

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final draft guidance

# Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment [ID6338]

## 1 Recommendations

- 1.1 Epcoritamab can be used as an option to treat relapsed or refractory follicular lymphoma in adults after 2 or more lines of systemic treatment, only if:
- epcoritamab is stopped after 3 years of treatment or earlier if the lymphoma progresses, and
  - the company provides it according to the commercial arrangement (see [section 2](#)).
- 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 healthcare professional consider it appropriate to stop.

## What this means in practice

Epcoritamab must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Epcoritamab must be funded in England within 90 days of final publication of this guidance.

Epcoritamab must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Epcoritamab must be funded in England within 90 days of final publication of this guidance. There is enough evidence to show that epcoritamab provides benefits and value for money, so it can be used routinely across the NHS in this population.

## Why the committee made these recommendations

Usual treatment for relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment includes various combinations of chemotherapy and rituximab-based treatment.

For this evaluation the company included a rule that epcoritamab is stopped at 3 years, or earlier if the lymphoma progresses. This does not include everyone who it is licensed for.

Epcoritamab has not been directly compared in a clinical trial with usual treatments after 2 or more lines of systemic treatment. But indirect comparisons suggest that it is likely to increase how long people have before their condition gets worse and how long people live compared with usual treatment.

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, epcoritamab can be used.

## 2 Information about epcoritamab

### Marketing authorisation indication

2.1 Epcoritamab (Tepkinly, AbbVie) is indicated for 'the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) 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 epcoritamab](#).

## Price

- 2.3 The list price of epcoritamab is £547.33 for 1 vial of 4 mg/0.8 ml concentrate for solution for injection and £6,568.00 for 1 vial of 48 mg/0.8 ml solution for injection (excluding VAT; BNF online accessed September 2025).
- 2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes epcoritamab available to the NHS with a discount. The size of the discount is commercial in confidence.

## Sustainability

- 2.5 Information on the Carbon Reduction Plan for UK carbon emissions for AbbVie will be included here when guidance is published.

## 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.

## The condition

### Follicular lymphoma

- 3.1 Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Follicular lymphoma is a slow-growing, low-grade lymphoma that affects B lymphocytes. It is the most common type of low-grade lymphoma. People with this condition typically present with painless lumps (enlarged lymph nodes) in the neck, armpit or groin. Some people may have additional symptoms such as night sweats and recurrent fevers. Some people do not have symptoms so the cancer may have advanced

by the time it is diagnosed. Follicular lymphomas are commonly staged from stage 1 (best prognosis) to stage 4 (worst prognosis). The staging depends on how many groups of lymph nodes are affected and where they are in the body, the size of the areas of lymphoma and whether organs outside of the lymphatic system are affected (such as the bone marrow or liver). In England in 2022 there were 2,404 diagnoses of follicular lymphoma (1,217 in females and 1,187 in males). The 5-year survival rate for people diagnosed with follicular lymphoma is about 90%. But this is likely to be lower for people with additional risk factors or whose cancer has relapsed or is refractory after treatment. Follicular lymphoma has a high risk of relapse or becoming refractory (when the cancer returns or stops responding to treatment). Once people have cancer that is refractory to multiple lines of treatment, follicular lymphoma is no longer considered slow growing. The patient experts explained that follicular lymphoma is not curable, which has a profound emotional impact. The most common fear is that the cancer will return or transform into a more aggressive form, and that there will be no remaining treatment options. People with follicular lymphoma described this as a 'slow torture' because they know treatments will stop working and the cancer will return at some point. Also, because the cancer is defined as low grade, people feel isolated and misunderstood despite the huge emotional burden of having an incurable cancer. The patient experts explained the significant impact on carers because of anxiety, feeling helpless and providing daily support to people with follicular lymphoma. During the committee meetings, a patient expert described their personal experience of follicular lymphoma. They explained their cancer had relapsed 3 times since diagnosis in 2015. They have had several treatments and expressed anxiety that they will eventually run out of treatments, as would many other people. The patient experts outlined how heterogeneous the course of follicular lymphoma is because some people are diagnosed, have treatment and live to a 'normal' age. But about 20% of people have aggressive disease that keeps coming back and requires multiple treatments. The patient expert

described the profound psychological impact of the repeated relapses. The committee acknowledged the first-hand experiences shared by people with follicular lymphoma. It concluded that the condition is progressive, incurable and substantially impacts people in many different ways. It also noted the substantial burden on the families and carers of people with the condition.

## Clinical management

### Treatment options

3.2 The company explained that when follicular lymphoma is relapsed but not refractory, third-line treatment options include rituximab plus chemotherapy (with or without rituximab maintenance), or lenalidomide plus rituximab. When follicular lymphoma is relapsed and refractory, third-line treatment options include lenalidomide plus rituximab or obinutuzumab plus bendamustine (with or without obinutuzumab maintenance). Fourth-line treatments include rituximab plus chemotherapy, lenalidomide plus rituximab, chemotherapy or best supportive care. The patient experts explained that current treatments such as chemotherapy can have many side effects and cumulative toxicity. They explained there is an unmet need for more accessible and better tolerated treatments. They also explained that more treatments are needed because for some people most treatments will be used and exhausted at some point, so another treatment being available will provide a crucial treatment option. This will also support more individualised long-term care. The patient experts noted clear advantages of epcoritamab over current treatments, including simpler administration because it is given subcutaneously. They also thought that fewer side effects would be expected compared with current treatment. But they noted that further evidence would be needed for confidence in the use of epcoritamab to increase. A patient expert who had had epcoritamab explained how easy the treatment was and that they were able to continue working during treatment. The clinical experts outlined that third-line treatment is based

on chemotherapy plus other treatments or rituximab plus other treatments. They explained that treatment options at fourth line will depend on what has been used previously, so there is no single specific comparator. They advised that current treatment at fourth line in the UK is very limited, especially for people whose condition was diagnosed at a young age. This is because most available treatments have already been used and worked for a while, but stopped working by the fourth line. The clinical experts estimated that less than 25% of people with follicular lymphoma will have third-line or later lines of treatment. The clinical experts said that the UK lacks treatment options that are available for relapsed or refractory follicular lymphoma in comparable countries.

The company did not include best supportive care in its base case. It explained this was because it expected people having best supportive care would not be considered fit enough to be eligible for an active intervention such as epcoritamab. It also noted that UK clinical experts it consulted confirmed the company's summary of treatments and omission of best supportive care as generalisable to the UK. The EAG disagreed, noting that it received clinical advice that some people not fit enough for chemotherapy would be eligible for epcoritamab. But the EAG did not raise this as a key issue. The committee noted that treatment options for relapsed or refractory follicular lymphoma at third line or later include varied combinations of 2 chemotherapies and rituximab. It understood that treatment lines are not strictly defined with variations on previously used treatments used at later lines. And that it was appropriate to consider a basket comparator that represents the heterogenous population that has these treatments. The company's initial submission focused on the fourth-line or later population. During consultation, the company provided analyses for epcoritamab at third line or later. The committee noted there was an unmet need for treatment options at third-line and fourth-line or later. It acknowledged that treatments get exhausted and a notable proportion of people will have very limited options at fourth line. The

committee concluded that the company's treatment pathway was appropriate and that it had modelled appropriate comparator treatments at third-line and fourth-line or later. Also, it concluded that best supportive care is not a relevant comparator.

### **Treatment positioning of epcoritamab**

3.3 The marketing authorisation for epcoritamab specifies the line of treatment as 'after 2 or more lines of systemic therapy' (third-line or later; see [section 2.1](#)). Initially, the company decided to restrict the population to after 3 or more lines of systemic treatment (fourth-line or later) in its submitted model. It explained the restriction was to allow it to focus on the population with the greatest clinical unmet need and for whom there are limited treatment options. The company said that the evidence available for a comparison at third line may be limited. The EAG's clinical experts advised that there is a greater unmet need for epcoritamab at third line. This is because most people will have already had a rituximab combination treatment, and bendamustine (an option with obinutuzumab) would not be desirable because of how it affects T-cell function and thus the efficacy of other treatments. So, the EAG supported considering the broader population that included third-line treatment. At the first committee meeting, the clinical experts explained that epcoritamab showed clinical effectiveness in achieving disease response and extending survival at third-line or later and fourth-line or later, but it is more effective at earlier lines. They said there is strong unmet need for both populations. But at third line, the main challenge is showing comparative effectiveness against available treatments. This is because comparator trials typically include lines of treatment used earlier than third line. The clinical experts also advised that defining the population eligible for treatment at fourth line may be difficult because of the variability in earlier treatments. The committee understood that the company could choose to restrict the population in its submission to fourth line or later. But it also considered its objective, which is to evaluate a technology in its full marketing authorisation. The committee concluded that this very important issue had

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not been explored in enough detail. It understood the arguments raised against modelling third-line treatments, but decided these were insufficient and not based on a lack of available evidence. The committee noted that there may be more suitable clinical evidence for third-line treatment from registries and trials. So, it decided that restricting the evidence presented to the fourth treatment line or later increased the uncertainty by limiting the clinical data. The committee concluded that it would like to see cost-effectiveness modelling for the full marketing authorisation population (to include people having third-line treatment). It noted that a full justification, including a full breakdown of available evidence, and clear definition of the fourth-line or later population would be needed should this modelling of people having third-line treatment still not be possible.

During consultation, the company prepared an analysis of epcoritamab at third line or later. It argued that the greater unmet need was at fourth-line or later, so it retained that analysis as its base case. It also noted that epcoritamab is being appraised in an ongoing technology appraisal as a combination therapy at second line or later. The company's new third-line or later analysis reflected the methods and model used in its first submission for fourth-line or later treatments. This compared epcoritamab against a basket of treatments based on usage in the third-line or later population of the Haematological Malignancy Research Network (HMRN) dataset (see [section 3.5](#)). The EAG and committee welcomed the third-line or later analysis. The EAG's clinical experts advised that greater clinical need starts at third line and clinicians would prefer to use epcoritamab as early as possible. So, it focused on the third-line comparison in its base case. The clinical expert at the second committee meeting said the unmet need starts from the first relapse, so from second line onwards. They welcomed any access to epcoritamab at third-line or fourth-line. The committee noted that there is great unmet need for treatments and that clinicians would prefer to offer epcoritamab as early as possible. It also noted that by evaluating epcoritamab at third-line or

later meant that more data could be included and certainty increased. Finally, the committee reflected that defining lines of treatments beyond third-line and establishing an optimised population is difficult. So the committee concluded it would evaluate epcoritamab at third-line or later, which encompasses its full marketing authorisation.

## Clinical effectiveness

### EPCORE NHL-1

3.4 EPCORE NHL-1 is an open-label, single-arm phase 1 and 2 trial investigating epcoritamab in people with diffuse large B-cell lymphoma, follicular lymphoma or mantle cell lymphoma after at least 2 previous treatments. It started in June 2020 and is currently ongoing. The study included dose-escalation, dose-expansion and dose-optimisation phases. The main evidence included in the company's submission was from the follicular lymphoma dose-expansion cohort. The company provided evidence in the third-line or later population (n=128) and fourth-line or later population (n=81). People had 48 mg of epcoritamab once weekly. The EAG was concerned that some information shared by the company could not be validated. This included some adverse event data and trial data for third-line treatment. The EAG also expressed concerns about generalisability of the trial data to the UK. This was because of the small sample and differences in the age, sex and family background of participants compared with the UK population (specific characteristics are confidential and cannot be reported here). But the EAG noted that its clinical experts did not raise concerns about generalisability. The company explained that clinical experts it consulted also thought the trial baseline characteristics are generalisable to the UK. And that the trial results are expected to reflect outcomes seen in clinical practice. The results of the trial cannot be reported here because the company presented data that it considered confidential. During the first committee meeting, the company explained that longer follow-up data was available for the dose-optimisation cohort. But this information was not shared in

time for the committee meeting. The committee concluded that the EPCORE NHL-1 trial data was suitable for decision making. But it noted the data was limited by being from a single-arm trial instead of a randomised trial. It understood that longer follow-up data was recently made available for the dose-optimisation cohort. So, it requested to see this data. During consultation, the company provided the latest dose-optimisation cohort data from participants recruited after the peak of the COVID-19 pandemic. But it chose to retain the dose-expansion data for epcoritamab in its base case because it was more conservative and was designed to measure efficacy, unlike the dose-optimisation data which was designed to look at safety. The EAG noted that the dose-optimisation cohort had a small sample size with shorter follow-up than the dose-expansion cohort. Also, the generalisability concerns around differences in baseline characteristics and longer-term outcomes persisted. The committee concluded that EPCORE NHL-1 is sufficient for decision making and that it preferred the dose-expansion cohort for epcoritamab because of the longer follow-up and larger sample size.

### **Comparator data**

- 3.5 In its initial submission, the company did a systematic literature review to identify relevant clinical evidence for treatments for relapsed or refractory follicular lymphoma at fourth line and later. This was done to generate comparative evidence for epcoritamab and comparator treatments because EPCORE NHL-1 is a single-arm trial. The company identified 3 studies but decided none were suitable for generating comparative effectiveness data with epcoritamab because of generalisability concerns (either with the population characteristics or treatments used in the study). So, the company worked with the HMRN to identify suitable data. The HMRN is an ongoing population-based cohort consisting of data for UK patients with a haematological malignancy or related precursor condition. The HMRN covers the Yorkshire and Humber and Yorkshire Coast regions. The HMRN data shared by the company was retrospective observational data for adults with relapsed or refractory follicular

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lymphoma and starting treatment at fourth-line or later. The EAG raised concerns with using the HMRN data alongside EPCORE NHL-1 data to generate comparative evidence. This is because of the following differences between the 2 data sources:

- study design (a phase 1 and 2 open-label clinical trial compared with a retrospective observational dataset)
- the number of years over which the data was collected, sample size and median follow-up (figures are confidential and cannot be reported here)
- inclusion criteria (the HMRN dataset was not specific for relapsed or refractory follicular lymphoma)
- baseline characteristics including treatment-effect modifiers such as previous treatments, and lack of reporting in HMRN on race, ethnicity, body mass index, and renal and hepatic function.

The EAG was unable to identify suitable alternative data for comparators at fourth-line or later. But it noted suitable data may be available for comparators at third line or later. The clinical experts advised that the HMRN data was very generalisable to the rest of the UK. They noted some differences in age and sex to the UK population but thought these differences would bias results in a small way in opposite directions that would cancel out any meaningful differences. They understood that the HMRN data covered a long time period but did not expect older data on older treatments to be much different from data on treatments used today. And they expected any adjustments needed to account for any differences would be minor. The committee understood the views of clinical experts, but noted that the HMRN data might include time periods before rituximab was routinely available in the UK. The committee noted potential inconsistencies between alternative sources of comparator data and the HMRN dataset that required further exploration. At the first committee meeting, it requested that data for use of comparators as a third-line treatment should be

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explored (see [section 3.3](#)). And that a full assessment of feasibility for all available comparator data should be explored within scenario analyses and this data should be used to validate model outcomes. It also requested that a more complete assessment of generalisability should be provided for all analyses.

During consultation, the company reviewed the sources from its systematic literature review for use as comparator data from third-line or later. It also provided third-line or later HMRN data. Based on its clinical expert opinion, the company said that the HMRN data remains the most relevant source of comparator data for both third- and fourth-line comparisons. It stated that sources like the LEO cohort, SCHOLAR-5, ReCORD-FL and US Flatiron datasets were not generalisable to the UK because they include:

- international populations that may differ in background characteristics and may include fitter people who live close to medical services
- specialist academic centres that offer more treatments, such as bispecific antibodies and chimeric antigen receptor T-cell (CAR-T) therapies
- cohorts designed to represent comparators for CAR-T eligible people who tend to tolerate aggressive treatment and have favourable disease characteristics for long-term survival.

The EAG considered the company's review and found [Wasterlid \(2024\)](#), a large Swedish follicular lymphoma registry study, to be the most appropriate alternative data source. It noted Sweden has a similar treatment pathway with the UK and data on third-line and fourth-line treatment is available. The company had discounted the study because it only reports baseline characteristics at the first line of treatment. The EAG found the third-line HMRN data representative of third-line or later comparator care in the UK and used it in its base case. It explored [Wasterlid \(2024\)](#) as a source of comparator data in a scenario that

naively compared it against Omicron-censored epcoritamab data from EPCORE NHL-1. The clinical expert agreed with the company that the LEO cohort and ReCORD-FL were designed to be comparator groups for CAR-T therapy and tend to be fitter and younger than the UK population. They also noted that those populations had better outcomes because of access to better treatments than are available in the UK. The clinical expert said that the Swedish treatment pathway may appear similar to the UK, but it is not. In Sweden, first-line treatment is usually rituximab monotherapy. But in the UK, treatment starts with immunochemotherapy. The clinical expert said this leads to a Swedish follicular lymphoma population at second- or third-line treatment with better outcomes than the equivalent UK population because of the treatment difference at first line. The clinical experts identified other studies, including the FOUNDATION UK and REFRACT trials. They expected these trials to produce very useful data, but the outcomes will not be available for some time. The committee noted that the overall-survival outcomes across the different comparator sources varied substantially. It acknowledged limitations across all data sources but, in the absence of any better data, agreed the HMRN data was the most generalisable comparator data source. The committee concluded that the HMRN data should be used for comparator data.

### **Adjusting survival data for COVID-19 deaths**

- 3.6 The EPCORE NHL-1 trial started in June 2020 and was impacted by the COVID-19 pandemic. The company reported that excess mortality was observed in the trial and clinical review identified a confidential number of COVID-19-attributable deaths. Some of these people had complete response before death, so the company decided the condition would not have progressed in these people had they survived. So, these deaths were censored by the company in survival outcomes used in its submission. The HRMN data was not as impacted by COVID-19 deaths. The EAG raised concerns about the censoring of COVID-19 deaths in the EPCORE NHL-1 data. It explained that the EAG's clinical experts thought

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the COVID-19-adjusted survival data was too optimistic. The EAG noted uncertainty about determining whether COVID-19 was the sole cause for a person's death or merely present during a death caused by other reasons. So, the EAG decided to use the EPCORE NHL-1 survival data that was not adjusted for COVID-19 deaths in its initial base case. During the committee meeting, the clinical experts explained that the COVID-19 pandemic caused a distinct increase in mortality in people with follicular lymphoma of about 15%. They explained that recently published evidence showed survival before and after the COVID-19 pandemic was very similar to that in the trial. And that the number of COVID-19 infections has significantly reduced in the latest trial data for the dose-optimisation cohort. The clinical experts advised that COVID-19 was the sole reason for the observed increase in mortality and must be accounted for in the clinical evidence. The committee agreed that in principle the impact of COVID-19 should be accounted for in the clinical evidence. But it decided that censoring COVID-19 deaths was a suboptimal approach. It also noted the cost-effectiveness results were very sensitive to COVID-19 censoring. The committee requested more complex methods for accounting for COVID-19 deaths, instead of only censoring them, such as using causal inference. During consultation, the company produced new data and analyses across treatment lines with:

- data from the dose-optimisation cohort from EPCORE NHL-1 (which was recruited after the peak of the pandemic)
- censoring deaths during only the Omicron wave from EPCORE NHL-1
- inverse probability of censoring weights (IPCW) methods to account for bias associated with informative censoring.

The committee welcomed the company's exploration of other approaches and the more sophisticated IPCW approach. The company found that the dose-optimisation data predicted even better survival for epcoritamab than the original COVID-censored dose-expansion analysis. The Omicron adjustment and IPCW approach generated

similar outcomes to the original analysis provided by the company. The survival outcomes and hazard ratios from the subsequent matching-adjusted indirect comparisons (MAICs) for these analyses are confidential and cannot be reported here. The company retained the original COVID-censored approach in its base case. But it said most COVID-19 deaths occurred in the Omicron wave and the results of the Omicron-censored analysis were similar so also appropriate. The clinical expert agreed that the timing of most deaths coincided with the Omicron wave and noted that the company's approach was reasonable. The EAG agreed that the dose-optimisation cohort validated the company's base case, but uncertainty persisted for longer-term outcomes beyond the follow-up period. It approved of the IPCW approach but noted some limitations and missing reporting. Based on clinical opinion, the EAG used the Omicron-censored analysis for its base case as a 'middle ground'. The committee acknowledged the differences in outcomes between the company's and EAG's preferred COVID-adjustment approaches. It decided that fully censoring people who had died from COVID-19 was not appropriate because this approach implies that the characteristics of people who died from COVID-19 are the same as those who did not. It preferred the IPCW adjustment to the EPCORE NHL-1 data and concluded that this analysis should be used for decision making. The committee noted there were a small number of COVID-19 deaths in the third-line HMRN data (the exact number is confidential and cannot be reported here). Complete censoring of COVID-19 deaths in the HMRN data had minimal impact on survival outcomes compared with no censoring. The committee concluded that IPCW adjustment of EPCORE NHL-1 sufficiently accounted for COVID-19 deaths in the third-line population. It also concluded that IPCW adjustment of the HMRN data would be preferable but that, in this case, it would have a limited impact. So, the committee accepted full censoring of COVID-19 deaths in the HMRN dataset.

## Indirect treatment comparisons

3.7 To generate comparative evidence for epcoritamab and current treatments at fourth line for relapsed or refractory follicular lymphoma, the company did unanchored MAICs. In its initial submission the company provided this at fourth-line or later and at consultation it provided it at third-line or later. This involved reweighting EPCORE NHL-1 data to match characteristics of HMRN data for relevant treatment-effect modifiers and prognostic variables. Specifically, the data were adjusted so the cohorts had the same proportions of people for the following variables:

- aged 60 years or over
- male
- disease stages 3 to 4
- previous autologous stem cell transplant
- previous CAR-T therapy
- disease progression within 24 months of first-line treatment
- disease refractory to most recent treatment
- disease refractory to both anti-CD20 and alkylator treatments
- number of previous lines of treatment
- previous treatment with lenalidomide plus rituximab.

These adjustments reduced the effective sample size of the EPCORE NHL-1 cohort from 128 to 79 people in the third-line or later population and 81 to 40 people in the fourth-line or later population. The analysis produced progression-free survival, overall survival, objective response rate and complete response outcomes for epcoritamab and current treatments. The results are confidential and cannot be reported here. But the outcomes for epcoritamab were better with the MAICs. The EAG had concerns about the indirect comparisons. First, the effective sample size for the indirect comparison was small, especially at fourth-line or later, so the results are more likely to be biased. Second, strict trial selection criteria mean

the indirect comparison is unlikely to account for differences in the trial and real-world populations. Third, the indirect comparison produces unexpected results compared with unadjusted data because survival with epcoritamab improved (the results are confidential and cannot be reported here). Fourth, the Eastern Cooperative Oncology Group (ECOG) and Follicular Lymphoma International Prognostic Index (FLIPI) scores were not adjusted for in the analysis but are key prognostic factors. The company explained that ECOG and FLIPI scores were not included because they were only available in the HMRN data at baseline and not over time. The clinical experts explained why the survival outcomes for epcoritamab improved when adjusted in the indirect comparison. They pointed out that the EPCORE NHL-1 population was older, had more refractory disease and had more previous treatments than other populations. This was to reflect a higher-risk population with no treatment options. But this meant that adjusting the epcoritamab population to match the HMRN population excluded people at higher risk and weighted down the overall risk of the epcoritamab population. The company thought that the overall fitness of the EPCORE NHL-1 population was worse than the HMRN population. The committee asked the company whether it did simulated treatment comparisons (STCs). The company explained that it did not do these analyses because they rely on a large number of events, which were not present in the small sample. The committee noted that the company's technical approach to the indirect treatment comparison was appropriate. But STCs may be possible and the committee would like to see these analyses to validate the MAICs. At the first meeting, the committee concluded that sufficient evidence had not been provided to understand the differences between the EPCORE NHL-1 and HMRN database populations. It requested that the company:

- produce STCs, if feasible, to validate the MAICs

- consider indirect comparisons of epcoritamab with alternative comparator data sources (see [section 3.5](#))
- provide sufficient evidence to understand differences between the EPCORE NHL-1 and HMRN populations
- explore key prognostic variables, especially for people with refractory disease.

After consultation, the company said there was limited time to produce STCs, so it prioritised the other requested analyses. It said that the STC good practice requires 10 events per covariate for stable, unbiased estimates, but the few mortality and progression events limited the feasibility of this. The company stated that the MAICs have sufficient overlap in population characteristics, balance matching and sample size well, and are in line with methods used in other NICE appraisals. It did sensitivity analyses around different definitions of refractory status in the MAICs at both treatment lines. The EAG stated the company's justifications against doing STCs are inadequate. It expected a quantitative feasibility assessment or exploration of semi-parametric or reduced covariate approaches. The EAG also challenged the company's claim of having high covariate overlap, noting that covariates seemed to be chosen based on availability as opposed to prognostic importance. The committee asked the clinical expert which variables in the available MAICs played a key role in prognosis. It referred to [Ubiato et al. \(2023\)](#) which suggested that progression of disease within 2 years (POD24) was the most important prognostic factor. The clinical expert said that POD24 is significant at second line, but diminishes in importance at later lines of treatment. They said that refractoriness and number of lines of previous treatment are more important prognostic factors at third-line or later. So, the clinical expert said that the HMRN data population was higher risk than the EPCORE NHL-1 population, because it had higher proportions of people with refractory disease who had also had more than 3 lines of treatment.

The committee decided the sample size and matching of the indirect comparison contribute to uncertainty. It was also disappointed that no STCs had been attempted. The committee concluded that when the hazard ratios generated by the MAICs were used in the model, the survival curves that were generated did not fit the underlying data well (see [section 3.9](#)).

## **Economic model**

### **Company's modelling approach**

3.8 The company built a partitioned survival model with a weekly cycle length and a 35.2-year time horizon to compare the cost effectiveness of epcoritamab with current treatments. The model included 3 health states: progression-free, progressed disease and death. People were modelled to start in the progression-free health state until disease progression or death. People with progressed disease remained in this health state until death. Background mortality was used in the model to ensure that the modelled survival did not exceed the survival of an age- and sex-matched population within the UK. The company modelled the comparator as a basket of current treatments. The basket was weighted based on relative use of each treatment reported in HMRN data. This data is confidential and cannot be reported here. People were modelled to stop epcoritamab treatment because of progression or other reasons and a 3-year stopping rule was applied for people reaching complete response. Treatment discontinuation for comparator treatments was obtained directly from HMRN data reflecting the impact of the varied durations of different treatments. The company did not apply treatment waning in the model. The committee concluded that the company's model was appropriate for decision making.

### **Modelling of epcoritamab and comparator efficacy**

3.9 Initially, the company and EAG prepared base cases for the fourth line or later population. The committee requested modelling of the third-line or

later population (see [section 3.3](#)), which was produced during consultation. The company provided analyses in the third-line or later population using epcoritamab as the reference curve and applying the hazard ratios from the MAICs. It provided a scenario using the HMRN data as the reference curve and applying the inverse hazard ratios from the MAICs. It noted that the HMRN reference curve approach increased the relative overall-survival benefits of epcoritamab compared with comparator treatments. So, the company used of epcoritamab as the reference curve in its base case. The company also provided formal assessment of the underlying hazards and statistical fit of curve extrapolations. The EAG, in its base case, used the HMRN data as the reference curve and applied the inverse hazard ratio. It selected the log-normal curve for overall survival and the generalised gamma for progression-free survival based on best statistical fit. At the committee meeting, the company stated that either reference curve approach is reasonable. It noted that the EAG's approach fit latter parts of the Kaplan–Meier curves better but also that those parts are based on fewer numbers. The committee decided that neither the company nor EAG's approach represented both treatment arms well. It asked if independently fitting the curves had been considered. Both the company and EAG had considered independently-fitted curves but opted for jointly fitted curves in the absence of a proportional hazard's violation. The committee noted that using the HMRN data as the reference curve approach was consistent with best practice, but the consequent curves from applying the hazard ratios from the MAICs to generate curves for epcoritamab were inadequate. It noted the MAICs had limitations that contributed to uncertainty (see [section 3.7](#)). The committee concluded that independently-fitted curves would more adequately represent the long-term clinical effectiveness of epcoritamab and the HMRN data-based comparator treatments. The company adopted the committee's preference for independently extrapolating each treatment arm. For epcoritamab, the company used the IPCW-adjusted reweighted EPCORE

NHL-1, selecting the log-logistic curve for overall survival and generalised gamma for progression-free survival. It applied a constraint to cap the progression-free survival curve after 21.6 years by the overall-survival curve to avoid crossing of those curves. Because of data limitations, the company could not do the IPCW adjustment to account for COVID-19 deaths on the comparator arm's third-line HMRN data (see [section 3.6](#)). For comparator treatments, the company used the HMRN data with COVID-19 deaths censored and it selected the log-normal curve for overall survival and the generalised gamma for progression-free survival. It applied a survival cap to limit survival on third-line comparator treatments to 25 years. The EAG, also using the IPCW-adjusted reweighted EPCORE NHL-1 data for epcoritamab, selected log-normal extrapolations for progression-free and overall survival. The EAG thought the company's choice of generalised gamma for progression-free survival overestimated mean life years in the progression-free state relative to the progressed disease state. It thought that the log-normal curves provided more clinically plausible long-term estimates of progression-free and overall survival, while avoiding the need for the artificial constraint. For the comparator treatment arm, the EAG adopted the company's approach with full censoring of HMRN data and noted that COVID-adjustment approach made limited difference to survival (see [section 3.6](#)). The committee considered the company and EAG's analysis and noted that the impact on the incremental cost-effectiveness ratio (ICER) was small. It concluded that the EAG's analysis was appropriate.

## **Utility values**

### **Utility in the progression-free disease state for the comparator**

3.10 In the company's original base case, utility values for the progression-free disease state were weighted according to the proportion of people reaching complete response on epcoritamab or the comparator treatments. The company noted that the clinical experts explained that people reaching complete response would be expected to have higher

health-related quality of life, supporting this approach. The exact utility values used for each treatment arm are confidential and cannot be reported here. Clinical experts consulted by the EAG agreed that complete response is a determinant of health-related quality of life. But they also suggested that the impact of adverse events should be considered too, because people who reach complete response are likely to be on treatments for longer. The EAG also noted that other factors such as duration of complete response should be included, otherwise the company approach is biased. So, the EAG's base case used the same utility values for the progression-free disease states for epcoritamab and the comparator. This was taken from the EPCORE NHL-1 EQ-5D-3L data and not adjusted for complete response status. The committee noted that the utility values used by the company may be biased because they did not capture other factors linked to complete response that impact utility, including time in complete response and adverse events. During consultation, the company aligned progression-free utility values with the EAG's approach. The committee concluded that utility values used by the EAG that did not vary by complete response status were likely to be more appropriate for decision making.

## **Costs**

### **Subsequent treatment costs**

3.11 The company modelled subsequent treatment costs to be the same as the basket comparator it used. It explained that this approach was in line with clinical expert opinion. The EAG noted that clinical experts it consulted agreed that modelled subsequent treatments are appropriate. But the EAG raised concerns that the clinical effects of subsequent treatments are modelled without associated costs in the company's base case. This is because other treatments were included in EPCORE NHL-1 including systemic anti-lymphoma therapy, autologous stem cell transplant and CAR-T therapy. The proportions of people having these treatments are confidential and cannot be reported here. The company explained that

people who had CAR-T therapy were censored in the MAICs, so the costs should not be included. The EAG suggested that a scenario analysis that fully removed people who had CAR-T therapy, or included the associated CAR-T therapy costs, would help explore the uncertainty. The committee requested the analysis that was suggested by the EAG. During consultation, the company presented Kaplan–Meier overall-survival plots that censored patients who had subsequent CAR-T therapy. These were very similar to the original, uncensored Kaplan–Meier data. The EAG agreed that there was minimal impact on the overall survival, so the impact on cost-effectiveness results would likely be small. But it was concerned that informative censoring from excluding patients eligible for CAR-T therapy could introduce bias. The clinical expert noted that the number of people having CAR-T therapy in EPCORE NHL-1 was low (number not reported because of confidentiality). The committee agreed that the impact of any adjustment for subsequent CAR-T therapy would likely be small. It concluded that the modelling of subsequent treatment costs based on the basket of treatments used in NHS practice was appropriate in this case.

### **Resource-use costs**

- 3.12 The company's initial base case included once-monthly haematologist consultations for epcoritamab and did not include positron emission tomography (PET) scans. It explained that the resource-use estimates included in its base case were verified by clinical experts. The EAG explained that clinical advice it received outlined that haematologist visits are weekly for the first month and then decrease to monthly. The experts also suggested including 12-monthly PET scans. So, the EAG included weekly haematologist visits for the first month and then monthly visits in its base case. It included 12-monthly PET scans in a scenario analysis. Submissions from the clinical experts for the committee meeting agreed that haematologist visits are weekly for the first month before reducing to monthly. At the second committee meeting the clinical expert said that, except for people having CAR-T therapy, PET scans are not time-

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dependent and the need for PET scans would be based on symptoms. The clinical expert advised that a PET scan every 18 months to 2 years is reasonable for people having current treatment options. The EAG produced a scenario analysis with annual PET scans, but its base case included no PET scans. There was little impact to the cost-effectiveness results with the addition of annual PET scans. The committee concluded that clinical opinion was clear that weekly haematologist visits for the first month then monthly visits are expected in clinical practice. So, it preferred to use these costs in cost-effectiveness modelling, as in the EAG's base case. During the consultation, the company updated its base case to align with the EAG's approach. The committee concluded that the assumption of no cost of PET scans was sufficient because of the limited impact of including PET scans on the cost-effectiveness results.

### **Adverse events costs**

- 3.13 The company noted that limited adverse event data was available for chemotherapy (the most frequently used treatment in the comparator basket). Rituximab plus chemotherapy was the second most frequently used treatment in the comparator basket. So, adverse event incidence data for rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone was used to generate costs for the entire comparator basket. This data was taken from [NICE's technology appraisal guidance on axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma](#) (TA894). The EAG asked the company to provide a scenario analysis including costs based on adverse event data for lenalidomide plus rituximab and obinutuzumab plus bendamustine. This data was also available in TA894 as well as [NICE's technology appraisal guidance on lenalidomide with rituximab for previously treated follicular lymphoma](#) (TA627). The company used the adverse event rates for each treatment to represent the costs for the entire basket in separate scenarios. The EAG incorporated this analysis in its base case by weighting the adverse event rates for the relative use of each treatment, rather than using 1 treatment to represent the entire basket. The EAG also included grade 2

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cytokine-release syndrome events that required treatment with tocilizumab in its base case. The committee concluded that the EAG's approach to weighting adverse events was appropriate and should be used to model costs. During consultation, the company updated its base case to align with the EAG's approach to weighting adverse events and their costs. But it retained its exclusion of cytokine-release syndrome. The committee heard from clinical experts that clinical management of grade 2 cytokine-release syndrome events had changed and the occurrence was very low. So, it concluded it was not appropriate to include these adverse event costs in modelling.

## Severity

3.14 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The committee noted that it was evaluating epcoritamab in the third line or later population (see [section 3.3](#)). Neither the EAG nor the company made a case for a higher-than-normal severity modifier to be applied to this population. So, the committee concluded that a severity weight of 1.0 applied to the QALYs was appropriate.

## Cost-effectiveness estimates

### Acceptable ICER

3.15 [NICE's manual on health technology evaluations](#) notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that some

uncertainty remained from using data from a single-arm trial, but this was lower in the third-line population because it is a clearly definable population with more data available for both epcoritamab and the comparator. The committee acknowledged the substantial clinical benefit of epcoritamab over currently available treatments. The committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

### Cost-effectiveness estimates and further analyses

3.16 The committee noted its preferred assumptions, which include:

- evaluating epcoritamab for the full marketing authorisation population, that is, third-line or later (see [section 3.3](#))
- using the dose-expansion data from EPCORE NHL-1 (see [section 3.4](#))
- using data from the HMRN registry for comparator data (see [section 3.5](#))
- adjusting for COVID-19 related deaths using IPCW (see [section 3.6](#))
- modelling progression-free and overall-survival curves independently, rather than applying the hazard ratios from the MAICs (see [section 3.7](#) and [section 3.9](#))
- not using treatment-specific utility values (see [section 3.10](#))
- applying subsequent treatment costs based on treatments available in the NHS (see [section 3.11](#))
- modelling weekly haematologist visits for the first month then monthly visits, and no PET scans (see [section 3.12](#))
- costing adverse events by weighting rates by the relative use of each treatment, but excluding grade 2 cytokine-release syndrome events that required treatment with tocilizumab (see [section 3.13](#)).

The cost-effectiveness results include confidential prices for comparator treatments, so the exact results cannot be reported here.

Using the committee's preferred assumptions, the committee

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concluded that the ICER for this evaluation was in the acceptable range.

## Other factors

### Equality

3.17 The committee did not identify any equality issues.

## Conclusion

### Recommendation

3.18 The committee acknowledged the significant unmet need for treatment options for relapsed or refractory follicular lymphoma. Using the committee's preferred assumptions, the ICER is within the range that NICE considers an acceptable use of NHS resources. So, epcoritamab can be used.

## 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 90 days of its date of 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, at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#)

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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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.
- 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 or refractory follicular lymphoma and the healthcare professional responsible for their care thinks that epcoritamab 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.

## **Chair**

### **Richard Nicholas**

Vice 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, a project manager and a principal technical adviser.

### **Sammy Shaw and Owen Swales**

Technical leads

### **Michelle Green**

Technical adviser

### **Leena Issa**

Project manager

### **Adam Brooke**

Principal technical adviser

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