NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using epcoritamab 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: October 2023

Note that this document is not NICE's final guidance on epcoritamab. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using epcoritamab in the NHS in England.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: 21 November 2023
- Second evaluation committee meeting: 12 December 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Epcoritamab is not recommended, within its marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults after 2 or more systemic treatments.

1.2 This recommendation is not intended to affect treatment with epcoritamab 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for DLBCL after 2 or more treatments is rituximab-based chemoimmunotherapy, polatuzumab vedotin with bendamustine plus rituximab (polatuzumab-BR), or axicabtagene ciloleucel.

Epcoritamab has not been directly compared with usual treatment in a clinical trial. An indirect comparison suggests that people having epcoritamab live for longer than people taking rituximab-based chemoimmunotherapy, but the results are uncertain. It is not clear from indirect comparisons if people taking epcoritamab live longer or have longer before their cancer gets worse than people having polatuzumab-BR or axicabtagene ciloleucel.

Because of the uncertainties in the clinical evidence and some uncertainties with the assumptions in the economic model, it is not possible to determine a reliable cost-effectiveness estimate. So epcoritamab is not recommended.

2 Information about epcoritamab

Marketing authorisation indication

2.1 Epcoritamab (Tepkinly, AbbVie) is indicated for ‘adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy’.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for epcoritamab.

Price

2.3 The list price for epcoritamab is confidential until confirmed by the Department of Health and Social Care.

2.4 The company has a commercial arrangement, which would have applied if the epcoritamab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by AbbVie, 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 have 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) has recently been recommended for untreated DLBCL (NICE technology appraisal guidance 874). So its use earlier in the treatment pathway has increased, which is 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 T-cell (CAR-T) 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. At the time of the committee meeting, glofitamab – which has a similar mechanism of action to epcoritamab – was being evaluated (NICE technology appraisals guidance TA927). An evaluation of loncastuximab tesirine in the same indication was also underway. 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 available treatments all have limitations. Although there are a number of CAR-T centres in the UK, another option such as epcoritamab would be useful for some people whose disease is rapidly progressing or for people who live a long way from a CAR-T centre or do not want to be separated from their families for the duration of their treatment and monitoring. The clinical experts noted that bispecifics such as epcoritamab can be administered in the outpatient setting in non-CAR-T centres and this can improve access to treatment. Epcoritamab is the only subcutaneous treatment currently available. This could improve access to treatment compared with other treatments such as CAR-T therapies, particularly for people who would like to avoid longer stays in hospital to avoid potentially catching other illnesses. The clinical expert noted that epcoritamab is easier to deliver, needs less hospital time and

does not need a cannula to be put in, compared with current treatments. But they noted that epcoritamab is taken until progression or unacceptable toxicity, rather than for a fixed number of cycles, which some people may find burdensome. Rituximab-based chemoimmunotherapy (R-based CIT) can be debilitating because of its 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 that epcoritamab 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 therapy. After 2 or more previous treatments, the available options at the time of this evaluation were:

- 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 (through 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)
- R-based CIT regimens.

The company used R-based CIT as the comparator for people who cannot have or choose not to have intensive treatment ('population A') and axicabtagene ciloleucel for people who can have intensive treatment ('population B'). Intensive treatment was defined as either an autologous stem cell transplant or CAR-T therapy. The company did not consider polatuzumab-BR a relevant comparator in the third line. This was because polatuzumab is now being used in untreated disease as part of polatuzumab R-CHP (see section 3.1) and would not likely be used again. The company's clinical experts had noted that, by approximately February 2025, they would expect less than 5% of people to be having polatuzumab-BR as third-line treatment. The company did a scenario in population A with polatuzumab-BR as a comparator. The EAG considered that polatuzumab-BR was a relevant comparator because its clinical experts noted it will still be an option for some people. 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 have R-based CIT because of not being eligible for axicabtagene ciloleucel or polatuzumab-BR. The company did not consider pixantrone a relevant comparator because it is rarely used in clinical practice; this was confirmed by the clinical experts during the meeting. Additionally, tisagenlecleucel was not included as a comparator because it is only available in the Cancer Drugs Fund. The committee noted that NICE had very recently recommended glofitamab, but it could not be considered a comparator because it was not yet routine clinical practice. A clinical expert noted that while the treatment pathway previously depended on eligibility for intensive treatment, it now depended on time to relapse after initial treatment because of the introduction of more treatments that are easier to deliver. The committee concluded that although the pathway is changing quickly,

axicabtagene ciloleucel, polatuzumab-BR and R-based CIT are the relevant comparators after 2 or more systemic treatments.

Clinical evidence

Data sources

3.4 Clinical evidence for epcoritamab came from the expansion part of an ongoing single-arm, phase 1 to 2 trial (EPCORE TM NHL-1) collecting data on 3 cohorts of people having epcoritamab. One of the cohorts included adults with DLBCL and other types of large B-cell lymphoma (LBCL) that had relapsed after, or had not responded to, at least 2 previous systemic treatments, and was included in the submission. The EAG noted that EPCORE TM NHL-1 only included people with Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 to 2, and people who were ineligible for an autologous stem cell transplant or for whom the transplant failed, but the decision problem was broader than this. The EAG's clinical expert noted that most of the people who would have epcoritamab in clinical practice would have ECOG scores of 0 to 2. But, the clinical expert would prefer not to exclude people with higher ECOG scores. Clinical experts agreed at technical engagement, noting that approximately 5% to 10% of people eligible for epcoritamab will have an ECOG score of 3. They also noted that most people who are eligible for epcoritamab will be ineligible for an autologous stem cell transplant. The clinical experts considered that a high proportion of people in the trial had complete remission of disease with epcoritamab (the company considers the exact figures confidential so they cannot be reported here). The committee concluded that the study was broadly generalisable to clinical practice and the results were promising.

Indirect comparison

3.5 There were no trials directly comparing epcoritamab with any of the comparator treatments. So, the company did an indirect treatment comparison against each comparator, in which the pivotal epcoritamab

trial, EPCORE TM NHL-1, 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 in which the epcoritamab trial population was matched to the populations included in the comparator trials on important reported characteristics. In the MAICs, data for some people in the epcoritamab population was removed to match the population in the comparator trial (see section 3.6). 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 epcoritamab population for each comparison. The company used MAICs that were adjusted for only some reported factors ('partially adjusted') in its economic model base case. The EAG had substantial concerns about the partially adjusted MAICs and considered that full adjustment for all reported baseline characteristics is necessary for unanchored MAICs, as noted in the NICE Decision Support Unit's technical support document 18. The company provided MAICs with adjustment for all reported factors ('fully adjusted') for all comparators but considered that these produced clinically implausible results. The company also considered that the fully adjusted MAICs had a risk of over-adjustment, because UK clinical experts noted that several variables are correlated (such as disease stage and International Prognostic Index score). It noted that bias may be introduced by reducing the sample size further. The EAG acknowledged that the smaller sample sizes in the fully adjusted MAICs made the results less precise and more uncertain (that is, increased the confidence intervals), but it preferred accuracy of results over precision. The EAG considered that using partially adjusted MAICs did not make the trials more comparable, but instead obscured the potential lack of comparability between trials. It noted that it was possible that the differences between studies may be too great to adjust for. The EAG preferred using fully adjusted MAICs for the polatuzumab-BR and axicabtagene ciloleucel comparisons, and an analysis with 9 of 10 reported variables adjusted for

in the comparison with R-based CIT because the fully adjusted MAIC produced clinically implausible results. But it noted that the company only provided fitted curves from the fully adjusted results (to enable the results to be used in the model) for the comparison with R-based CIT. This meant the EAG was unable to test the impact of using the fully adjusted MAICs on the cost-effectiveness estimates for the comparisons with polatuzumab-BR and axicabtagene ciloleucel. In general, the committee was concerned about the lack of direct treatment comparisons, because indirect comparisons are inherently uncertain and potentially biased. This is because it is not possible to fully account for all the confounding variables and differences between populations. The committee concluded that the results from the indirect treatment comparisons were very uncertain. It would like to see further scenario analyses using the fully adjusted MAICs in the model (for polatuzumab-BR and axicabtagene ciloleucel) to understand the full impact on the cost-effectiveness estimates.

People who cannot have or do not want intensive treatment (population A)

3.6 For the MAICs for population A, the company included a subgroup from EPCORE TM NHL-1 that only included people who had not had prior CAR-T therapy. This was because the comparator trials did not include people who had had prior CAR-T. The EAG noted that in clinical practice some people will have had prior CAR-T therapy and that it was unclear if results from the MAICs would apply to this population. The EAG was also concerned that it was unclear whether the EPCORE TM NHL-1 population included in the MAICs was ineligible for intensive treatments, as it was possible some eligible people were also included. To assess the impact of this on the results of the MAIC, the EAG requested:

- the baseline characteristics used to determine ineligibility for intensive treatments

- efficacy outcomes for the subgroup that was ineligible for intensive treatments
- MAICs including the subgroup from EPCORE TM NHL-1 ineligible for intensive treatments (for both efficacy estimates and to derive utilities).

The company did not provide this information but noted that the epcoritamab population used in the MAICs was ineligible for CAR-T therapy (which the EAG noted was not the same as being ineligible for intensive treatments). The company also considered that it was inappropriate to adjust the epcoritamab population by eligibility for intensive treatments without doing the same to the comparator populations, but it did not have individual patient data from comparator populations to do this analysis. The committee concluded that there was some unresolvable uncertainty about whether the results were applicable to people who had previously had CAR-T therapy. It acknowledged the uncertainty about whether the populations included in the MAICs were ineligible for intensive treatments, but considered the additional information and analyses requested by the EAG may help to reduce this uncertainty.

Comparison with rituximab-based chemoimmunotherapy

3.7 For the comparison with R-based CIT, data from the EPCORE TM NHL-1 trial was matched to data from SCHOLAR-1. This was a retrospective observational study which pooled together data from 2 phase 3 clinical trials and 2 observational cohorts of people with refractory LBCL having R-based CIT. The data used in the company's submission was taken from a paper published by Neelapu et al. which included 340 people from SCHOLAR-1. The EAG was concerned because this paper did not report censoring or proportions of people with different types of LBCL. It was also unclear if the paper was restricted to people who had 2 or more prior treatments. The EAG was also concerned that the Neelapu et al. paper may not represent population A because it involved propensity score matching to ZUMA-1, a CAR-T therapy-eligible population. It was unclear

if participants from SCHOLAR-1 included in this paper were re-weighted to the population in the ZUMA-1 study, or the reverse. This may have excluded or reduced the weighting of people whose characteristics aligned with population A. The EAG preferred to use a paper published by Crump et al. (another paper reporting results from SCHOLAR-1) because:

- it reported the proportions of people with each type of LBCL, which was unclear in Neelapu et al. – this allowed for adjustment for types of LBCL, rather than DLBCL, in the MAICs
- it reported censoring (so the company's assumptions on censoring would not be needed)
- it did not restrict participants to those with ECOG scores of 0 and 1.

The company acknowledged the limitations of the Neelapu et al. paper but noted that the overall survival (OS) reported was similar to that in other studies. It noted that though it was not explicitly reported, Neelapu et al. was cited as including people who had 3 or more prior treatments, while 28% of the people included in the Crump et al. paper had only had 1 prior treatment. The EAG also noted some unresolvable limitations in the SCHOLAR-1 cohort, which contributed to the overall uncertainty in the MAIC. These included that all participants' cancer was refractory to at least 1 prior treatment, whereas in EPCORE TM NHL-1, the participants' cancer could be relapsed or refractory. The EAG noted that this was particularly important because refractory status is a prognostic factor. It was also unclear how many people had had R-based CIT. The company acknowledged the limitations but noted that 21% of people in SCHOLAR-1 experienced relapse within 12 months of an autologous stem cell transplant, which was comparable to the EPCORE TM NHL-1 trial. The company used a partially adjusted MAIC in its base case (7 adjusted factors) but the EAG preferred the MAIC with 9 of the 10 reported variables adjusted for (see section 3.5). But the EAG noted that several factors were still unbalanced in the MAIC with 9 of 10 reported variables adjusted for

(3 or more lines of chemotherapy and autologous stem cell transplantation, as well as stem cell transplantation any time after refractory disease). Both the company and EAG's preferred comparisons showed that epcoritamab was more effective than R-based CIT for all of the efficacy outcomes evaluated (the company considers the exact results to be confidential, so they cannot be reported here). But the committee noted that there was a considerable level of uncertainty because of a lack of comparability between the studies and a small effective sample size (see section 3.5). The committee concluded that the comparison appeared to show that epcoritamab was more effective than R-based CIT, but a scenario including data from the Crump et al. paper in the MAIC should be done to explore the uncertainty.

Comparison with polatuzumab-BR

3.8 For the comparison with polatuzumab-BR, data from the EPCORE TM NHL-1 trial were matched to data from the GO29365 trial. The company used data from the EUnetHTA submission for baseline characteristics, and from Sehn et al. (2020) and Sehn et al. (2022) to estimate survival curves. The GO29365 trial compared polatuzumab-BR with BR alone after 1 or more treatments, and included 131 people in the polatuzumab-BR arm. The EAG noted unresolvable limitations in the GO29365 study, which contributed to the overall uncertainty in the MAIC. The EAG considered that the polatuzumab-BR survival outcomes may have been overestimated compared with a UK population (based on a real-world study by Northend et al.). It noted that this may bias the cost-effectiveness results against epcoritamab. It also noted that GO29365 did not report on primary refractoriness, which is a potentially important prognostic factor. The company did additional MAICs including a subgroup from the Northend study that included people who had had 2 or more prior treatments. The EAG did not consider it appropriate to use the study by Northend et al. in the base case because comparing a trial with real-world data would introduce more bias. The company used a partially

adjusted MAIC in its base case (6 factors adjusted), but the EAG noted that some factors were still unbalanced: refractory to last anti-lymphoma treatment, 2 prior lines of treatment, and 3 or more lines of chemotherapy and autologous stem cell transplantation. So it preferred to use the fully adjusted MAIC in the model (10 factors adjusted; see section 3.5). The company did not provide OS, progression-free survival (PFS) or time to treatment discontinuation (TTD) curves based on the fully adjusted MAICs, so it was not possible to use these in the model (see section 3.5). Both the company and EAG's preferred comparisons showed that there were no significant differences in OS or PFS between epcoritamab and polatuzumab-BR (the company considers the exact results to be confidential, so they cannot be reported here). The committee noted that there was a considerable level of uncertainty because of the lack of comparability between the studies and the small effective sample size (see section 3.5). It also noted very wide confidence intervals for the results. The committee concluded that there do not appear to be substantial differences in efficacy between epcoritamab and polatuzumab-BR but noted the substantial uncertainty around the results.

Comparison with axicabtagene ciloleucel

3.9 For the comparison with axicabtagene ciloleucel, data from the EPCORE TM NHL-1 trial was matched to data from the single-arm ZUMA-1 trial, which included 101 people with LBCL who had axicabtagene ciloleucel after 2 or more treatments. The company included the DLBCL population from EPCORE TM NHL-1 in the MAIC with ZUMA-1 in the analyses to align with the marketing authorisation. But the EAG preferred to use the LBCL population from EPCORE TM NHL-1 (plus adjustment for type of LBCL) to align more closely with the ZUMA-1 population. The EAG noted that the definition of PFS varied between EPCORE TM NHL-1 and ZUMA-1 (Lugano versus International Working Group criteria) and that this may have biased the results against epcoritamab. The EAG noted additional unresolvable limitations in ZUMA-1 which contributed to the overall uncertainty in the MAIC. The EAG and company agreed that the

available data from ZUMA-1 did not include people who were assigned to CAR-T therapy in the trial but did not have it. The clinical experts advised that most of these people would have had cancer that had rapidly progressed between being approved for treatment and having the infusion. They also advised that axicabtagene ciloleucel needs a period of bridging therapy before it is administered. So, people who could not wait long enough for treatment were unlikely to have been referred for axicabtagene ciloleucel treatment at all. This meant that the axicabtagene ciloleucel population was likely to be healthier than the epcoritamab population. 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. The EAG noted that 1 potentially important prognostic factor (refractory to last anti-lymphoma treatment) was not reported in ZUMA-1 so could not be adjusted for. The company used a partially adjusted MAIC in its base case (7 factors adjusted; see section 3.5). But the EAG noted that some factors were still unbalanced (DLBCL versus other LBCL, International Prognostic Index score of 3 or more, 3 or more prior treatment lines, and refractory to second-line or subsequent therapy) so it preferred to use the fully adjusted MAIC in the model (11 factors adjusted) that was focused on LBCL. The company did not provide OS, PFS or TTD curves based on the fully adjusted MAICs, so it was not possible to use these in the model (see section 3.5). Both the company and EAG's preferred comparisons showed that there were no significant differences in efficacy outcomes (PFS, OS, complete remission and overall response) between epcoritamab and axicabtagene ciloleucel (the company considers the exact results to be confidential, so they cannot be reported here). The committee noted that there was a considerable level of uncertainty because of the lack of comparability between the studies and the small effective sample size (see section 3.5). It also noted very wide confidence intervals for the results. The committee concluded that there are likely to be no substantial differences in efficacy between

epcoritamab and axicabtagene ciloleucel, but noted the substantial uncertainty around the results.

Economic model

Company's model

3.10 The company used a partitioned survival model to estimate the cost effectiveness of epcoritamab. 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 that were based on the MAICs. The committee concluded that the model structure was acceptable for decision making.

Long-term remission assumptions

3.11 In the company's original submission, it assumed that all people who are progression free 2 years after starting treatment enter long-term remission. When entering long-term remission, the company assumed that people would have:

- no further progression events
- an adjusted background mortality rate (standardised mortality ratio of 1.41 compared with the general population)
- no further follow-up costs
- the utility value associated with the PFS health state.

Based on its clinical experts' opinions, the EAG considered that long-term remission should start 2 years after the end of treatment, rather than 2 years after the start of treatment. After technical engagement, the company removed the long-term remission assumption from the model, as it considered long-term remission was now captured in the modelled curves which included more mature data from EPCORE TM NHL-1 and ZUMA-1. The EAG considered it inappropriate to remove the long-term remission assumption for epcoritamab and all of the comparators because this did not align with clinical expert opinion. It

noted that this affected the clinical plausibility of the PFS curves for each treatment (see sections 3.14, 3.15, and 3.16). The EAG re-introduced the long-term remission assumption for each comparator, applied 2 years after the end of treatment. But it was unable to do this for epcoritamab because the model did not track when people stopped treatment with epcoritamab. This scenario increased the cost-effectiveness estimates for all comparisons. But the EAG also noted that the results of reintroducing long-term remission for the comparison with axicabtagene ciloleucel lacked face validity. The clinical experts considered it reasonable to assume a person's cancer is in long-term remission if it has not progressed 2 years after treatment ends. The committee concluded that, following clinical expert input, it was appropriate to include the long-term remission assumption in the model for all treatments.

More flexible survival curves

3.12 The EAG focused its assessment of the company's extrapolations for OS, PFS and TTD based on the EAG's preferred MAICs (see sections 3.7, 3.8 and 3.9). The EAG was concerned that the extrapolations presented were not flexible enough to capture the change in underlying hazards. It noted that the curves did not fit the data well and underestimated survival for the comparators, for which there was longer follow-up data. The EAG's preferred curves provided a better statistical and visual fit to the actual observed data for epcoritamab and the comparators but, overall, they still underestimated the survival outcomes for the comparators. The EAG noted that its preferred curves were also not sufficiently flexible and did not, for example, capture any crossing of curves. The committee acknowledged that standard parametric distributions did not fit the data well. It concluded that more flexible models should be explored to see if they fit the data better and provide more plausible extrapolations. See sections 3.13 to 3.16 for more details on the company's and EAG's extrapolations.

Epcoritamab treatment duration in the model

3.13 There is no stopping rule for epcoritamab except for disease progression or toxicity. The comparators are each given for a fixed duration. The company confirmed that some people remained on epcoritamab and were progression free in the latest data cut of EPCORE TM NHL-1 (median follow-up 25.7 months). The company estimated the long-term duration of treatment with epcoritamab in the model by fitting parametric extrapolations to the TTD Kaplan–Meier data from EPCORE TM NHL-1. Clinical experts consulted by the company said that the modelled TTD curve would be similar to but lower than the PFS curve. This is because people are likely to remain on treatment until progression, as epcoritamab is well tolerated. At technical engagement, the company's clinical experts stated that people are unlikely to remain on treatment after 5 years. The EAG considered that this was inconsistent with the clinical expert opinion in the company's original submission. It also noted that the modelled TTD curves for epcoritamab were not consistent with the underlying Kaplan–Meier data from EPCORE TM NHL-1. The EAG preferred to use log-normal curves to estimate TTD for epcoritamab compared with all comparators because this shape best fitted the data. But the EAG noted that none of the TTD curves reflected clinically plausible scenarios. It considered more flexible models are needed to fit to the data from EPCORE TM NHL-1. The committee concluded that more flexible models for TTD should be explored to better fit the data from EPCORE TM NHL-1.

Extrapolations for the comparison with rituximab-based chemoimmunotherapy

3.14 For the comparison with R-based CIT, the EAG preferred using the MAIC results from the company's scenario with 9 of 10 reported variables adjusted for (section 3.7). The EAG considered that the company's preferred OS curves overpredicted survival for epcoritamab, and underpredicted it for R-based CIT compared with the SCHOLAR-1 data

reported in both Neelapu et al. and Crump et al. at 5 years. The EAG noted that its preferred OS curve for R-based CIT was better fitting and had more plausible long-term survival, but was still an underestimate compared with the study data. As PFS was not reported in SCHOLAR-1, the company estimated PFS for R-based CIT by applying the hazard ratio from the MAIC for OS versus epcoritamab to the PFS curve for epcoritamab. The EAG did not consider that there was sufficient justification to assume that the PFS gain for epcoritamab compared with R-based CIT was proportionately the same as the OS gain. It would have preferred a scenario analysis in which the hazard ratio between the epcoritamab OS and PFS Kaplan–Meier curves was applied to the OS curve for SCHOLAR-1 for R-based CIT, to estimate a PFS curve for R-based CIT. The company did not provide this, because it considered it inappropriate to assume that the relationship between OS and PFS for epcoritamab was the same as that for R-based CIT. The EAG considered that the company's approach underestimated the number of people who would be progression free on R-based CIT at 2 years. The company assumed that the TTD curve for R-based CIT would be the same as the PFS curve, based on expert opinion and lack of suitable data on discontinuation of R-based CIT. The EAG considered that it was implausible to assume people on R-based CIT do not stop treatment for reasons other than progression, because of the high toxicity of the treatment. So, it considered that the company's approach overestimated the cost of R-based CIT. The EAG used a better fitting curve in its exploratory analyses. It noted a substantial difference between the mean PFS and mean TTD for epcoritamab in the company's base case. When using the EAG's preferred curves, there was a smaller difference between mean PFS and mean TTD, which was more realistic. The exact difference between mean PFS and mean TTD when using the company and EAG's preferred curves is considered to be academic in confidence by the company and so it cannot be reported here. Overall, the EAG considered that there were no ideal curves and that the available curves were not

flexible enough. The committee concluded that it preferred the EAG's partially adjusted MAIC (9 of 10 reported variables adjusted for; see section 3.7) and would like to see more flexible models explored to better fit the data. The committee would also like to see scenarios in which people on R-based CIT stop treatment for reasons other than progression.

Extrapolations for the comparison with polatuzumab-BR

3.15 For the comparison with polatuzumab-BR, the EAG preferred using the results from the fully adjusted MAIC with 10 variables adjusted for (section 3.8). But as the curves from the fully adjusted MAIC were not available to include in the model (see section 3.5), the EAG used the company base case with 6 variables adjusted for. The EAG noted that both the company and EAG's preferred OS curves overestimated the benefit of epcoritamab compared with the fully adjusted MAIC, which showed the epcoritamab and polatuzumab-BR curves converging at around 15 months. The EAG noted that the company's preferred extrapolation curve underestimated survival with polatuzumab-BR compared with that reported from the GO29365 trial. It noted that no extrapolation curves represented the possible plateau in OS seen in the GO29365 trial. between 18 and 27 months. It also noted that the extrapolated PFS curves had a poor fit to the fully adjusted Kaplan–Meier data used by the company for epcoritamab, and to the data from the GO29365 trial which had a potential plateau at 24 months. As with R-based CIT (section 3.14), the company assumed that the TTD curve for polatuzumab-BR would be the same as the PFS curve. The EAG considered that it was implausible to assume people on polatuzumab-BR would not stop treatment for reasons other than progression, because of the high toxicity of the treatments, and that this assumption overestimated the cost of polatuzumab-BR. As with R-based CIT, the company noted there was limited suitable data on discontinuation of polatuzumab-BR. The EAG used a slightly better fitting TTD curve in its exploratory analyses. As with the comparison with R-based CIT, the EAG noted a substantial difference between mean PFS and mean TTD for epcoritamab in the company's base case. When using

the EAG's preferred curves, there was a smaller difference between mean PFS and mean TTD, which it felt was more realistic. The exact difference between mean PFS and mean TTD when using the company's and EAG's preferred curves is considered academic in confidence by the company and so it cannot be reported here. The committee concluded that it would like to see the impact of including fully adjusted MAICs in the analyses (section 3.8) and would like to see more flexible models explored to better fit the data. The committee would also like to see scenarios in which people on polatuzumab-BR stop treatment for reasons other than progression.

Extrapolations for the comparison with axicabtagene ciloleucel

3.16 For the comparison with axicabtagene ciloleucel, the EAG preferred using the results from the fully adjusted MAIC including the LBCL population with 11 variables adjusted for (section 3.9). Because the curves from the fully adjusted MAIC were not available to include in the model (see section 3.5), the EAG used the company's scenario using the LBCL population with 7 factors adjusted for. The EAG considered that the company's preferred OS and PFS curves did not align with the Kaplan–Meier curves for either treatment. For PFS, the EAG considered that the company's curve for epcoritamab was clinically implausible. The EAG noted its preferred curve was clinically plausible, and in line with the company's clinical experts' opinion that 20% to 30% of people having epcoritamab would be progression free at 5 years. The EAG did a scenario analysis allowing the PFS curves for axicabtagene ciloleucel and epcoritamab to cross (excluding the long-term remission assumption, see section 3.11). This had a large impact on the cost-effectiveness estimates. The EAG also noted that both the company's base case and the EAG's exploratory analyses had large differences between mean PFS and mean TTD that were unlikely to be plausible, and underestimated the costs for epcoritamab. The exact difference between mean PFS and mean TTD when using the company's and EAG's preferred curves is considered academic in confidence by the company and cannot be reported here.

The EAG did a scenario analysis exploring a smaller difference between mean PFS and mean TTD by estimating TTD using a hazard ratio of 1.2 between the curves. This had a substantial impact on the cost-effectiveness estimates. The committee concluded that it would like to see the impact of including fully adjusted MAICs in the analyses (section 3.8) and would like to see more flexible models explored to better fit the data.

Subsequent treatments

3.17 In its original submission, the company applied the same assumptions for subsequent treatments after third-line therapy for epcoritamab in both population A and B, and for all 3 comparators. The EAG's clinical experts noted that this was inappropriate, as the third-line therapy that a person has affects the choice of subsequent treatment. So, the EAG did a scenario analysis in which subsequent treatments were different depending on the third-line therapy. The proportions of people having each subsequent treatment were informed by the EAG's clinical experts. The company noted that the EAG's preferred subsequent treatment proportions included a higher proportion of people receiving CAR-T therapy after epcoritamab than in EPCORE TM NHL-1. The company considered it possible that a higher proportion of people might receive subsequent treatment with CAR-T therapy than in its preferred model base case (5% of people having subsequent CAR-T therapy after epcoritamab, for populations A and B). But it considered that it was inappropriate to assume an increased proportion of people having CAR-T therapy without including the associated efficacy benefit. So, the company did a scenario analysis using the EAG's preferred subsequent treatment assumptions, in which it applied an additional quality-adjusted life year (QALY) adjustment for the epcoritamab treatment arm. The EAG noted that in the most recent data cut from EPCORE TM NHL-1, the proportion of people having subsequent CAR-T therapy was similar to the EAG's clinical experts' opinion of 11% for population A. The EAG's preferred estimate of 30% of people having CAR-T therapy after epcoritamab for population B was higher than in EPCORE TM NHL-1. The EAG noted that

the subsequent treatment data from EPCORE TM NHL-1 did not differentiate between populations A and B. The exact proportions of people having subsequent CAR-T therapy in EPCORE TM NHL-1 are considered academic in confidence by the company so they cannot be reported here. The EAG noted that in EPCORE TM NHL-1, people had other active, effective treatments after epcoritamab which were not considered in the cost of subsequent treatments in the model. So, the EAG removed the company's QALY adjustment for both populations. The clinical experts at the meeting noted that the EAG's assumption of 30% of people having CAR-T therapy after epcoritamab in population B was higher than they would expect in clinical practice. The EAG also considered that people having R-based CIT or polatuzumab-BR would not have further R-based CIT and would instead have palliative chemoimmunotherapy. The committee concluded that there was uncertainty associated with the most appropriate subsequent treatments to include in the model for each population and that this had a substantial impact on the cost-effectiveness estimates. The committee would like to see further scenarios in which the subsequent treatments included in the model better reflected NHS clinical practice. If this is not possible, it would prefer that subsequent treatments in the model were aligned with EPCORE TM NHL-1. The committee considered that it was not appropriate to include an additional QALY adjustment to reflect an increased proportion of people receiving CAR-T in the EAG's scenario, compared with EPCORE TM NHL-1.

Treatment costs

3.18 After technical engagement, the company's model applied a one-off cost of £41,101 as the total cost for the first 100 days of treatment with axicabtagene ciloleucel, as specified in 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. The company also included monitoring costs, to account for excess bed days from adverse effects. The EAG felt it was

inappropriate to include these monitoring costs, but noted that including them had a minimal impact on the cost-effectiveness results. The company also included a one-off cost of £24,368 for bridging therapy to axicabtagene ciloleucel. This was a weighted average based on clinical expert opinion of the proportion of people who would have polatuzumab-BR, radiotherapy, steroids or no bridging therapy. The EAG applied a one-off cost of £23,850 for bridging therapy to axicabtagene ciloleucel. This was a weighted average based on information from the Cancer Drugs Fund clinical lead. The committee saw that the estimated total cost of bridging therapy to axicabtagene ciloleucel was similar in the company and EAG's calculations, and the impact of the EAG's changes on the cost-effectiveness results was small. The Cancer Drugs Fund clinical lead also noted that the costs for chemotherapy used in the company's and EAG's model were not up to date. The committee preferred the total cost of bridging therapy used by the EAG because this was based on information from the Cancer Drugs Fund clinical lead, so was likely to best reflect current NHS clinical practice. It also concluded that the monitoring costs for axicabtagene ciloleucel used by the company should not be included, and that the corrected costs for chemotherapy should be used in the model.

Epcoritamab follow-up treatment costs

3.19 In the company's model, people having epcoritamab were assumed to incur less follow-up costs after a certain time point. The company considers the exact time point to be academic in confidence so it cannot be reported here. The company explained that this time point was the median PFS for partial responders in EPCORE TM NHL-1. It was also the point at which the dosing frequency of epcoritamab decreases from once weekly to every other week. The company also noted that most people who experienced a complete response had done so by this time point. The company's clinical experts said that the intensity of follow up (such as the number of appointments and tests) for people having epcoritamab was likely to decrease over time once people have a complete response.

The EAG's clinical experts said that they would follow people up in the same way for as long as they continued to have epcoritamab. The EAG considered that the company's approach underestimated the costs of follow up for epcoritamab and biased the results in favour of epcoritamab, without a plausible clinical explanation. So, the EAG did an exploratory analysis in which people having epcoritamab continued to incur the same follow-up costs for the duration of treatment. The company said that this analysis overestimated resource use and was clinically implausible. At the committee meeting, the clinical experts stated that they would reduce follow-up intensity for people having epcoritamab while in complete remission. For example, they would no longer use routine PET or CT scans after a complete remission unless clinical signs suggested progressed disease. So, the committee felt that the EAG's exploratory analysis was not likely to reflect NHS clinical practice. The committee concluded that it was appropriate to reduce the intensity of follow up once people having epcoritamab had a complete remission, but the costs used in the model in this situation should be clinically validated.

Severity

3.20 The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. 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 company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual for population A (comparisons with R-based CIT and polatuzumab-BR). Based on the QALYs generated from the company's and EAG's models, the company and EAG agreed that for the comparison with R-based CIT, the QALYs should have a higher weighting (1.2 times). The company also applied a severity weighting (1.2 times) for the comparison with polatuzumab-BR. But the EAG considered it inappropriate to apply the severity modifier in its exploratory analyses with long-term remission re-introduced, because the proportional QALY

shortfall with polatuzumab-BR did not meet the severity modifier threshold. The committee noted that the recent and ongoing evaluations of glofitamab (NICE technology appraisal guidance 927) and loncastuximab tesirine had concluded that a QALY weighting should not be applied for the comparisons with polatuzumab-BR or axicabtagene ciloleucel. Recalling its preference that long-term remission be included in the model (see section 3.11), the committee considered that it may not be appropriate to apply a severity modifier, and that this would be consistent with the conclusions in recent evaluations. But it noted that the QALYs used in the calculation for severity weighting were generated from models that did not use all its preferred assumptions (see section 3.23). The company, EAG and committee agreed it was not appropriate to apply a severity modifier for the comparison with axicabtagene ciloleucel. The committee concluded that it was appropriate to apply the severity weight of 1.2 to the QALYs for the comparison with R-based CIT. The committee considered that it was unlikely to be appropriate to apply a severity modifier to the comparison with polatuzumab-BR for this evaluation.

Cost-effectiveness estimates

Acceptable ICER

3.21 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 will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- whether it was appropriate to conduct partially or fully adjusted MAICs (see section 3.5)

- whether the intervention and comparator trials were sufficiently comparable to draw meaningful results from the MAICs (see sections 3.7 to 3.9)
- whether the results for population A (people who cannot have or do not want intensive treatment) were applicable to people who had had CAR-T therapy (see section 3.6)
- whether the populations included in the MAICs for population A were ineligible for intensive treatments (see section 3.6)
- the appropriateness of the indirect comparison with R-based CIT (including the choice of data source for R-based CIT, unresolvable limitations of the SCHOLAR-1 study, and whether it was appropriate to assume the PFS gain for R-based CIT would be similar to the OS gain) (see sections 3.7 and 3.14)
- the appropriateness of the indirect comparison with polatuzumab-BR (including the impact of using the fully adjusted MAICs in the model, and unresolvable limitations of the GO29365 trial) (see section 3.8)
- the appropriateness of the indirect comparison with axicabtagene ciloleucel (including the impact of using the fully adjusted MAICs in the model, differing definitions of PFS across studies, that the ZUMA-1 study did not include an intention-to-treat population, and other unresolvable limitations of ZUMA-1) (see section 3.9)
- poor fitting of the extrapolations for OS, PFS and TTD for epcoritamab and all comparators to the available data (see sections 3.14 to 3.16)
- whether it was appropriate to include a long-term remission assumption for epcoritamab and the comparators (see section 3.11)
- the appropriate proportions of people receiving each subsequent treatment, to best reflect UK clinical practice (see section 3.17)
- follow-up costs for people having epcoritamab (see section 3.19)

So, the committee concluded that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

The company's and EAG's cost-effectiveness estimates

3.22 Because of confidential commercial arrangements for epcoritamab, the comparators, and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company's ICERs for the comparison with R-based CIT were within the range normally considered an effective use of NHS resources, when there is relative certainty about the ICERs. The company's ICERs for the comparison with polatuzumab-BR were higher than the range normally considered an effective use of NHS resources (with and without the severity modifier applied). All the EAG exploratory analyses for the comparisons with R-based CIT and polatuzumab-BR increased the ICERs, which were higher than the range normally considered an effective use of NHS resources. For the comparison with axicabtagene ciloleucel, in the company's base case, epcoritamab cost less but produced more QALYs. In the EAG's cumulative exploratory analysis, the ICER compared with axicabtagene ciloleucel was higher than the range normally considered an effective use of NHS resources.

The committee's preferences

3.23 The committee preferred the model to:

- include polatuzumab-BR as a comparator (see 3.3)
- use the partially adjusted MAIC (9 of 10 reported variables) for the comparison with R-based CIT (see 3.7)
- re-introduce the long-term remission assumption for all comparators (see 3.11)
- use subsequent treatment distributions that better reflect NHS clinical practice (see 3.17)
- not include additional monitoring costs added by company for axicabtagene ciloleucel, use the EAG's calculated cost of bridging to treatment with axicabtagene ciloleucel, and use the up to date costs for chemotherapy (see 3.18)

- not include the company's QALY adjustment for subsequent axicabtagene ciloleucel (see 3.17)
- have reduced follow-up intensity for people who had a complete remission while taking epcoritamab (see 3.19).

The committee's additional requests

3.24 The committee could not arrive at a preferred ICER because of the high level of uncertainty in the clinical inputs to the model and the uncertain appropriateness of the survival extrapolations (see section 3.21). The committee would like to see the following additional exploratory or confirmatory work:

- scenarios incorporating the fully adjusted MAICs for the comparisons with polatuzumab-BR and axicabtagene ciloleucel (see 3.5)
- baseline characteristics and efficacy outcomes from the subgroup of EPCORE TM NHL-1 that was ineligible for intensive treatments (see 3.6)
- scenarios using the 'no prior CAR-T, ineligible for intensive treatment' subgroup of EPCORE TM NHL-1 in MAICs adjusted to the comparator trials (see section 3.6)
- a scenario using data from Crump et al. for comparison with R-based CIT (see 3.7)
- a scenario using the fully adjusted MAIC in the LBCL population for the comparison with axicabtagene ciloleucel (see section 3.9)
- clinical validation of the costs incurred for people in long-term remission having epcoritamab (see section 3.11)
- scenarios using more flexible survival extrapolations for OS, PFS and TTD to better fit the data from EPCORE TM NHL-1 and the comparator trials (see 3.12)
- a scenario in which the hazard ratio between the epcoritamab OS and PFS Kaplan–Meier curves is used to estimate a PFS curve for R-based CIT (see 3.14)

- scenarios in which people on R-based CIT and polatuzumab-BR stop treatment for reasons other than progression (see sections 3.14 and 3.15)
- scenarios in which the subsequent treatments included in the model better reflect NHS clinical practice, or are aligned with EPCORE TM NHL-1 (see section 3.17)
- absolute and proportional QALY shortfall estimates calculated from a model that incorporates the committee's preferred assumptions and includes extrapolations that better fit the data (see 3.20).

The committee noted the high level of uncertainty in the model, particularly around the MAICs and the poor-fitting survival extrapolations. As the clinical and economic evidence was too uncertain, there was no plausible cost-effectiveness estimate on which to base a decision.

Other factors

Managed access

3.25 The company had not prepared a formal proposal for managed access. The committee noted that there is an ongoing phase 3 trial, EPCORE TM DLBCL-1, comparing epcoritamab with investigator's choice of chemotherapy for people with relapsed or refractory DLBCL after 2 or more systemic treatments. But, as the trial includes only 1 of the 3 relevant comparators, the committee concluded that it was unlikely to resolve the main uncertainties such as the efficacy of epcoritamab compared with polatuzumab-BR and axicabtagene ciloleucel.

Uncaptured benefits

3.26 The committee did not identify any additional benefits of epcoritamab not captured in the economic modelling. So it concluded that all of the benefits of epcoritamab had already been taken into account.

Equality

3.27 The company, clinical experts and patient experts outlined that there are barriers related to the delivery of CAR-T 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 therapies, but that access to therapy centres could not be directly addressed through its recommendations. The patient experts noted that epcoritamab may need to be delivered in larger transplant or CAR-T centres initially before training and support at smaller centres is provided, particularly to manage the potential adverse events. They noted that this may introduce short-term inequities for people who live further from treatment centres and cannot pay for travel or are unable to travel longer distances. The clinical experts acknowledged this but noted many regional hospitals are having training in managing side effects. They noted that bispecific monoclonal antibodies are deliverable by non-CAR-T centres in an outpatient setting and that these treatments have been delivered successfully in exceptional circumstances through individual funding requests. They noted that, overall, offering another treatment such as epcoritamab would improve access to treatment for people with relapsed or refractory DLBCL, particularly for those who have to wait to have CAR-T therapy. The committee acknowledged that disability (which may contribute to the inability to travel long distances) is a protected characteristic under the Equality Act 2010. It noted that socioeconomic status and geographical distance are not protected characteristics, but that NICE has due regard to promote the reduction of health inequalities. The committee considered that the addition of epcoritamab as another treatment option that does not need people to travel to a specialist centre could help ensure more people have access to effective treatments, if it was recommended.

Conclusion

3.28 The committee agreed that further information was needed to understand the full impact of the uncertainties. It considered that the indirect comparisons and the cost-effectiveness estimates presented by the

company and EAG were highly uncertain, and that given the uncertainty, it would like to see additional analysis. As there were no plausible cost-effectiveness estimates, the committee was unable to recommend epcoritamab for use in the NHS for treating relapsed or refractory DLBCL in adults who have had 2 or more systemic treatments.

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.

Committee members are asked to declare any interests in the epcoritamab 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 C

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 and a project manager.

Heather Stegenga

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