NICE National Institute for Health and Care Excellence

NICE guidance

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Glofitamab is recommended, within its marketing authorisation, as an option for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic treatments. Glofitamab is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Treatment for relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments includes axicabtagene ciloleucel, polatuzumab vedotin with bendamustine plus rituximab, and rituximab-based chemotherapies.

Clinical trial evidence suggests that some people taking glofitamab reach complete remission, but in the trial, it was not compared with other treatments. Indirect comparisons suggest that glofitamab is likely to increase how long people live and how long people have before their condition gets worse, by:

- as much as polatuzumab vedotin with bendamustine plus rituximab
- more than bendamustine plus rituximab (which was used to represent all rituximab-based chemotherapies)
- less than axicabtagene ciloleucel, but the results might favour axicabtagene ciloleucel because of the way the trial was designed.

The cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. So, glofitamab is recommended.

2 Information about glofitamab

Marketing authorisation indication

2.1 Glofitamab (Columvi, Roche) 'as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy'.

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; company submission). An average course of glofitamab treatment per person, based on 5 cycles, is £46,536 including £3,312 for obinutuzumab pre-treatment (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes glofitamab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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.

Clinical need and treatment pathway

Evolving treatment pathway

3.1 At the time of this evaluation, there had been several recent changes to the treatment pathway for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after 2 or more systemic treatments. Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone (polatuzumab R-CHP) had recently been recommended for untreated DLBCL (NICE technology appraisal guidance 874). So its use earlier in the treatment pathway had increased, which was likely to lead to a reduction in the use of polatuzumab vedotin with bendamustine plus rituximab (polatuzumab-BR; NICE technology appraisal guidance 649) at later stages of treatment. Additionally, chimeric antigen receptor (CAR) T-cell therapies have been recommended: axicabtagene ciloleucel is used after 2 or more treatments (NICE technology appraisal guidance 872) and is available in the Cancer Drugs Fund after first-line chemoimmunotherapy (NICE technology appraisal guidance 895), and tisagenlecleucel is available in the Cancer Drugs Fund after 2 or more treatments (NICE technology appraisal guidance 567). Treatments in the Cancer Drugs Fund were not considered comparators in this evaluation because their availability in the NHS in the future is not guaranteed. The committee concluded that the treatment pathway has changed rapidly and that this would be considered in the decision-making process.

New treatment option

3.2 DLBCL is an aggressive type of cancer. Symptoms usually develop rapidly and

progress quickly. Treatments aim to cure DLBCL, but in many people, it is refractory to treatment, or it relapses after initial treatment. Patient and clinical experts highlighted the need for more treatment options after 2 or more treatments, because of the relapsing nature of DLBCL and the limited number of options after 2 or more treatments. They explained the significant impact that DLBCL has on quality of life for both people with DLBCL and their carers. The patient and clinical experts advised that the treatments that are available all have limitations. Because there are not many CAR T-cell therapy centres in the UK, access to CAR T-cell therapy can be restricted for people with DLBCL. Some people cannot travel to a different location for treatment, and some people do not want to be separated from their families for the duration of their treatment and monitoring. Rituximab-based chemotherapies (R-chemotherapies) can be debilitating because of their side effects, and the time needed to administer the treatment can interfere with everyday life. The committee concluded that there is an unmet need in this population and glofitamab offers a potential new treatment option after 2 or more treatments.

Comparators

3.3 The committee noted that treatment options for relapsed or refractory DLBCL after 2 previous systemic treatments, depend on which treatments the person has previously had and whether they are eligible for CAR T-cell therapy. After 2 or more previous treatments, the available options at the time of this evaluation were:

- polatuzumab vedotin plus rituximab and bendamustine (polatuzumab-BR; see NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma)
- axicabtagene ciloleucel (see NICE's technology appraisal guidance on axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies)
- tisagenlecleucel (for use in the Cancer Drugs Fund, see NICE's technology appraisal guidance on tisagenlecleucel for treating relapsed or refractory

diffuse large B-cell lymphoma after 2 or more systemic therapies)

- pixantrone (see NICE's technology appraisal guidance on pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma)
- rituximab-based chemotherapy (R-chemotherapy) regimens.

The company included polatuzumab-BR, axicabtagene ciloleucel and R-chemotherapy as comparators. The company did not consider pixantrone a relevant comparator because it is rarely used in clinical practice. Additionally, tisagenlecleucel was not included as a comparator because it is not routinely available in the NHS and is only available in the Cancer Drugs Fund. The clinical experts advised that rituximab with gemcitabine plus oxaliplatin (R-GemOx) is the most commonly used R-chemotherapy at this stage of treatment. Because of a lack of evidence, bendamustine plus rituximab (BR) was used to represent all R-chemotherapies used in this setting. The committee agreed that BR was an appropriate substitution for R-GemOx. The clinical experts and the NHS England Cancer Drugs Fund clinical lead advised that axicabtagene ciloleucel and polatuzumab-BR are still relevant comparators after 2 or more treatments, despite their increasing use at earlier stages of treatment. Additionally, they advised that some people would be treated with R-chemotherapy because of not being eligible for axicabtagene ciloleucel or polatuzumab-BR. The committee concluded that although the pathway is changing quickly, axicabtagene ciloleucel, polatuzumab-BR and R-chemotherapy are the relevant comparators.

Clinical evidence

Data sources

3.4 Clinical evidence for glofitamab came from an ongoing single-arm, phase 1 to 2 trial (called NP30179) collecting data on 17 cohorts of people having glofitamab. Three of the 17 cohorts in the trial were relevant to this evaluation and were combined for analysis. All 3 cohorts had pre-treatment with obinutuzumab followed by stepped-up dosing of glofitamab. The population

included adults with DLBCL that had relapsed after, or had not responded to, at least 2 previous systemic treatments. The clinical expert agreed that the trial showed a high rate of complete remission (the exact figures are considered confidential by the company and cannot be reported here). The committee concluded that the study suggests that glofitamab has a good chance of achieving complete remission but noted that the trial only had a single arm, meaning there was no evidence directly comparing glofitamab with another treatment.

Indirect comparison

3.5 There was no trial directly comparing glofitamab with any of the comparator treatments. So, the company did an indirect treatment comparison against each of the comparators, in which the pivotal glofitamab trial, NP30179, was compared with data from 1 key trial for each comparator. All comparisons were made between single arms and so were unanchored. Matching-adjusted indirect comparisons (MAICs) were done to compare glofitamab with axicabtagene ciloleucel and with BR (a proxy for R-chemotherapy). In the MAICs, data for some people in the glofitamab population was removed in line with the exclusion criteria in the comparator trial, and the remaining observations were matched and re-weighted based on the baseline characteristics of the comparator trial. This considerably reduced the effective sample size of the glofitamab population for each comparison. For the comparison with polatuzumab-BR, individual patient data was available from the trials for both treatments, allowing for inverse probability of treatment weighting to be used to more accurately match people. This also reduced the effective sample size of both populations. The committee noted that the sample size for the NP30179 trial was already small (155 people) and the indirect comparisons reduced this further, which increased uncertainty in the results. Additionally, the EAG was concerned about the lack of direct treatment comparisons, because indirect comparisons are inherently biased. This is because it is not possible to fully account for all the confounding variables and differences between populations. Also, the EAG noted that matching the NP31079 trial to 3 comparator trials resulted in 3 different sub-populations of the NP30179 trial being used. The EAG noted that this limited the ability to compare the 3 different indirect comparisons, because the baseline characteristics differed between the adjusted glofitamab populations. The committee concluded

that the indirect treatment comparisons could be used for decision making but that they were uncertain.

Comparison with axicabtagene ciloleucel

3.6 The comparison with axicabtagene ciloleucel compared data from the NP30179 trial with data from the single-arm ZUMA-1 trial, which included 101 people who had axicabtagene ciloleucel after 2 or more treatments. The data from the ZUMA-1 trial came from a modified intention-to-treat analysis that excluded people who were assigned to axicabtagene ciloleucel but did not have it. The clinical experts advised that this group of people would mostly be those whose cancer had rapidly progressed in the time between being approved for treatment and having the infusion. The glofitamab population was well matched to the baseline characteristics of the ZUMA-1 population. But it was likely that the ZUMA-1 population excluded the more unwell people, and it was not possible to adjust for this. The clinical experts also advised that axicabtagene ciloleucel needs a period of bridging therapy before it is administered. So, more unwell people who could not wait long enough for treatment were unlikely to have been referred for axicabtagene ciloleucel treatment at all. This means that it is likely that the axicabtagene ciloleucel population was healthier than those of the other comparators. The EAG agreed that this would bias the indirect comparison in favour of axicabtagene ciloleucel but that it was not possible to quantify the extent of this bias. Also, people in the ZUMA-1 trial were more likely to have re-treatment compared with people in the NP30179 trial, which may have biased the results further in favour of axicabtagene ciloleucel. The indirect comparison showed that axicabtagene ciloleucel improved progression-free survival (PFS) and overall survival (OS), and had higher rates of complete remission and overall response compared with glofitamab (the exact results cannot be reported here because they are considered confidential by the company). The committee noted the limitations with this comparison and that it was likely to be biased in favour of axicabtagene ciloleucel, but it concluded that axicabtagene ciloleucel was more effective than glofitamab.

Comparison with polatuzumab-BR

3.7 The comparison with polatuzumab-BR compared data from the NP30179 trial with data from the GO29365 trial. The GO29365 trial compared polatuzumab-BR with BR in people after 1 or more treatments, and included 152 people in the polatuzumab-BR arms. The comparison showed that there were no significant differences in efficacy outcomes between glofitamab and polatuzumab-BR. But, the committee noted that the glofitamab survival curves had a slightly lower rate of events, favouring glofitamab. Also, glofitamab had significantly reduced odds of discontinuation because of adverse events compared with polatuzumab-BR (the exact results cannot be reported here because they are considered confidential by the company). The committee concluded that there are likely to be no substantial differences in efficacy between glofitamab and polatuzumab-BR.

Comparison with bendamustine plus rituximab

3.8 The comparison with bendamustine plus rituximab (BR; a proxy for R-chemotherapy) compared data from the NP30179 trial, with data from a retrospective analysis of people having BR after 1 or more treatments (Hong 2018). The EAG advised that this study took place solely in South Korea and so may not be generalisable to the UK. It advised that the GO29365 trial (which informed the comparison with polatuzumab-BR) may have been more appropriate because it had an arm in which people had BR. The company noted that using the GO29365 trial led to balancing issues and a very small effective sample size. The comparison showed that glofitamab was more effective than BR for all of the efficacy outcomes evaluated (PFS, OS, overall response and complete remission; exact results cannot be reported here because they are considered confidential by the company). The committee concluded that despite some concerns with generalisability and small effective sample size, the comparison was valid and demonstrated that glofitamab was more effective than BR.

Economic model

Company's model

3.9 The company used a partitioned survival model to estimate the cost effectiveness of glofitamab. The model included 3 health states: progression-free, progressed disease and death. The probability of being in a given health state was calculated using the OS and PFS curves. The committee concluded that the model structure was acceptable for decision making.

Cure assumptions

3.10 The company model assumed that people whose cancer had not progressed for 3 years after starting their third treatment (with glofitamab or any of the comparators) would remain progression-free. It assumed their cancer would not progress at a later date and they would have a 10% utility decrement compared with the age-matched general population. The EAG advised that a 3-year cure point is reasonable but that there is uncertainty because of limited follow-up data. It advised that an assumption of a cure is more established for CAR T-cell therapies and that an assumption of no cure for glofitamab should also be considered. The company provided several sources of real-world and trial evidence to validate its assumption of cure for people not having CAR T-cell therapy. These studies showed that the risk of mortality begins to plateau after an initial period of 2 to 3 years. In particular, the Haematological Malignancy Research Network (HMRN) provided data on a group of people who had a third treatment, which shows that the risk of mortality begins to plateau after 1 to 3 years. However, the EAG noted that it was unable to critique the methodology and generalisability of this study because of the lack of information provided. The SCHOLAR-1 study, a retrospective study of around 600 people who had salvage therapy, none of whom had CAR T-cell therapy, showed a similar plateau. An updated data cut of the pivotal NP30179 study showed that remission lasted at least 18 months in 67% of people whose cancer was in complete remission. Clinical experts advised that they would consider people cured if their cancer remained in complete remission at 2 years. But they noted that longer follow up was needed to be sure of the proportion of people treated

with glofitamab that this would apply to. The committee concluded that there is uncertainty about the exact point at which people would no longer have a higher risk of cancer progression, but that assuming a cure point of 3 years was reasonable.

Excess mortality

3.11 The company's base-case model included the assumption that people who were still alive 3 years after starting a third treatment, only had a 9% increased risk of mortality compared with the age-matched general population. This rate of excess mortality was based on a French study (Maurer et al. 2014) which showed an excess mortality of 9% in 820 people with newly diagnosed DLBCL that had been progression-free for 2 years. The EAG said that this low level of excess mortality was too optimistic, citing another study (Howlader et al. 2017) which showed 41% excess mortality in people whose DLBCL had been in remission and progression-free 2 years after treatment. The committee also noted a third study (Jakobsen et al. 2017) which showed an excess mortality of 27% in people whose DLBCL was in complete remission and progression-free 2 years after treatment. Excess mortality rates of 27% and 41% were explored in sensitivity analyses. One clinical expert advised that people whose DLBCL is progression-free for 5 years would only be at slight (or no) increased risk of mortality compared with the age-matched general population. The clinical expert also advised that people who had had more intensive treatment regimens may be exposed to a higher risk of mortality after 3 years. The HMRN study showed that people whose DLBCL was progression-free 2 years after starting their first treatment were only at a very slightly increased risk of mortality compared with a healthy cohort matched for age. The committee noted that the scenario analyses that adjusted the excess mortality rate only had a small impact on the cost-effectiveness estimates. It concluded that there is uncertainty about the exact mortality risk for people whose disease has been progression-free for 3 years but that the company's assumption of 9% increased risk was reasonable.

Modelled cohort age

3.12 The company modelled background mortality as a function of the age distribution

in the NP30179 study, rather than the mean cohort age. The EAG advised that the age-distribution approach could better account for the heterogeneity seen in survival outcomes at this stage of treatment for DLBCL. But the company only applied the age-distribution approach to all-cause mortality and health-related quality of life. The EAG advised that it should also be applied to other outcomes, and its impact on costs must be fully explored. The EAG advised that because the company's approach was not correctly implemented, it would be more appropriate to use the mean cohort age to model background mortality. The committee preferred the EAG's approach because the company's approach was not consistently implemented but noted that the method of modelling background mortality only had a small impact on the cost-effectiveness estimates.

Severity

3.13 The committee considered the severity of DLBCL after 2 previous treatments (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company and EAG agreed that for the comparison with BR, the QALYs should have a higher weighting (1.2 times) for people having BR for DLBCL after 2 or more treatments, because of the severity of the condition. The company and EAG agreed that for the comparison with polatuzumab-BR the severity weighting did not apply. So, the committee concluded that the severity weight of 1.2 applied to the QALYs for the comparison with BR was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.14 NICE's health technology evaluations manual notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained,

decisions 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 evidence presented, but will also take into account other aspects including uncaptured health benefits. The committee agreed that the indirect treatment comparisons showed that glofitamab is more effective than BR (a proxy for R-chemotherapy), has comparable effectiveness to polatuzumab-BR, and is less effective than axicabtagene ciloleucel. But it agreed that there was inherent uncertainty because of the lack of direct evidence (see section 3.5). It also heard from clinical experts about the importance of glofitamab's high complete remission rate and of having more effective and accessible treatment options available after 2 or more treatments. The committee agreed that there were uncertainties around the cure assumption and the rate of excess mortality compared with the age-matched general population after 3 years. So, it agreed that it would accept an ICER at the lower end of the acceptable range because of these uncertainties. This would then allow the committee to have more confidence that the residual uncertainties would not result in the cost-effectiveness estimates being above the range that NICE considers an acceptable use of NHS resources.

Company and EAG cost-effectiveness estimates

3.15 Because of confidential commercial arrangements for glofitamab and the comparators, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company and EAG base cases differed in 2 areas, which were the key areas of remaining uncertainty:

- the excess mortality risk compared with the general population after 3 years; the company assumed 9% and the EAG assumed 41% (see section 3.11)
- how cohort age was used to model background mortality (see section 3.12).

In addition, there was some uncertainty as to whether a cure point of 3 years was appropriate for all treatments. However, in the absence of further evidence, the committee agreed that a cure point of 3 years was reasonable. The committee agreed that its preferred assumptions for the comparisons with glofitamab used the EAG's approach to model background mortality and

a 9% increase in background mortality compared with an age-matched general population. When comparing glofitamab with BR (as a proxy for R-chemotherapy) and with polatuzumab-BR, the ICERs were comfortably below £30,000 per QALY gained. When comparing with axicabtagene ciloleucel, glofitamab had substantially lower overall costs but a loss in QALYs, so it was less effective. The committee noted that in situations in which an ICER is estimated for a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment becomes. Using the committee's preferred assumptions, the ICER was substantially higher than £30,000 per QALY lost, so glofitamab was considered cost effective. The committee recalled that the indirect comparison was likely biased in favour of axicabtagene ciloleucel (see section 3.6), so the QALY loss may be overestimated. The committee also agreed that glofitamab would be more accessible than CAR T-cell therapies, including axicabtagene ciloleucel (see section 3.2), so some people may prefer to have glofitamab if it is an option. The committee concluded that glofitamab was a cost-effective treatment option compared with all relevant comparators.

Other factors

Innovation

3.16 The committee considered if glofitamab was innovative. It did not identify additional benefits of glofitamab not captured in the economic modelling. So, it concluded that all additional benefits of glofitamab had already been taken into account.

Equality

3.17 The company, clinical experts and patient experts outlined that there are barriers related to the delivery of CAR T-cell therapies, with many people having to travel long distances, or being unable to travel to therapy centres. The committee

agreed that access was an issue with CAR T-cell therapies, but that access to therapy centres could not be directly addressed through its recommendations. But the addition of glofitamab as another treatment option that does not need people to travel to a specialist centre will help ensure more people have access to effective treatments.

Conclusion

3.18 The most likely cost-effectiveness estimates for glofitamab are within the range that NICE considers an acceptable use of NHS resources compared with all 3 comparators. So, the committee concluded that glofitamab could be recommended for routine use in the NHS for treating relapsed or refractory DLBCL in adults who have had 2 or more systemic treatments.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because glofitamab has been available through the early access to medicines scheme, NHS England and integrated care boards have agreed to provide funding to implement this guidance 30 days after publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed of refractory diffuse large B-cell lymphoma after 2 or more systemic treatments and the doctor responsible for their care thinks that glofitamab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Committee 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.

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 appraisal), a technical adviser and a project manager.

Thomas Jarratt
Technical lead

Alexandra Filby
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Update information

Minor changes since publication

November 2023: We updated sections 2.1 and 2.2 upon publication of the summary of product characteristics for glofitamab.

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Accreditation