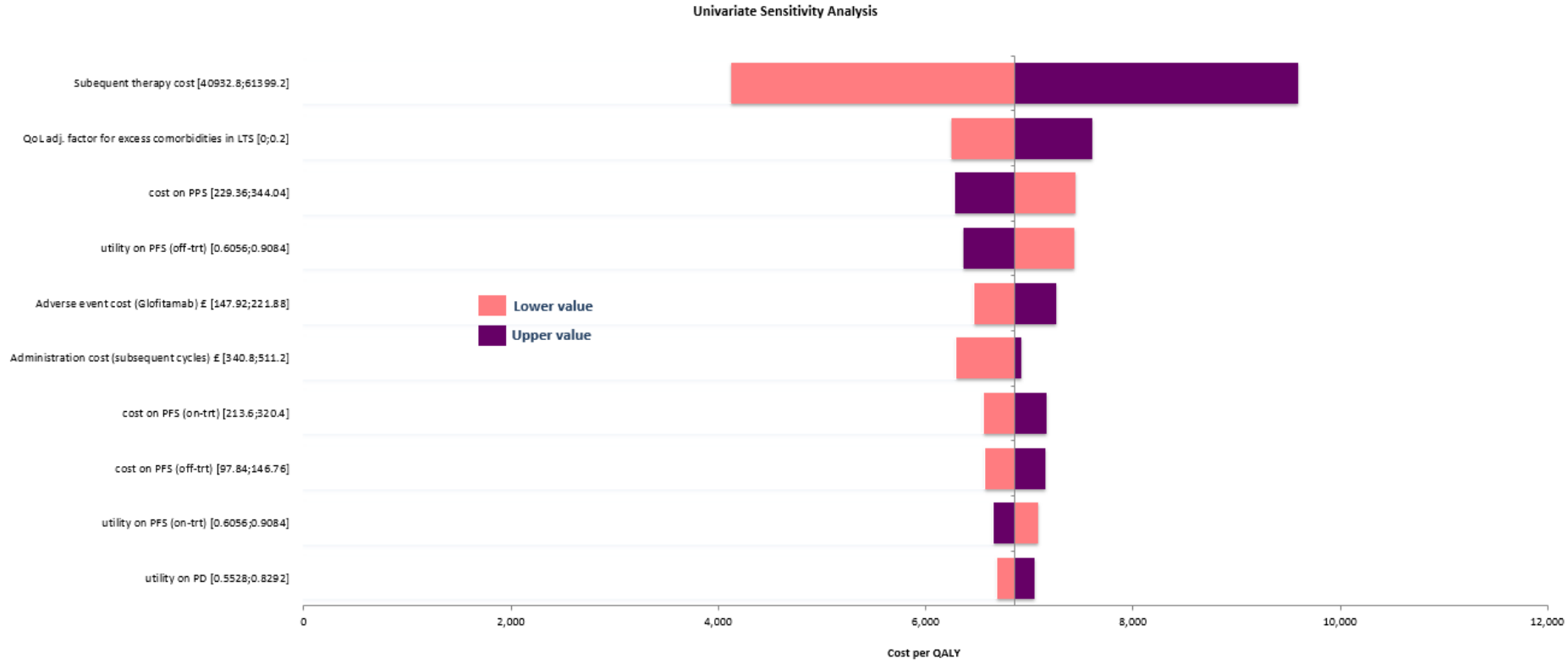
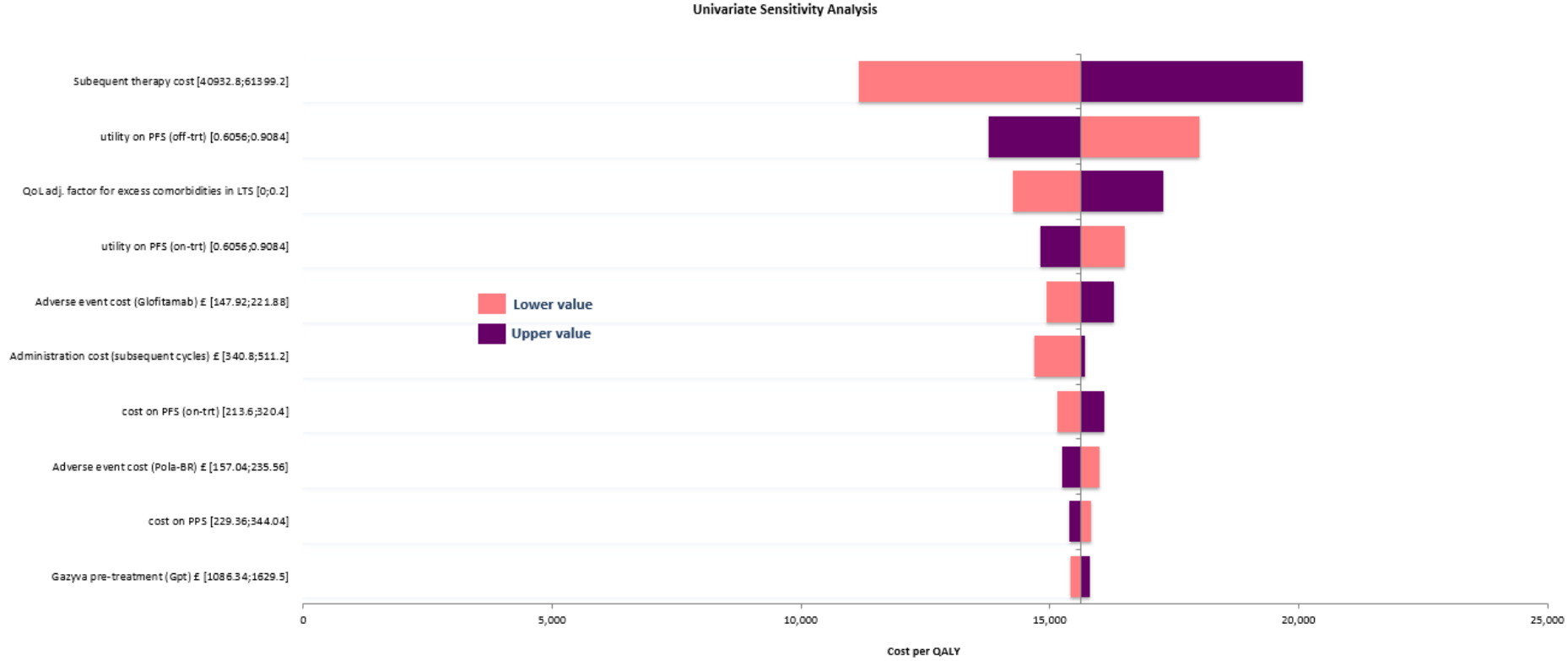


Figure 18: Tornado diagram showing OWSA results on NMB – Glofit-GemOx vs. Pola-BR (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

[redacted]

Figure 19: Tornado diagram showing OWSA results on cost per QALY – Glofit-GemOx vs. Pola-BR (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)



4.3.4 Scenario analysis

Conducted scenario analyses are provided below and include a scenario in which the log-normal distribution is applied at 20 months to the Glofit-GemOx PFS and Kaplan-Meier curves, as per the original submitted analysis based on CCOD2. Glofit-GemOx continues to be cost-effective at a £20,000 threshold vs Pola-BR.

Table 12: Scenario analyses (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)	NMB at £20,000
Glofit-GemOx vs Pola-BR – 20-month extrapolation for Glofit-GemOx								
Glofit-GemOx	[redacted]	5.77	[redacted]					
Pola-BR	[redacted]	3.82	[redacted]	[redacted]	1.95	[redacted]	£17,294	[redacted]
Discounting - 1.5% discounting for costs and effects (Glofit-GemOx vs R-GemOx)								
Glofit-GemOx	[redacted]	7.70	[redacted]					
R-GemOx	[redacted]	3.62	[redacted]	[redacted]	4.07	[redacted]	£5,718	[redacted]
Discounting - 1.5% discounting for costs and effects (Glofit-GemOx vs Pola-BR)								
Glofit-GemOx	[redacted]	6.80	[redacted]					
Pola-BR	[redacted]	4.42	[redacted]	[redacted]	2.38	[redacted]	£12,873	[redacted]

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

4.3.5 Fully incremental analysis

As requested in the draft guidance, a fully incremental analysis is provided below; however, the company has significant reservations with this approach and does not consider it to be appropriate for decision making.

Based on the results of the fully incremental analysis, R-GemOx should be excluded as a comparator as it is dominated by Pola-BR, leaving Pola-BR as the sole comparator for consideration in this appraisal. The company feels strongly that the cost-effectiveness of Glofit-GemOx in comparison with R-GemOx must be considered in decision making since clinical experts have confirmed this regimen represents the standard of care for the second-line treatment of transplant-ineligible R/R DLBCL patients due to concerns associated with the suitability of Pola-BR as a treatment in this setting.

The relevance of Pola-BR has been debated not only in the current appraisal but in other R/R DLBCL appraisals (TA954, TA947) (6),(7). The company acknowledges that the use of

Pola-BR in NHS clinical practice today is sufficient for the committee to consider it a relevant comparator for the current appraisal, however it should be noted that clinical experts consulted by NHS England stated they were surprised the usage of this regimen was so high, suggesting that this may be reflective of use in loco-regional hospitals rather than expert centres. Clinical experts from expert treatment centres consulted by the company concur with this view, stating that Pola-BR is not used in these settings due to restrictions on prior exposure to polatuzumab vedotin following the approval of Pola-RCHP in the first-line setting, and concerns regarding the negative impact that bendamustine has on subsequent CAR T-cell therapy and bispecific antibodies. This concern is now acknowledged in the BSH guidelines for R/R DLBCL, published in May 2025, which state that "Pola-BR should be avoided for patients who may be suitable for third-line CAR T-cell therapy given that bendamustine exposure prior to apheresis is associated with increased risk of CAR T-cell manufacturing failure and inferior outcomes after CAR T-cell therapy" (2).

The company also acknowledges that the NHS England representative stated that the use of Pola-BR has declined in the first four months of 2025. The company expects this trend to continue as the uptake of Pola-RCHP increases across the country and the recommendations in the BSH guidelines around the avoidance of Pola-BR are followed at a loco-regional level.

As such, the company feels that a pairwise comparison for both R-GemOx and Pola-BR should be considered in decision making rather than the fully incremental analysis as this would factor in the most-relevant comparator for this population.

Table 13: Fully incremental analysis (glofitamab PAS price, polatuzumab PAS, obinutuzumab PAS, comparator and subsequent treatment list)

Technologies	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER (£/QALY)
R-GemOx	[redacted]	[redacted]			
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Gloft-GemOx (Pola-BR population)	[redacted]	[redacted]	[redacted]	[redacted]	£15,612

5. Conclusion

The updated data from STARGLO, together with analysis regarding the generalisability of the study population to NHS clinical practice addresses the uncertainties in the clinical evidence for Glofit-GemOx cited in the draft guidance.

- Several post-hoc analyses were conducted to demonstrate support the generalisability of outcomes in the ITT population of STARGLO to the European population. Following review of these analyses, the CHMP stated that the benefits demonstrated in the STARGLO study had been satisfactorily substantiated in the European context. The EMA subsequently approved the STARGLO indication, followed by recommendation of Glofit-GemOx in this indication by the European Society of Medical Oncology (ESMO) in the July publication of their lymphoma treatment guideline. The MHRA approval of the STARGLO indication on 16 July 2025, via the International Recognition Procedure with the EMA as the reference regulator, further endorses the generalisability of the STARGLO results to the UK population. In addition, the BSH guideline for the management of R/R large B-cell lymphoma, published in May 2025, recommends the use of Glofit-GemOx in this indication, demonstrating acceptance of the applicability of the STARGLO results to the UK population by UK lymphoma experts. The uncertainty of the NICE Committee with respect to the generalisability of the STARGLO results to the UK population, as stated in the Draft Guidance Document, should be resolved with the approval of the STARGLO indication by the European and UK regulatory authorities and recommendation of Glofit-GemOx in this indication by European and UK lymphoma experts in the ESMO and BSH guidelines, respectively.
- With approximately 3 years' median follow-up in the pre-specified subgroup analysis of patients with 1 prior line of treatment (a stratification factor in STARGLO), there is a continued benefit in OS for Glofit-GemOx relative to current standard of care, R-GemOx, as demonstrated in the HR of 0.58 with a 95% CI of 0.38 to 0.89 and a nominal p-value of [redacted]. This result, combined with the continued substantial benefit in PFS in the 2L subpopulation, and a landmark analysis of OS estimated that [redacted] of patients who had a complete response with Glofit-GemOx at EOT would be alive 24 months after EOT reduces the uncertainty regarding the clinical benefit of this regimen in these patients stated in the Draft Guidance Document.
- The longer follow-up data from STARGLO (CCOD3) was used to update the ITC vs Pola-BR. While the updated analyses demonstrate a clear separation in the PFS and OS curves for Glofit-GemOx and Pola-BR at approximately 12 months and a further plateau on the Glofit-GemOx curves,

[redacted]

[redacted]. This updated analysis has been incorporated into the updated cost-effectiveness model.

- The company base case has been updated to reflect the committee's preferred assumptions and to align with the EAG preferred assumptions that have a negligible impact on the ICER. The updated cost-effectiveness analysis results based on the most recent data from STARGLO indicated that Glofit-GemOx is cost-effective versus R-GemOx and Pola-BR at a £20,000 threshold.
    - The company does not consider a fully incremental analysis to be appropriate as this would exclude R-GemOx as a relevant comparator – this regimen must be considered in decision making since clinical experts have confirmed this represents the standard of care for the second-line treatment of transplant-ineligible R/R DLBCL patients due to concerns associated with the suitability of Pola-BR as a treatment in this setting.

In summary, the latest data cut resolves uncertainty over the OS benefit of Glofit-GemOx in the 2L subpopulation and demonstrates the potential for long-term remission in these patients. There is an urgent need for effective treatments in the 2L transplant-ineligible setting; the updated BSH guidelines recommend that Pola-BR should be avoided for patients suitable for third-line therapy, and while clinical experts acknowledge the R-GemOx is the standard of care for this population, this regimen is seen as a 'stepping stone' to access approved 3L treatments. Glofit-GemOx addresses this unmet need and should therefore be reimbursed for patients with R/R DLBCL who are ineligible for transplant.

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Single Technology Appraisal

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

Company response regarding multiple imputation analysis v2.0

The company has updated the economic model to include the inverse probability treatment weighting (IPTW) with multiple imputation analysis for the PolaBR indirect treatment comparison (ITC). However, the company has significant reservations regarding its suitability for decision making as outlined below.

Moreover, the company feels that this issue should not detract from the significant unmet need in the 2L transplant-ineligible DLBCL population and the benefit that Glofit-GemOx clearly offers to these patients. There is an urgent need for effective treatments in this setting; the updated BSH guidelines recommend that Pola-BR should be avoided for patients suitable for third-line therapy, and while clinical experts acknowledge the R-GemOx is the standard of care for this population, R-GemOx is seen as a 'stepping stone' to access approved 3L treatments. Glofit-GemOx addresses this unmet need and [redacted] offered to patients, it has the potential to alleviate the burden on the healthcare system in the long-term as [redacted] would negate the need for subsequent treatments in the future, thereby freeing hospital capacity and healthcare resource use.

Company position on multiple imputation analysis

The company does not consider the IPTW with multiple imputation analysis to be appropriate for decision making since it does not offer an improvement to the current limitations of the analyses, indeed it even introduces further uncertainty due to several factors.

Multiple imputation of missing data is appropriate if the missing covariates are important prognostic variables. In this instance, clinical experts categorised the two variables with missing data, cell-of-origin and bone marrow involvement, as low-priority prognostic variables for adjustment in the ITC. Neither of these covariates are typically considered by clinicians in decision-making for treatments of relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL), which is reflected by their absence in the disease assessment and prognostic factors at relapse section of the R/R DLBCL guidelines published by the British Society of Haematology (BSH) (1).

Moreover, multiple imputation of missing data should not be used to handle missing data when large proportions of data are missing, with literature sources stating that multiple imputation would not be appropriate when the degree of missing data exceeds 40% (2, 3). In this instance, the degree of missing data in the PolaBR GO29365 study for bone marrow involvement is 24%

but 51% for cell-of-origin. Given the degree of missing data and the low prognostic value of the missing data, the main analysis was performed with no adjustment for these variables; a sensitivity analysis with multiple imputation was only conducted as an exercise to evaluate robustness of the IPTW results.

It is important to also acknowledge the fact that the KM curves generated by the IPTW analysis with multiple imputation are not an accurate description of the reported hazard ratios (see appendix). For instance, there were residual imbalances following matching adjustments conducted as part of the propensity score analysis for Glofit-GemOx vs PolaBR. These were further controlled for in subsequent outcome analysis using a doubly robust approach, however this second adjustment could only be performed for summary statistics (e.g. HRs) and not for KM curves. Furthermore, due to the high degree of missingness, there is significant variation in KM curves generated for each imputation, which is a significant factor given the economic model is based on extrapolations of the KM curves and not the hazard ratio (proportional hazards do not apply). This therefore does not facilitate a robust analysis for this comparison since there is a large degree of variation in the calculated incremental costs and QALYs with each imputation. This variation is to be expected given the wide confidence intervals in the HR for this analysis [redacted], which are wider than that seen for the IPTW analysis [redacted]. Moreover, each imputation is associated with a decrease in the effective sample size (ESS), which in 2 out of 5 imputations is below 30 and the remaining 3 below 33, signifying that these imputations are not generating a robust comparison and reducing the ESS that is already small in the base case analysis ([redacted])[1].

Median PFS in the economic model with each imputation is presented in Table 1 and demonstrates that this is increased with each imputation compared to the base case analysis. This is of significant importance since clinical experts state the evidence from GO29365 study outperforms the experience of Pola-BR in clinical practice (real world evidence from UK patients with R/R DLBCL demonstrate that median PFS for Pola-BR was 4.8 months, compared to 9.2 months in GO29365 (4)); this discrepancy between clinical trial and real-world experience is therefore further exaggerated with the multiple imputation analysis, particularly with imputation 3. Furthermore, a landmark analysis looking into the proportion of patients progression-free at 5 years demonstrates that this is also increased compared to the base case analysis for each imputation and exceeds clinical expert estimates of how patients would perform on PolaBR in clinical practice (clinical experts at the Company advisory board estimated [redacted] of patients to be progression-free on PolaBR at 5 years).

Table 1: PolaBR Median PFS and 5 year progression-free survival estimates by analysis

Analysis	Median PFS (months)	5-year progression-free (%)
Base case (no multiple imputation)	[redacted]	[redacted]
Imputation 1	[redacted]	[redacted]

[1] Please note that risk tables in the provided KM curves show the sum of weights, which is different from ESS, and should not be interpreted

Imputation 2	[redacted]	[redacted]
Imputation 3	[redacted]	[redacted]
Imputation 4	[redacted]	[redacted]
Imputation 5	[redacted]	[redacted]

The results of the five individual imputations are presented in Table 2, with the average incremental costs, QALYs and ICER provided in Table 3.

Table 2: Cost-effectiveness results by individual imputation

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)	NMB at £20,000
Imputation 1 [redacted]								
Glofit-GemOx	[redacted]	5.58	[redacted]					
Pola-BR	[redacted]	4.24	[redacted]	[redacted]	1.34	[redacted]	£27,395	[redacted]
Imputation 2 [redacted]								
Glofit-GemOx	[redacted]	5.58	[redacted]					
Pola-BR	[redacted]	4.56	[redacted]	[redacted]	1.02	[redacted]	£31,472	[redacted]
Imputation 3 [redacted]								
Glofit-GemOx	[redacted]	5.63	[redacted]					
Pola-BR	[redacted]	4.80	[redacted]	[redacted]	0.82	[redacted]	£43,436	[redacted]
Imputation 4 [redacted]								
Glofit-GemOx	[redacted]	5.62	[redacted]					
Pola-BR	[redacted]	4.49	[redacted]	[redacted]	1.13	[redacted]	£31,005	[redacted]
Imputation 5 [redacted]								
Glofit-GemOx	[redacted]	5.44	[redacted]					
Pola-BR	[redacted]	4.18	[redacted]	[redacted]	1.26	[redacted]	£23,886	[redacted]

Table 3: Cost-effectiveness of Glofit-GemOx vs PolaBR (IPTW with multiple imputation)

Technologies	Inc costs (average)	Inc LYG (average)	Inc QALYs (average)	ICER (£/QALY) (average)
Glofit-GemOx vs Pola-BR	[redacted]	1.11	[redacted]	£30,352

Summary

Given the factors outlined above, the Company strongly considers the IPTW analysis without adjusting for cell-of-origin and bone marrow involvement to be the most appropriate analysis for decision-making. The IPTW analysis with multiple imputation should only be interpreted as a sensitivity analysis; this is not a robust reflection of the comparison as it adds additional uncertainty to a comparison that is already associated with limitations given the small ESS of Pola-BR in the IPTW analysis.

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4. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D, et al. Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. Blood advances. 2022;6(9):2920-6.

Appendix: IPTW with multiple imputation – KM curves

PFS

Imputation 1

Imputation 2

Imputation 3

Imputation 4

Imputation 5

OS

Imputation 1

Imputation 2

Imputation 3

Imputation 4

Imputation 5

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Tuesday 19 August 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Tuesday 19 August 2025. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	• Roche £20,000 towards helpline, information provision and preparing for treatment project • AbbVie £25,000 towards preparing for treatment project, helpline and information provision • Bristol-Myers Squibb £8,000 towards provision of support groups
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Whilst we understand that this decision has been reached based on uncertainties in the clinical evidence, we would like to ensure that any further discussions will take the patient experience into account.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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	The guidance states that having another treatment option available after the first relapse or treatment failure would be an advantage. We would like to reiterate that our patients feel that having glofitamab available as a second line treatment, and one which seems to be well tolerated and effective, is not just another option but a vital new path forward.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

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

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comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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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 [ID6202]

EAG critique of company's response to the draft guidance following the first Advisory Committee Meeting

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Emma Maund, Research Fellow, Evidence synthesis Geoff Frampton, Principal Research Fellow, Evidence synthesis Fay Chinnery, Research Fellow, Health economics Keith Cooper, Principal Research Fellow, Health economics
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
Date completed	02 September 2025

1 INTRODUCTION

This document is the External Assessment Group's (EAG) critique of the response by the company, Roche, to the NICE Draft Guidance Document (DGD), issued on 29th July 2025, following the NICE Advisory Committee Meeting (8th July 2025) for the technology appraisal of glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma (ID6202).

The EAG received the company's response documents and their revised economic model on 20th August 2025.

The NICE Committee's preferred assumptions specified in the Draft Guidance and the company's responses to these are summarised in Table 1.

Table 1 Committee's preferred analyses and the company's responses to these

Committee's Preferred Analyses specified in the DGD	Company's responses	EAG critique
Further follow-up data from STARGLO, specifically for the second-line subgroup (DGD section 3.13)	Updated outcomes from STARGLO reported in Company comment #3 and Company Appendix section 2.	Section 2.1
	Updated STARGLO results applied in the indirect treatment comparison: Company comment #5 and Company Appendix section 3.	Section 2.2
Additional statistical analyses exploring the uncertainty in the STARGLO subgroup data (DGD section 3.13)	Generalisability of the STARGLO trial subgroups discussed in Company comment #2 and Company Appendix section 1.	Section 2.3
Inclusion of Pola-BR as a comparator (DGD section 3.4)	Relevance of Pola-BR discussed in Company comment #4.	Section 2.4
A fully incremental cost-effectiveness analysis including Glofit-Gem-Ox, R-GemOx and Pola-BR (DGD section 3.13)	Updated economic analysis reported in Company comment #6 and Company Appendix section 4.	Section 2.5

Committee's Preferred Analyses specified in the DGD	Company's responses	EAG critique
The cost-effectiveness analysis should include the following assumptions (DGD section 3.14): • Mortality should revert to near the general population (standardised mortality ratio of 1.09) after 6 years • 15% of people in the Glofit-Gem-Ox arm should go on to have subsequent palliative care. • One-off end of life healthcare costs should be applied, rather than being included in weekly healthcare resource-use costs.	The company have updated their economic analysis	Section 2.5

2 EAG CRITIQUE OF THE COMPANY'S RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT

2.1 Updated outcomes from STARGLO

To address uncertainties in the survival outcomes from the STARGLO trial the company have provided results from the latest data cut (1st May 2025, referred to as clinical cut-off date 3, CCOD3) which gives an additional 14.5 months of follow-up data for OS (Company Appendix Table 1) and an additional 10.7 months of follow-up data for PFS (Company Appendix Table 2) from the previous data cut reported in the original company submission (CCOD2, 16th February 2024). To support their response the company provided a copy of their Applicant's response to the European Medicines Agency (EMA)'s questions which was considered during the European regulatory approvals process. We refer to this as the "EMA Document".

2.1.1 Sensitivity analyses on the whole trial (ITT) population

The company conducted sensitivity analyses to explore the impact of COVID-19 and the impact of next anti-lymphoma therapy (NALT) on survival outcomes.

2.1.1.1 Censoring for effects of COVID-19

The company conducted sensitivity analyses exploring the impact on the OS hazard ratio of three ways of censoring patients who experienced death or discontinuation due to COVID-19 (EMA Document Table 19). Results of these sensitivity analyses are briefly summarized in Table 6. We provide a recap for the OS results in section 2.1.2 below and further discussion of COVID censoring in relation to geographical subgroups in section 2.3.2.2 below.

2.1.1.2 Adjustments for receipt of next anti-lymphoma therapy (NALT)

The company acknowledges that NALT was administered more frequently in the R-GemOx arm of STARGLO (Company Appendix Table 4) and this contributed to survival differences both between the trial arms and geographic region subgroups (EMA Document Table 11). The company states that simply censoring patients at the time of NALT before estimating a treatment effect would introduce bias because patients are likely to receive NALT due to various measures of poor prognosis.

Given that standard censoring could introduce bias, the company explored two alternative ways to account for the imbalance of patients receiving NALT in the STARGLO trial (Company Appendix section 1.2). The company's rationale for these approaches is stated in EMA Document section C.3.3:

Event-free survival (EFS) analysis. This approach uses events of time to progression, death, or initiation of NALT, and can provide a NALT adjusted treatment effect for PFS but not for OS. We note that this analysis had been conducted by the company and reported in the CSR for CCOD2, but was not reported in their original CS.

Inverse probability of censoring weighting (IPCW). This approach can provide a NALT-adjusted treatment effect for both OS and PFS and aims to reduce NALT-censoring related bias. This is a new company analysis that had not been reported in the CS or CSR, although it was applied to the previous data cutoff (CCOD2) which we assume was because the EMA discussion took place before CCOD3 of the STARGLO trial. A description of the statistical approach is given in EMA Document Appendix 3. Five covariates were included in the final adjustment of OS and four were included in the final adjustment of PFS (EMA Document Table 12). As noted by the company, IPCW belongs to a family of methods that can adjust for biases introduced by treatment switching.[1] However, the company does not explain why they considered IPCW more suitable than other methods that are available to adjust for treatment switching.[1] We note that a key assumption of the IPCW approach is that there are no unmeasured confounders. The company does not discuss the likelihood of there being unmeasured confounders but states in the EMA Document Appendix 3 that results of the IPCW analysis should be interpreted with caution due to this assumption. According to the reported methodology (EMA Document Appendix 3), the IPCW analysis was applied to the ITT population and to the analysis of geographical subgroups, but not to the second-line subpopulation which is of interest in the current appraisal.

2.1.2 Overall survival (OS) results

The OS hazard ratio from CCOD3 comparing Glofit-GemOx against R-GemOx in the second-line subpopulation is now statistically significant (HR=0.58; 95% CI 0.38 to 0.89). Median OS for the second-line subpopulation in the Glofit-GemOx and R-GemOx arms at CCOD3 was not reached (lower CI 22.8 months) and 14.4 months respectively, representing an improvement in OS compared to CCOD2 (Company Appendix Table 1). Kaplan-Meier OS curves for the ITT and second-line population at CCOD3 are provided in Company Appendix Figures 1 and 2 respectively. These show clear separation of the Glofit-GemOx and R-GemOx curves, albeit with extensive censoring of the Glofit-GemOx data after 24 months. The company does not explain the extent of censoring or any implications of this.

2.1.2.1 COVID sensitivity analyses results

We note that, according to EMA Document Table 19, the ITT population OS results reported in Company Appendix Table 1 were not censored for COVID-19 deaths or treatment discontinuations. As summarized in Table 6 and in EMA Document Table 19, the three

sensitivity analyses that censored for COVID-19-related events gave slightly lower hazard ratios than the unadjusted analyses for Glofit-GemOx versus R-GemOx and the hazard ratios remained statistically significant (see Table 6 below). These sensitivity analysis results are for ITT population. The company does not discuss whether they would also apply to the second-line subpopulation, but the EAG has no reason to believe that they would not.

2.1.2.2 IPCW analysis results

The company's response does not mention whether the reported OS results (as summarized above) are for the unadjusted or IPCW-adjusted analysis, but states that the IPCW-adjusted analysis led to numerically lower OS hazard ratios compared to the unadjusted analysis. The data to support this assertion are not reported in the company's response. Figure 1 in the EMA Document confirms the company's interpretation but shows the previous (CCOD2) data cutoff, not the latest data from STARGLO.

2.1.2.3 Post-hoc multivariate analysis results

Company Appendix section 1.2 states that a post-hoc multivariate analysis was conducted for OS, adjusting for several potentially prognostic covariates. For the ITT population this gave a similar hazard ratio to the unadjusted analysis. This appears to be the same analysis as reported in section E.1.1.1 and Appendix 4 of the EMA Document which describes it as 'pre specified' rather than post hoc. According to the EMA Document this analysis was applied to the previous data cutoff (CCOD2) for the ITT population rather than the latest data from STARGLO (CCOD3) for the second-line population.

2.1.3 Progression-free survival (PFS) results

The hazard ratio for independent review committee (IRC)-assessed PFS remains statistically significant ([redacted]). IRC-assessed PFS for the second-line subpopulation was 20.4 months in the Glofit-GemOx arm and 5.5 months in the R-GemOx arm at CCOD3. These results are unchanged from those seen at CCOD2. PFS in the second-line subpopulation was higher than that seen for the ITT population by around 6 months in the Glofit-GemOx arm and 2 months in the R-GemOx arm although hazard ratios for the second-line and ITT populations were similar (Company Appendix Table 2). Kaplan-Meier curves showing PFS for the ITT and second-line populations at CCOD3 are provided in Company Appendix Figures 3 and 4 respectively, showing results after censoring for NALT. There is a clear separation of the Glofit-GemOx and R-GemOx curves, albeit with relatively low numbers at risk in the R-GemOx arm, especially for the second-line subpopulation. However, as noted in section 2.1.1.2 above, simple censoring for NALT could introduce bias and therefore there is uncertainty in the results shown in these Kaplan-Meier curves. The EAG is uncertain whether the results reported in Company Appendix Table 2, as

summarized above, were also from the analysis that censored for NALT as there is no label or footnote to clarify which data are reported. The company does not discuss reasons for censoring other than for NALT, or mention the implications of any other imbalances in censoring between the trial arms.

2.1.3.1 EFS analysis results

Results of the EFS analysis are not reported for the latest (CCOD3) data cutoff. At CCOD2 the EFS analysis gave nearly identical results to the PFS analysis for the ITT population (see Table 33 below). However, as discussed below in section 2.3.2.1.1, the company claim that the EFS analysis for the ITT population showed improved HRs favouring Glofit-GemOx compared to R-GemOx. Due to this discrepancy the EAG is uncertain whether the company is describing CCOD3 data which they have not provided with their response. There is also uncertainty regarding whether the EFS results for the ITT population would be similar for the second-line subpopulation.

2.1.3.2 IPCW analysis results

The company does not discuss results of the IPCW analysis for PFS except with reference to the subgroup analysis by geographical region (see section 2.3.2.1.2 below). Figure 2 in the EMA Document shows that the unadjusted and IPCW-adjusted PFS analyses gave similar and [redacted] hazard ratios at CCOD2. The company response and EMA Document do not provide IPCW analysis results for the latest STARGLO data cutoff.

2.1.4 Response rate and duration of complete response

Company Appendix section 2.1.2.2 reports that the updated CCOD3 data from STARGLO did not alter the compete response rate observed at CCOD2 for either trial arm since all patients had completed study treatment at CCOD2.

Company Appendix section 2.1.2.3 reports that at the latest data cut, CCOD3, the median duration of complete response (DOCR) was [redacted] in the Glofit-GemOx arm and the hazard ratio for the Glofit-GemOx versus RGemOx comparison was [redacted] for the ITT population or for the second-line subpopulation. This is consistent with the results previously reported for CCOD2.

2.1.5 Safety

The company assert in their response that the safety profiles of Glofit-GemOx and R-GemOx in the STARGLO trial remained unchanged at the latest data cutoff and that no new safety signals were identified. The EAG agrees that summary-level adverse events data provided in Company Appendix section 2.3 support this assertion. One grade 5 adverse event (i.e. death) occurred after CCOD2, in the Glofit-GemOx arm of the second-line population subgroup (Company Appendix Table 5), although the company do not mention whether this was treatment-related. Other than this, we agree that the latest safety data from STARGLO do not raise any concerns.

EAG conclusion on the updated clinical efficacy and safety results from STARGLO

Clinical efficacy: For OS and PFS additional follow-up has reduced uncertainty in the hazard ratios for Glofit-GemOx versus R-GemOx which are statistically significant for both outcomes, favouring Glofit-GemOx. However, some uncertainty in the reported hazard ratios remains for the OS and PFS outcomes because: (i) Sensitivity analysis results, though consistent with the results of the main analyses, are reported only for the ITT population at the previous data cutoff (CCOD2) rather than for the second-line subpopulation at the latest data cutoff (CCOD3). (ii) For PFS, there is lack of clarity around which analysis the reported results are based on; these appear to be for patients censored for NALT rather than for the EFS or IPCW analyses, even though the company acknowledge that NALT censoring may introduce bias. (iii) The company has not justified why the IPCW method was selected from those available for adjusting for treatment switching and it is unclear whether an alternative method would have yielded similar results. The company states that IPCW results should be interpreted with caution due to uncertainty whether the key assumption that there are no unmeasured confounders is supported. **Safety:** The EAG agrees that the company's updated analysis has not identified any safety concerns.

2.2 Updated indirect treatment comparison (ITC)

Given the lack of any head-to-head trials directly comparing Glofit-GemOx against Pola-BR, an ITC is required. However, the company does not consider Pola-BR to be a relevant comparator and therefore did not include an ITC in their original submission to NICE. Following consideration of the EAG Report, the company subsequently provided an ITC to NICE before the first Advisory Committee Meeting (ACM1) which they referred to as

"Scenario: Comparison to Pola-BR" (5th June 2025). The EAG provided a critique of the company's ITC in an Addendum to the EAG Report (Addendum 1, 16th June 2025).

The company's ITC followed a propensity score approach and included the second-line patients from the STARGLO trial (Glofit-GemOx) for comparison against second-line only patients from the GO29365 trial (Pola-BR). A subset of the data from each trial was included in the ITC to remove differences in enrolment criteria, which the EAG considered appropriate. The company performed four ITC analyses as follows:

- **Unadjusted**
- **Inverse probability of treatment weighting** (**IPTW**) to adjust for imbalances in patient characteristics, but without adjustment for cell type of origin and bone marrow involvement. The missing values of the adjusted covariates were set to be equal to the mean or mode of each covariate, so that patients were not dropped from the analysis. This was the company's main analysis and referred to by the EAG as the "main analysis".
- **IPTW with multiple imputation** (the same as the main analysis, but included cell type or origin and bone marrow as covariates and used multiple imputation for any missing values of covariates). This is the EAG's preferred approach as it is the most appropriate approach to account for missing data whilst capturing all the identified covariates.
- **Full matching** (without adjustments for cell type of origin and bone marrow involvement. Missing values of other covariates were set to be equal to the mean or mode of each covariate, so that patients were not dropped from the analysis)

As stated in our EAG Report Addendum, we agreed with the company's overall statistical approach, although some aspects either lacked detail of the methods used (e.g. how the "Full matching" analysis was conducted) or were not reported (lacking a rationale for the choice of covariates in analyses, quantity of missing data, and distribution of weights). No further information on the ITC methods has been provided in the company's current response document.

The company has updated their existing ITC by including the latest OS and IRC-assessed PFS results (CCOD3) from the STARGLO trial. The EAG assumes that no other changes were made to the ITC methods, although the company do not explicitly state this.

Results from the ITC using the updated survival outcomes data from STARGLO were similar to those obtained at CCOD2. That is, the hazard ratios for each of the four ITC methods at CCOD3 [redacted] for both OS (Company Appendix Table 6) and PFS (Company Appendix Table 7). The hazard ratios were similar for the unadjusted, IPTW with multiple imputation, and full matching approaches: OS HRs ranged from [redacted] to [redacted] (Company Appendix Table 6) and PFS HRs ranged from [redacted] to [redacted]However, the hazard ratios were lower for the IPTW approach without imputation, which is the company's preferred analysis for informing their economic model (OS HR [redacted]; PFS HR [redacted]). As noted above, the EAG's preferred analysis is the IPTW approach with multiple imputation.

The company acknowledge the limitations of the ITC (Company Appendix section 3.3). These are the same limitations as were identified in the original ITC prior to ACM1, namely: remaining imbalances in covariates between trial arms that could not be adjusted for; a relatively small sample size for the Pola-BR arm; and some uncertainty based on clinical expert opinion as to whether the GO29365 trial overestimated OS and PFS relative to clinical practice.

The EAG agrees with the company that the ITC approach using individual patient data for propensity score analysis reflects the most robust indirect comparison feasible with the available data.

EAG conclusion on the updated ITC

The company's updated ITC comparing Glofit-GemOx against Pola-BR gives similar results to the ITC based on an earlier data cutoff that was discussed at ACM1. The hazard ratios remain [redacted]. The EAG agrees with the company's caution that, although the most appropriate method was employed, the ITC results are subject to several uncertainties.

2.3 Generalisability of the STARGLO trial and subgroups

Given the inconsistencies observed in OS and PFS hazard ratios by geographical region and race compared to the ITT population (DG 3.13), Company Appendix section 1, reports on the generalisability of the STARGLO trial to the European population and therefore the UK NHS population. The company states there were extensive discussions with the EMA regarding the generalisability of the ITT population of the STARGLO trial to the European population. The company's full response to EMA, including several post-hoc statistical analyses, are contained in the EMA Document and we provide a recap in the following sections.

2.3.1 Baseline demographic and disease characteristics of the STARGLO trial

To demonstrate generalisability of the results of the ITT population of the STARGLO trial to the European population, the company compared:

- The baseline and demographic characteristics of the European subgroup with those of the ITT population of the STARGLO trial.
- The baseline characteristics and efficacy outcomes of the European based NIVEAU trial with those of the ITT population of the STARGLO trial.

2.3.1.1 European subgroup and overall ITT population of the STARGLO trial

Company comment #1, Company Appendix section 1.1 and EMA Document sections E.3.1 and E.3.3 discuss the similarities and differences between the baseline demographic and disease characteristics of the European subgroup and the ITT population of the STARGLO trial. A detailed breakdown of these characteristics for the European subgroup and for the ITT population is provided in EMA Document Table 1 and Table 22.

The company state that baseline and demographic characteristics were broadly comparable although there were some differences. Specifically:

- **Age** - slightly older in the European subgroup compared to the overall ITT population (median age of 71 years versus 68 years respectively)
- **Race** - mostly White in the European subgroup (76.1%) compared to a mix of White (42%) and Asian (50%) in the overall ITT population
- **Ann Arbor Stage** – a slightly higher percentage of patients with Stage III/IV disease in the European subgroup (75%) compared to the overall ITT population (58.4%)
- **Prior CAR-T therapy** – a slightly higher proportion in the European subgroup (13.6%) compared to the overall ITT population (7.7%)
- **Refractory status** – a lower proportion refractory to prior therapies in the European subgroup.
    - Refractory to last therapy (64.5% versus 52.3% in Europe).
    - Primary refractory disease or relapse within 12 months after first-line therapy (75.8% versus 63.6% in Europe).
    - Double refractory disease to any prior anti-CD20 and anthracycline-based regimen (58.6% versus 48.9% in Europe).

With respect to the difference in age, Company Appendix section 1.1 states that this did not appear to translate into a difference in OS benefit, as all age subgroups in the ITT population showed an OS benefit for Glofit-GemOx over R-GemOx (EMA document Table 23). The

EAG agree with this, and with the statement in EMA Document section E3.1 that this finding implies that the older age of the European subgroup does not translate into a difference in OS benefits.

With respect to race, the EAG note that Company Appendix 1 states that there is no biological reason that outcomes of glofitamab therapy would differ by race. Furthermore, results of pharmacokinetic analyses for glofitamab exposure and exposure-response data in the STARGLO trial did not vary significantly by patient race. The company's response does not comment on whether the differences in the other baseline demographic and disease characteristics between the European subgroup population and the ITT population were of clinical significance.

2.3.1.2 ITT population of the STARGLO trial and of the NIVEAU Study

To determine the generalisability of the STARGLO trial population characteristics to a European population, the company selected a multi-country European trial conducted in the same indication. The company compared the baseline demographic and disease characteristics, as well as 1-year and 2-year event-free rates for PFS and OS, of the STARGLO trial (CCOD2) with those from the European NIVEAU trial (Company comment #1, Company Appendix 1.1, EMA Document sections E.3.2 and E.3.3). It appears that the NIVEAU trial was identified through a systematic literature search to identify studies investigating R-GemOx regimens (EMA Document section B.1). However, it is unclear to the EAG whether any of the other studies identified in the systematic literature search, which included real world studies, could also be considered European and used for comparative purposes (EMA Document Table 2). The NIVEAU trial (NCT03366272) is a randomised phase 3 trial comparing R-GemOx plus nivolumab versus R-GemOx alone as therapy in transplant ineligible patients with large B-cell lymphoma (LBCL).[2] The NIVEAU trial publication cited in the company's responses provides brief details of the trial.[3] The clinicaltrials.gov entry for the NIVEAU trial states it was conducted in Austria, Belgium, France, Germany, Netherlands, Poland and Israel.[2] The EAG therefore agrees with the company that the NIVEAU trial population can be considered almost exclusively European, while noting there were no UK centres involved in the study.

The company note the main difference between the inclusion/exclusion criteria of the NIVEAU trial and the STRAGLO trial is that the NIVEAU trial only included patients with one prior line of therapy, whereas the STARGLO trial included patients with one or more prior lines of therapy (EMA Document section E3.2).

EMA Document Table 24 provides an overview of baseline characteristics on the NIVEAU trial compared to those of the STARGLO trial (European subgroup and ITT population, CCOD2). In both the NIVEAU trial and ITT population of the STARGLO trial, the percentage of female participants, the median age of participants, and the percentage of patients with Ann Arbor stage III/IV were comparable. However, a higher percentage of patients in the NIVEAU trial were aged over 75 years (52% versus 23.7%), had an ECOG performance status >1 (17% versus 10.11%), and had an IPI score of 3-5 (62% versus 48.9%). Conversely, a higher percentage of patients in the STARGLO trial were refractory to first line therapy (55.8% versus 37%) and relapsed within 12 months after the first line of therapy (71.9% versus 58%). Results were similar when comparing the NIVEAU trial to the European subgroup of the STARGLO trial. Company comment #2 states that baseline demographic and disease characteristics of STARGLO were found to be similar to those of the ITT population of the NIVEAU trial. The EAG considers that whilst the trials have broadly similar characteristics, they do differ in some potentially prognostic respects as noted above.

Company Appendix section 1.1 states that a comparison of the 1-year and 2-year rates of PFS and OS from both trials showed overall comparable results between the NIVEAU trial R-GemOx arm and the STARGLO trial R-GemOx arm (for both the ITT population and European subgroup). However, numerical results were only reported in EMA document Table 25, which is reproduced in Table 2 below.

Table 2 Rates of overall survival and progression-free survival for the R-GemOX arms of the NIVEAU Study (R-GemOx) and STARGLO trial (overall ITT population and European subgroup, CCOD2)

	NIVEAU Trial R-GemOx arm (N=90)	**STARGLO Trial ITT population R-GemOx arm (N=91)**	**STARGLO Trial European subgroup R-GemOx arm (N=26)**
Overall survival			
1-year rate, % (95% CI)	48% (38, 59)	[redacted]	[redacted]
2 year rate, % (95% CI)	34% (22, 46)	33.5% (22, 45)	[redacted]
Progression-free survival			
1-year rate, % (95% CI)	28% (18, 37)	25.2% (14, 37)	[redacted]
2 year rate, % (95% CI)	15% (7, 23)	[redacted]	[redacted]
Source: Reproduced from EMA Document Table 25 CI, confidence intervals; EFS, ITT, intent-to-treat; NE, not estimable			

The EAG considers that the results in the R-GemOx arm from the NIVEAU study are more similar to those in the R-GemOx arm of the ITT population of the STARGLO trial than to the European subgroup. Whilst the EAG agrees that there are broad similarities between the trials suggesting that the ITT population of STARGLO may be generalisable to the European population, there is some uncertainty due to differences between trials in the factors noted above. Furthermore, it is unclear to the EAG whether any of the other studies identified in the company's systematic literature search (EMA Document Table 2), could be considered Europe-based and used for comparative purposes. The limited information reported in the NIVEAU trial publication cited by the company means it is difficult to assess whether the trial represents European clinical practice compared to real-world studies. As no UK centres were involved in the NIVEAU trial the relevance of the trial to UK clinical practice is unclear and is not discussed by the company.

2.3.2 Confounding factors in the European subgroup of the STARGLO trial

Company Appendix 1.2 states that the company performed thorough post-hoc exploratory subgroup evaluations using multiple methods to examine confounding factors. In the European subgroup, the use of subsequent therapies (new anti-lymphoma therapies; NALT) and the impact of COVID-19 were identified as the primary potential confounding factors that may have led to a higher OS hazard ratio compared to the overall ITT population. In their response the company does not explain the process for reaching this conclusion. All analyses were only for ITT and the European subgroup at CCOD 2 (i.e. not 2L at CCOD3 which is preferred by the DGD)

2.3.2.1 NALT

In all regional subgroups, NALT was administered more frequently in the R-GemOx arm compared to the Glofit-GemOx arm. However, regional differences in the type of NALT administered were observed. In the European subgroup R-GemOx arm, more patients received effective NALTs like CAR-T therapy, which may have biased the results (Company response #2, Company Appendix section 1.2, EMA Document Table 9).

2.3.2.1.1 Event-free survival (EFS)

The company conducted an event-free survival (EFS) analysis (see section 2.1.1.2 above). The Company response and EMA Document do not report numerical results for the EFS analysis for the overall ITT population or for the geographical subgroups. The EAG has therefore considered results for PFS and EFS reported in the CSR (CCOD2) and present these below in Table 3.

Table 3 IRC-assessed progression free survival and IRC-assessed event free survival by geographic region and overall ITT Population of the STARGLO trial (CCOD2)

	Unstratified HR (95% CI)			
	ITT population (N=274)	**Europe (N=88)**	**North America (N=25)**	**RoW (N=161)**
PFS	0.40 (0.28, 0.57)	0.84 (0.44, 1.59)	2.25 (0.48, 10.54)	0.27 (0.17, 0.42)
EFS	0.40 (0.29, 0.55)	0.76 (0.42, 1.38)	1.03 (0.35, 3.06)	0.23 (0.15, 0.36)

Source: Partly reproduced from Updated CSR Tables 52, 55, 56
CI, confidence intervals; EFS, event-free survival; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival; RoW, Rest of World.

Company Appendix 1.2 states the EFS analysis showed improved hazard ratios favouring Glofit-GemOx compared to R-GemOx, and that this pattern was observed in the ITT population and the European subgroup. The EAG does not consider there is an improved hazard ratio for the overall ITT population, but considers that the hazard ratio for the European subgroup is more favourable, although not statistically significant.

2.3.2.1.2 Inverse probability of censoring weighting (IPCW)

The IPCW models were developed for both OS and IRC-assessed PFS, in the ITT population and across regional subgroups. Missing data for the selected covariates were excluded from analysis, resulting in an analysis population of 265 (versus 274 in the ITT population). EAG concerns with the IPCW analysis are described in section 2.1.1.2. The company has not justified why the IPCW method was selected from those available for adjusting for treatment switching and it is unclear whether an alternative method would have yielded similar results. The company states that IPCW results should be interpreted with caution due to uncertainty whether the key assumption that there are no unmeasured confounders is supported.

Results of the original and IPCW adjusted analyses for OS and PFS are reported below in Table 4 and Table 5 respectively.

Table 4 Original and IPCW results for overall survival by geographic region and the overall ITT Population of the STARGLO trial (CCOD2)

Population	Analysis	R-GemOx n	Glofit-GemOx n	HR (95% CI)
ITT	Original	91	183	0.62 (0.43, 0.88)
ITT	IPCW	[redacted]	[redacted]	[redacted]
Europe	Original	26	62	1.09 (0.54, 2.18)
Europe	IPCW	[redacted]	[redacted]	[redacted]

Population	Analysis	R-GemOx n	Glofit-GemOx n	HR (95% CI)
North America	Original	10	15	2.62 (0.56, 12.34)
North America	IPCW	[redacted]	[redacted]	[redacted]
RoW	Original	55	106	0.41 (0.27, 0.64)
RoW	IPCW	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from EMA Document Figure 1
CI, confidence interval; Glofit-GemxOx, glofitamab in combination with gemcitabine and oxaliplatin HR, hazard ratio; IPCW, inverse probability of censoring weighting, IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin; RoW, Rest of World.

Table 5 Original and IPCW results for IRC-assessed PFS by geographic region and the overall ITT Population of the STARGLO trial (CCOD2)

Population	Analysis	R-GemOx n	Glofit-GemOx n	HR (95% CI)
ITT	Original	91	183	0.4 (0.28, 0.57)
ITT	IPCW	[redacted]	[redacted]	[redacted]
Europe	Original	26	62	0.83 (0.44, 1.59)
Europe	IPCW	[redacted]	[redacted]	[redacted]
North America	Original	10	15	2.25 (0.48, 10.54)
North America	IPCW	[redacted]	[redacted]	[redacted]
RoW	Original	55	106	0.27 (0.17, 0.42)
RoW	IPCW	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from EMA Document Figure 2
CI, confidence interval; Glofit-GemxOx, glofitamab in combination with gemcitabine and oxaliplatin HR, hazard ratio; IPCW, inverse probability of censoring weighting, IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin; RoW, Rest of World.

2.3.2.2 Impact of COVID-19

The STARGLO trial was conducted during the COVID-19 pandemic. EMA Document section E1.4 states that in the Europe subgroup and Rest of the World subgroup of the STARGLO trial there were higher rates of COVID-19 infections that led to the withdrawal of treatment in the Glofit-GemOx arm compared to the R-GemOx arm. Furthermore, fatal adverse events due to COVID-19 were more frequent in the Europe subgroup compared to other regional subgroups. To investigate the impact of COVID-19 on OS across regions, the three prespecified COVID-19 sensitivity analyses on OS in the ITT population (SAP version 6.0 section 5.3.3) were applied to the regional subgroups:

- Sensitivity analysis 1: Patients who died due to COVID-19 (within 3 months of treatment discontinuation) censored to study treatment discontinuation.
- Sensitivity analysis 2: OS for patients who died due to COVID-19 censored on their date of death.
- Sensitivity analysis 3: OS for patients who experienced a COVID-19 adverse event censored to study treatment discontinuation date

Results of these sensitivity analyses are reported in EMA Document Table 19, which is partly reproduced in Table 6 below

Table 6 Sensitivity analyses of the impact of COVID-19 on overall survival by geographic region and the overall ITT Population of the STARGLO trial (CCOD2)

	OS HR (95% CI)			
	Overall ITT pop. (N=274)	**Europe (N=88)**	**North America (N=25)**	**RoW N=161**
Naïve analysis[a]	0.62 (0.43, 0.88)	1.09 (0.54, 2.18)	2.62 (0.56, 12.34)	0.41 (0.27, 0.64)
Sensitivity analysis 1[b]	0.57 (0.40, 0.82)	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2[c]	0.56 (0.39, 0.81)	[redacted]	[redacted]	[redacted]
Sensitivity analysis 3[d]	0.60 (0.42, 0.88)	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from EMA Document Table 19
CI, confidence intervals; HR, hazard ratio; ITT, intent-to-treat; pop., population; RoW, Rest of World.
[a] Patients not censored due to COVID-19.
[b] Patients who died due to COVID-19 (within 3 months of treatment discontinuation) censored to study treatment discontinuation.
[c] OS for patients who died due to COVID-19 censored on their date of death.
[d] OS for patients who experienced a COVID-19 adverse event censored to study treatment discontinuation date

Company comment #2 states the sensitivity analyses resulted in more favourable OS hazard ratios for the European subgroup. The EAG agrees with the company but notes the results for the naïve analysis and all three sensitivity analyses for the Europe subgroup are [redacted].

EAG conclusion on the generalisability of the STARGLO trial and subgroups

The EAG has critiqued the company's exploration of the generalisability of the STARGLO trial findings across geographical regions, but the relevance of this to UK clinical practice depends on an assumption that the European subgroup of STARGLO is reflective of UK clinical practice which the company have not explicitly discussed. Moreover, we have concerns about whether the IPCW approach was appropriate given that the company has not justified why the assumption of no unmeasured confounders would hold, has not explored alternative methods of adjustment for treatment switching, and has not conducted any of the analyses in the second-line subpopulation using the latest data cutoff from STARGLO, which is the population of key interest in the Draft Guidance Document.

2.4 Inclusion of Pola-BR as a comparator

The company reiterated their concern that Pola-BR (polatuzumab vedotin with bendamustine and rituximab) should not be included as a comparator for the third-line population (Company comment #4). The company cite evidence from a retrospective analysis of a real-world UK cohort reported at the 2025 British Society of Haematology (BSH) Annual Conference that prior bendamustine exposure (and hence exposure to PolaBR) may adversely impact the efficacy of subsequent therapy with bispecific antibodies including glofitamab and epcoritamab.[4] However, we note that the inferior responses to subsequent bispecific antibody therapy (glofitamab monotherapy) among patients in the cohort who had previously received bendamustine were restricted to those who had received bemdamustine within 6 months prior to the glofitamab therapy.[4] The company cite the latest BSH guidelines which also acknowledge that prior bendamustine exposure may adversely impact the efficacy of subsequent bispecific antibody therapy, especially if the interval between these therapies is short.[5] The BSH guidelines also acknowledge the possibility of CAR-T cell therapy failure if a patient had received prior bendamustine therapy.[5] The EAG notes that these concerns about potential negative impacts of prior bendamustine use on subsequent bispecific antibody efficacy and CAR-T cell therapy success are acknowledged in section 3.4 of the Draft Guidance and therefore do not constitute new evidence.

EAG conclusion on the inclusion of Pola-BR

The company have restated their rationale for why they believe Pola-BR is not relevant as a comparator. The company's response does not include any new evidence beyond that considered at ACM1 and discussed in the Draft Guidance Document.

2.5 Updated cost effectiveness results

In response to the draft guidance, the company have updated their base case to use data from the most recent data cut from the STARGLO trial, which provides an additional 14.5 months' of clinical outcomes data.

Using information from the longer follow-up, the company now applies the log-normal distribution at 25 months for both PFS and OS (approximately 30% and 50% of patients remain at risk, respectively). The company provides a scenario analysis where the distribution is applied at 20 months as per their original economic analysis (Company Response Appendix Table 12, scenario 1). The EAG was able to reproduce the results of this scenario analysis.

The EAG considers the company's choice of parametric curve to be appropriate, because it is the same distribution as used previously for both the Glofit-GemOx and R-GemOx arms, and a reasonable proportion of patients remain at risk (30% for PFS and 50% for OS) when the curves are fitted.

The company's updated analysis includes the NICE committee's preferred assumptions (Draft Guidance section 3.14):

- Mortality reverts to near the general population mortality (standardised mortality ratio of 1.09) after 6 years
- 15% of people in the Glofit-GemOx arm receive subsequent palliative care
- The EAG notes that subsequent palliative care is described as 'Other/Clinical Trial' in the model and is associated with a weekly treatment cost of £600, which is the average weekly cost of treatment with:
    - Bendamustine and rituximab
    - R-GemOx
    - R-CHOP
    - Other R-chemo regimens
    - Other chemo regimens (not including rituximab)
    - Pola-BR

    We are unclear why this cost reflects palliative care appropriately (as it includes treatment costs), but we note that setting this weekly cost for 'Other/Clinical Trial' to £0 has a negligible effect on the ICER results, less than £100 per QALY for both comparisons. Consequently, we have not altered the cost for this category.

- A one-off end of life healthcare cost is applied
- The company's analysis aligns with the majority of the EAG's preferred assumptions:
  - The number of GemOx cycles has been reduced from eight to six
  - Progression resource costs have been applied as per the EAG base case
  - Administration costs have been applied once per combination, not once per treatment

The company presents the pairwise results of their revised base case (dated 18/08/2025) for Glofit-GemOx compared against R-GemOx and Pola-BR in Company comment #6 Table 1 and in the Company Appendix section 4.3.1. A fully incremental analysis is provided in section 4.3.5 of the Company Appendix. The EAG has checked and verified the company's revised base case.

The EAG notes that the incremental analysis uses a subset of both the STARGLO Glofit-GemOx patient population and a subset of the GO29365 study Pola-BR patient population to standardize the patient cohorts as much as possible (described in section 2.1 of the company's Pola-BR scenario analysis document, dated 05/06/2025). Furthermore, excluding R-GemOx leaves Pola-BR as the only comparator for consideration. But, during our assessment of the original CS, clinical advice to the EAG was that the majority of patients with diffuse large B-cell lymphoma who are transplant ineligible receive rituximab-chemotherapy regimens (appropriately represented by R-GemOx in this appraisal) second-line, with only an estimated 10-20% of patients receiving Pola-BR treatment second-line.

The company's cost-effectiveness results are reproduced in Table 7 and Table 8 below and include the confidential Patient Access Scheme (PAS) discount prices for glofitamab, polatuzumab and obinutuzumab. However, these results do not include existing discounts for subsequent therapies in the model. The EAG has repeated the company's deterministic pairwise and incremental base case analyses, and scenario analyses (shown in Company Response Appendix Tables 10-13), applying all appropriate PAS discounts in a confidential addendum to this document.

Table 7 Company deterministic revised base case, pairwise comparison (PAS discounts for glofitamab, polatuzumab and obinutuzumab)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Glofit-GemOx versus R-GemOx					
Glofit-GemOx	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
R-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	£6,862
Glofit-GemOx versus Pola-BR					
Glofit-GemOx	[redacted]	[redacted]			
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	£15,612
Source: Partly reproduced from Company Response Appendix Table 10 Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, Patient Access Scheme; Pola-BR, polatuzumab with bendamustine and rituximab; QALYs, quality-adjusted life years; R-GemOx, rituximab with gemcitabine and oxaliplatin					

Table 8 Company deterministic revised base case, fully incremental analysis (PAS discounts for glofitamab, polatuzumab and obinutuzumab)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
R-GemOx	[redacted]	[redacted]			
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Glofit-GemOx (Pola-BR population)	[redacted]	[redacted]	[redacted]	[redacted]	£15,612
Source: Reproduced from Company Response Appendix Table 13 Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, Patient Access Scheme; Pola-BR, polatuzumab with bendamustine and rituximab; QALYs, quality-adjusted life years; R-GemOx, rituximab with gemcitabine and oxaliplatin					

Pairwise results of the company's probabilistic sensitivity analysis are presented in Company Appendix Table 11. We agree with the company that results from the probabilistic sensitivity analysis are comparable to the deterministic base case results.

The cost-effectiveness acceptability curve is shown in Company Appendix Figure 14 and the incremental cost-effectiveness plane in Company e Appendix Figure 15. The probability of Glofit-GemOx being the most cost-effective treatment is [redacted] versus R-GemOx, and [redacted] versus Pola-BR, assuming a willingness-to-pay (WTP) threshold of £30,000 per QALY gained.

Company Appendix section 4.3.3 presents the updated deterministic sensitivity analysis. The EAG notes that the parameter with the largest effect on the ICER result, for both

comparisons, is the cost of subsequent therapy (Company Appendix Figure 17 and Figure 19).

EAG conclusion on the updated cost effectiveness results

The EAG considers the company's choice of parametric curve and applying the distribution at 25 months for both PFS and OS to be reasonable. We acknowledge the difficulties of providing an incremental analysis in this case and we consider that pairwise comparisons are worthwhile in this instance.

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