NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using glofitamab with gemcitabine and oxaliplatin in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2025

Note that this document is not NICE's final guidance on glofitamab with gemcitabine and oxaliplatin. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using glofitamab with gemcitabine and oxaliplatin in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 19 August 2025
- Second evaluation committee meeting: To be confirmed
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Glofitamab plus gemcitabine and oxaliplatin should not be used to treat relapsed or refractory diffuse large B-cell lymphoma not otherwise specified in adults who are not eligible for autologous stem cell transplant.

1.2 This recommendation is not intended to affect treatment with glofitamab plus gemcitabine and oxaliplatin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Glofitamab plus gemcitabine and oxaliplatin is not required to be funded in the NHS in England to treat relapsed or refractory diffuse large B-cell lymphoma not otherwise specified in adults who are not eligible for autologous stem cell transplant. It should not be used routinely in the NHS in England.

This is because there is not enough evidence to determine whether glofitamab with gemcitabine and oxaliplatin is value for money in this population.

Why the committee made these recommendations

Usual treatment for relapsed or refractory diffuse large B-cell lymphoma not otherwise specified in people who cannot have an autologous stem cell transplant is rituximab with gemcitabine and oxaliplatin (R-GemOx) or polatuzumab vedotin with rituximab and bendamustine (Pola-BR).

Clinical trial evidence shows that glofitamab plus gemcitabine and oxaliplatin increases how long people have before their cancer gets worse compared with R-GemOx. But there is uncertainty about how long people live after having glofitamab plus gemcitabine and oxaliplatin.

Glofitamab plus gemcitabine and oxaliplatin has not been directly compared in a clinical trial with Pola-BR. Indirect comparisons suggest it is likely to work as well. But this is uncertain because it is not clear if the evidence represents people who would have treatment in the NHS.

Because of the uncertainties in the clinical evidence, there are uncertainties in the economic model. It is not possible to determine the most likely cost-effectiveness estimate for glofitamab plus gemcitabine and oxaliplatin. So, it should not be used.

2 Information about glofitamab with gemcitabine and oxaliplatin

Marketing authorisation indication

2.1 Glofitamab (Columvi, Roche) in combination with gemcitabine and oxaliplatin is indicated for 'the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified who are ineligible for autologous stem cell transplant'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for glofitamab.

Price

2.3 The list price for glofitamab is £687 per 2.5-mg vial and £2,748 per 10-mg vial (excluding VAT, BNF online, accessed July 2025).

2.4 The list price for gemcitabine is £14 per 200-mg vial of powder for solution for infusion and £25 per 1000-mg vial of powder for solution for infusion (excluding VAT, BNF online, accessed July 2025).

2.5 The list price for oxaliplatin is £147.82 per 50 mg (10 ml) vial of concentrate for solution for infusion and £295.63 per 100 mg (20 ml) vial of concentrate for solution for infusion (excluding VAT, BNF online, accessed July 2025).

2.6 The company has a commercial arrangement. This makes glofitamab available to the NHS with a discount and it would have also applied to this indication if glofitamab with gemcitabine and oxaliplatin had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.7 Information on the Carbon Reduction Plan for UK carbon emissions for Roche will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Roche, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition and patient perspective

3.1 Diffuse large B-cell lymphoma (DLBCL) is a type of fast-growing blood cancer that affects white blood cells called B lymphocytes (B cells). There are subtypes of DLBCL. But most people will not have a specific type, so have DLBCL not otherwise specified (NOS). Symptoms such as fever, night sweats, weight loss and local effects of lymph node enlargement can have a significant impact on quality of life. Patients described the psychological impact of a diagnosis. People can have anxiety or insomnia, which can increase if their lymphoma has relapsed or treatment has not worked. Treatment aims to cure DLBCL-NOS but in many people it is refractory to treatment or relapses after a period of remission. Patients noted that having to wait for multiple relapses to access the newest treatments made a chance of cure smaller and could cause more physical side effects. Some people are not eligible for autologous stem cell transplant (ASCT). These people are generally older and frailer than people who are eligible for ASCT. So, having another treatment option

available after the first relapse or treatment failure would be an advantage.

Comparators

Treatment options

3.2 Initial treatment for DLBCL-NOS is rituximab in combination with cyclophosphomide, doxorubicin, vincristine and prednisolone (R-CHOP) or polatuzumab vedotin, rituximab, doxorubicin, cyclophosphamide and prednisolone (Pola-R-CHP; NICE technology appraisal 874). Treatment options if DLBCL-NOS relapses or is refractory to treatment depend on whether the person is eligible for an ASCT. When DLBCL-NOS is not cured after first-line treatment in people who are not eligible for ASCT, the possible treatments are rituximab combined with 1 or more chemotherapy or polatuzumab vedotin with rituximab and bendamustine (Pola-BR; NICE Technology appraisal 649).

Rituximab with gemcitabine plus oxaliplatin

3.3 The company stated rituximab with gemcitabine plus oxaliplatin (R-GemOx) represented the standard treatment in UK clinical practice in people who are not eligible for ASCT. The clinical experts agreed that R-GemOx is the most appropriate rituximab-chemotherapy option used as a second-line treatment for people with DLBCL-NOS who are not eligible for ASCT. The clinical experts also agreed that R-GemOx is the most commonly used treatment at this point in the pathway. The committee accepted the positioning of glofitamab with gemcitabine and oxaliplatin (Glofit-Gem-Ox) as a second-line treatment option for people with relapsed or refractory DLBCL-NOS who are not eligible for ASCT, and agreed that R-GemOx was a relevant comparator.

Pola-BR

3.4 Pola-BR is a treatment option for relapsed or refractory DLBCL-NOS in people who are not eligible for ASCT. Based on advice from UK clinical

experts, the company stated that Pola-BR is rarely used at second line because:

- polatuzumab vedotin is recommended as a combination first-line treatment for DLBCL-NOS and commissioning criteria do not allow retreatment with polatuzumab vedotin
- Pola-BR is not often used as a second-line treatment for relapsed or refractory DLBCL-NOS
- Pola-BR should be avoided by people who may have chimeric antigen receptor (CAR) T-cell therapy in the future. The British Society of Haematology's guidance states that previous bendamustine treatment is associated with CAR T-cell therapy manufacturing failure and inferior outcomes. There is also concern that bendamustine can have a negative impact on the efficacy of subsequent bispecific antibodies (glofitamab and epcoritamab).

The company stated that Pola-BR use at this point in the pathway would continue to decline. So, it did not consider it a relevant comparator. The NHSE clinical lead for the Cancer Drugs Fund explained that despite the number of new registrations of Pola-BR reducing from 34 per month in 2024 to 28 per month in the first 4 months of 2025, the proportion of these registrations that were for second-line use remained high (about 59%). So, NHSE's opinion is that Pola-BR should be a comparator. The clinical experts noted that the use of Pola-BR has reduced and will continue to do so. But they explained it would still be a treatment option in people who did not have Pola-R-CHP at first line because they were not eligible or were diagnosed before it was available. Also, 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 committee concluded that although Pola-BR use is reducing, there are still some people who would have it as second-line treatment. So, it is a relevant comparator.

Clinical effectiveness

Data sources

3.5 Clinical evidence came from an ongoing international, phase 3, open-label randomised study (STARGLO). This evaluated the efficacy and safety of Glofit-Gem-Ox (n=183) compared with R-GemOx (n=91) in people with relapsed or refractory DLBCL-NOS who had had at least 1 line of systemic therapy and were not eligible for ASCT. People in the Glofit-Gem-Ox arm had pre-treatment with a single dose of obinutuzumab before having stepped-up dosing of glofitamab. People who had had only 1 line of therapy were a post-hoc second-line subgroup (n=172) of the whole trial population (n=274). Evidence from this subgroup directly informed the company's economic model (see section 3.8). The second-line subgroup had a median follow-up of 20.2 months for overall survival. There was a 33% reduction in risk of death in people having Glofit-Gem-Ox compared with people having R-GemOx (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.41 to 1.07; p=0.092). The median follow-up for progression-free survival in the second-line subgroup was 15.5 months. The risk of a progression-free survival event was 59% lower for people having Glofit-Gem-Ox compared with R-GemOx (HR 0.41, 95% CI 0.25 to 0.67; p=0.0002). The committee noted that the confidence interval for the overall-survival hazard ratio crossed 1, so was not statistically significant. The company explained that more recent data from STARGLO has become available that reduces the uncertainty in the estimates. The committee noted that the results of these further follow-up analyses in the second-line subgroup may help resolve some of the uncertainties.

Generalisability of the STARGLO population to the NHS

3.6 The committee noted that the data for the second-line subgroup in STARGLO showed non-significant results for overall survival but was statistically significant for progression-free survival. It also noted there had been more censoring for people in the Glofit-Gem-Ox arm than in the R-GemOx arm. The EAG noted the analyses without censoring for patients

who had any new anti-lymphoma treatment, which were not permitted during the trial (including radiotherapy and systemic therapies).These analyses gave similar results to those with censoring for progression-free survival, which explained the consistent statistically-significant outcomes for progression-free survival across the analyses. But the second-line subgroup of STARGLO was a post-hoc subgroup of the full trial population and had not been pre-specified in the trial protocol. So, the EAG suggested that statistical analyses of the second-line subgroup should be considered exploratory. The EAG noted that subgroup analyses of STARGLO showed differences in outcomes between geographical regions. Ethnicity was a pre-specified subgroup in STARGLO but the results were not reported for the second-line subgroup. The company had also identified differences in the hazard ratio for OS in the subgroups from the full trial population by ethnicity (Asian HR 0.40, 95% CI 0.25 to 0.65; White HR 1.24, 95% CI 0.66 to 2.3) and by geographic region (Europe HR 1.09, 95% CI 0.54 to 2.18; North America HR 2.62, 95% CI 0.56 to 12.34; 'rest of world' HR 0.41, 95% CI 0.27 to 0.64). It stated this was because of the small patient numbers and the subgroups being underpowered resulting in wide confidence intervals. It also stated that geographical region was not a stratification factor so there are imbalances in populations. The clinical experts agreed that these results may have been influenced by small patient numbers and the differences may be because of different patient characteristics, which are imbalanced within subgroups. The committee noted that data presented to the European Medicines Agency showed a higher rate of people deciding not to have an ASCT (rather than not being ineligible for it) in Asia than in Europe. This might have contributed to regional differences between treatment arms. The committee noted this might have meant people in the Asian region may have been fitter than those who would not be eligible for an ASCT or eligible for second-line treatment with Glofit-Gem-Ox in UK clinical practice. The clinical experts explained that the open-label design and access to subsequent treatments might also contribute to uncertain

outcomes. The committee noted that evidence presented to the US Food and Drug Administration showed variation in the baseline data by region for the whole population of STARGLO because in Asia:

- people were younger (median age 62 years) than in the non-Asian region (median age 71)
- 65% of people had refused ASCT compared with 7% of people in the non-Asian region
- 2% of people had been previously treated with CAR T-cell therapy compared with 13% of people in the non-Asian region
- 81% of people had relapse within 12 months of first-line treatment compared with 64% of people in the non-Asian region
- people had shorter duration of treatment with R-GemOX (1.1 months) compared with the non-Asian region (3.1 months).

The committee agreed that the substantial variability contributed to uncertainty in interpreting the STARGLO data. It could not conclude if the trial was generalisable to the UK clinical population. So, it would like to see further statistical analyses to help explore this variability and to inform conclusions about the applicability of the STARGLO second-line data to UK clinical practice.

Indirect comparison for Pola-BR

3.7 The company did an inverse probability of treatment weighting analyses. It compared people having second-line treatment with Glofit-Gem-Ox from STARGLO with people having second-line treatment with Pola-BR in GO29365, a phase 1b/2 study that was the main trial informing NICE Technology appraisal 649. Subsets of the trial populations were used to remove differences in enrolment criteria and to limit the analyses to people who had previously had 1 line of therapy. But even after subsetting the populations, there were still imbalances between covariates of interest and the effective sample size was reduced. The company did 4 analyses.

But its main analysis did not adjust for 2 missing covariates (cell type or origin and bone marrow involvement) in the GO23965 study. Missing values of other covariates were set to be equal to the mean or mode of each covariate. The EAG was satisfied that the lack of adjustment for the missing covariates would not create any significant bias. But it was uncertain about the impact that other missing data might have on the results. So, it decided the most robust analysis was the analysis with multiple imputation for any missing values. It noted that the hazard ratios and 95% confidence intervals for overall survival and progression-free survival were similar across all analyses. But the proportional hazards assumption (that hazard ratios remain constant over time) did not hold in the economic model, so uncertainty from the indirect comparison was not captured in the model. The company considers all results from the indirect comparison confidential so they cannot be reported here. The committee noted that the evidence used to inform the company's scenario analysis comparing the cost effectiveness of Glofit-Gem-Ox with Pola-BR came from the second-line subgroup of STARGLO. It recalled its uncertainty about generalising about the STARGLO data to UK clinical practice (see section 3.6). So, it concluded that it would like to see further evidence on the effectiveness and generalisability of the STARGLO data to inform its decision about the appropriateness of the company's indirect comparison. Also, the GO23965 study had substantially longer follow up than STARGLO. So, the committee concluded that analyses updated with the latest data cut from STARGLO would help to reduce the uncertainty.

Economic model

Company's model

3.8 The company used a partitioned survival model to estimate the cost effectiveness of Glofit-Gem-Ox. The model included 3 health states: progression-free survival, post-progression survival and death. The proportion in each health state at different time points was calculated using progression-free survival and overall survival curves from

STARGLO. The committee concluded that the model structure was acceptable for decision making.

Assumptions

Overestimation of survival estimates

3.9 The company extrapolated time-to-event outcomes using parametric curves over the time horizon of the cost-effectiveness analysis. It chose to use the log-normal distribution for both Glofit-Gem-Ox and R-GemOx in its base case. It assumed that people who are alive and progression free at 3 years enter long-term remission. At this point, people do not continue to progress, revert to near general-population utility values and do not accrue further costs. The company also assumed that people who were alive at 3 years had a similar mortality to the general population (with a 9% excess applied). It stated this was in line with what had been accepted in the NICE technology appraisal for glofitamab monotherapy treating relapsed or refractory DLBCL after 2 or more systemic treatments (TA927). The company's clinical expert had agreed that at 3 years it is clinically plausible that people with DLBCL-NOS who are not eligible for ASCT would enter long-term remission if they were progression-free after second-line treatment. But the committee noted that the current evaluation is in an earlier treatment line than TA927, which assumed that mortality risk reverts to near the general population after 3 years. This was based on almost everyone in the cohort still alive being progression-free. But the EAG noted that at 3 years in this model there was still a substantial proportion of patients alive with progressed disease (about 14% in the Glofit-Gem-Ox arm and 18% in the R-GemOx arm). So, the EAG preferred to set mortality near to the general population from 6 years, because this was the point in the model when almost everyone in the cohort still alive was progression-free. The EAG also stated that the company's assumptions resulted in optimistic overall-survival estimates compared with the literature. Overall survival in the company's model was 39% at 2 years and 26% at 5 years for people having R-GemOx. The

EAG did a literature search of long-term survival in people with refractory or relapsed DLBCL-NOS having R-GemOx. It identified 2 studies: Cazalles et al. (2021) reported a 2-year overall-survival rate of 32% and Mounier et al. (2013) reported a 5-year overall-survival rate of 14%. Setting the time point at which mortality reverts to near general-population mortality to 6 years gave 5-year overall-survival estimates for R-GemOx of 17%, which was more aligned to the estimates reported in the literature. The committee noted that it was counterintuitive to consider someone 'cured' at 3 years if they have progressed disease. It concluded that it was most plausible to set the time point at which people are considered cured and mortality reverts to near general-population mortality to when most people still alive are progression free, and very few people have progressed disease. So, it agreed that the cure point should be set at 6 years and that doing so gave more plausible survival extrapolations.

Costs

Proportion having palliative care

3.10 In the company's model, the proportion of people having different subsequent treatments after progression was informed by data from STARGLO and UK clinical expert opinion. The company explained that this included a proportion of people who would go on to either a clinical trial or have palliative care. Based on clinical opinion, the company estimated that the proportion of people having palliative care or taking part in a clinical trial would be 15% after Glofit-Gem-Ox and less than 5% after R-GemOx. This was because the company's clinical experts advised that most people would go on to have third-line treatments. But the clinical advice to the EAG was that about 20% to 50% of people would not have subsequent treatment and would have palliative care instead. So, the EAG had assumed that costs of palliative care should be applied for 30% of people. The company noted that the proportion of people having palliative care had already been factored into its model calculations within the subsequent treatment costs. So, the company stated that applying the

EAG's additional proportion to the subsequent treatment costs was not appropriate. The clinical experts explained that the proportion of people going on to have palliative care was about 10% and closer to the company's estimate. The committee agreed that fewer people would now have palliative care since more subsequent treatments have become available. So, it accepted the costs for subsequent palliative care aligned with that in the company's base case.

End of life treatment costs

3.11 The company assumed that end of life care costs are included in the weekly resource-use costs used in the model. It had taken these from the NICE Technology appraisal for polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory DLBCL. The EAG noted that many inpatient bed days are used in the last year of life. The cost of inpatient bed days was not accounted for in the weekly resource-use costs. So, the EAG preferred to model the end of life costs separately using the one-off terminal care costs specifically for cancer patients (based on Georghiou and Bardsley 2014 and adjusting for inflation). The committee accepted the approach using a one-off cost.

Cost-effectiveness estimates

Acceptable ICER

3.12 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the level of uncertainty, specifically the issues of generalisability of STARGLO to NHS practice

and the impact on the clinical- and cost-effectiveness result (see section 3.6 and 3.7). This included:

- uncertainty in interpreting the trial results for the second-line subgroup for the comparison with R-GemOx (see section 3.6)
- uncertainty about the indirect treatment comparison with Pola-BR (see section 3.7)
- variability in trial outcomes by region contributing to uncertainty in interpreting the subgroup analyses.

The committee concluded that because of the uncertainties an acceptable ICER would be around £20,000 per QALY gained. But it considered that some of these uncertainties were potentially resolvable. So, it would reconsider the acceptable ICER if updated analyses are provided that reduce the uncertainties.

Committee's preferred analyses

3.13 Because of the uncertainties in the clinical and cost-effectiveness evidence, the committee concluded it was not possible to determine the most likely cost-effectiveness estimate. The ICERs cannot be reported here because there are confidential discounts for glofitamab and comparators. The committee agreed that to help address the uncertainty it would prefer to see:

- further follow-up data from STARGLO, specifically for the second-line subgroup
- additional statistical analyses exploring the uncertainty in the STARGLO subgroup data
- a fully incremental cost-effectiveness analysis including Glofit-Gem-Ox, R-GemOx and Pola-BR.

Assumptions used for the cost-effectiveness estimates

3.14 The company had done 2 pairwise comparisons evaluating the cost effectiveness of Glofit-Gem-Ox compared with R-GemOx and Glofit-Gem-Ox with Pola-BR separately. For the comparison with R-GemOx, the company's and EAG's base-case ICERs were below the upper end of the range normally considered an acceptable use of NHS resources. But for the comparison with Pola-BR, some results were above the range normally considered a cost-effective use of NHS resources. The company used the same assumptions in its analysis comparing Glofit-Gem-Ox and Pola-BR as the assumptions it had used in its base case for Glofit-Gem-Ox compared with R-GemOx. The committee would prefer to see a fully-incremental cost-effectiveness analysis, which should include its preferred assumptions:

- mortality should revert to near the general population (standardised mortality ratio of 1.09) after 6 years (see section 3.9)
- 15% of people in the Glofit-Gem-Ox arm should go on to have subsequent palliative care (see section 3.10)
- one-off end of life healthcare costs should be applied, rather than being included in weekly healthcare resource-use costs (see section 3.11).

Other factors

Equality

3.15 The committee did not identify any equality issues.

Conclusion

Recommendation

3.16 The committee concluded that it was unable to identify the most plausible ICER based on its preferred assumptions. So, Glofit-Gem-Ox should not be used for treating diffuse large B-cell lymphoma not otherwise specified in people who are not eligible for autologous stem cell transplant.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Steve O'Brien

Chair, technology appraisal committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Victoria Gillis-Elliott

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