Single Technology Appraisal

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Contents:

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1. **Comments on the Draft Guidance from AbbVie**
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2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Blood Cancer UK
   b. Royal College of Physicians-Association of Cancer Physicians-Royal College of Radiologists
   c. Gilead

3. **Comments on the Draft Guidance from experts:**
   a. Dr Wendy Osborne, clinical expert, nominated by the British Society for Haematology

4. **External Assessment Group critique of company comments on the Draft Guidance**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 21 November 2023. Please submit via NICE Docs.

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

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

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

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Summary	Based on the commentary in the draft guidance document (DGD), please find analyses incorporating the Committee's preferences (DGD Section 3.23) and the Committee's additional requests (DGD Section 3.24). The main topics addressed in this response are: • Scenarios incorporating matching adjusted indirect comparisons (MAICs) versus all comparators in which the maximum reported variables are adjusted for (DGD Section 3.5) • The source of comparator efficacy data for rituximab-based chemoimmunotherapy (R-based CIT), including the request for Crump *et al.* to be used (DGD Section 3.7) • The ineligible for chimeric antigen receptor T-cell (CAR-T) therapy population from EPCORE™ NHL-1, in particular the request for MAICs based on this population (DGD Section 3.6) • The long-term remission (LTR) assumption (DGD Section 3.11) • A scenario in which the hazard ratio (HR) between the epcoritamab overall survival (OS) and progression-free survival (PFS) Kaplan-Meier (KM) curves is used to estimate a PFS curve for R-based CIT (DGD Section 3.14) • Scenario analyses in which a proportion of patients discontinue treatment with R-based CIT and polatuzumab vedotin with rituximab and bendamustine (Pola + BR) for reasons other than PFS (DGD Section 3.14 and 3.15) • Subsequent treatment proportions used in the model (DGD Section 3.17) • The Committee's preferred assumptions for bridging, monitoring and chemotherapy costs (DGD Section 3.18) • The follow-up costs used in the model for patients receiving epcoritamab who are in complete remission (DGD Section 3.19) • Flexible survival models for OS, PFS and TTD (DGD Section 3.12)

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Alongside these comments, AbbVie have provided a revised base case taking into account the Committee's preferences, including reintroduction of the LTR assumption for all treatments, aligning the axicabtagene ciloleucel (axi-cel) bridging and monitoring costs with the External Assessment Group's (EAG's), and updating the resource use and subsequent treatment assumptions to reflect anticipated UK clinical practice as closely as possible.

A summary of the changes made to the base case cost-effectiveness analyses, including the change to the base case incremental cost-effectiveness ratio (ICER; from the technical engagement base case ICER) is presented in Table 1. Based on the updated base case cost-effectiveness results, when compared with R-based CIT, epcoritamab is associated with incremental costs of £[redacted] and incremental QALYs of [redacted], with a resulting ICER of £20,191 per QALY gained. For epcoritamab versus Pola + BR, epcoritamab is associated with incremental costs of £[redacted] and incremental QALYs of [redacted], with a resulting ICER of £6,205 per QALY gained. For the comparison of epcoritamab versus axi-cel, epcoritamab is associated with incremental costs of [redacted] and incremental QALYs of [redacted]; as such, epcoritamab is dominant versus axi-cel. Epcoritamab can therefore be considered a cost-effective use of NHS resources versus all comparators.

Table 1: Changes to the company's cost-effectiveness estimates (Deterministic results; epcoritamab PAS price):

	Incremental costs	Incremental QALYs	Updated ICER
Base case analysis A (epcoritamab versus R-based CIT)			
Company's base case following technical engagement (deterministic)	[redacted]	[redacted]	£25,488
Updates to base case following DGD response			
Response 4: Inclusion of LTR assumption 36 months after treatment initiation	[redacted]	[redacted]	£16,432
Response 8: EAG's preferred bridging therapy costs for axi-cel	[redacted]	[redacted]	£16,518

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	and updated chemotherapy costs			
	Response 7: Updated subsequent treatment assumptions	[redacted]	[redacted]	£20,116
	Response 9: Updated 'low intensity' resource use assumptions	[redacted]	[redacted]	£20,191
	Base case analysis A (versus R-based CIT) following DGD response	[redacted]	[redacted]	£20,191
	Base case analysis A (epcoritamab versus Pola + BR)			
	Company's base case following technical engagement (deterministic)	[redacted]	[redacted]	£9,766
	Updates to base case following DGD response			
	Response 4: Inclusion of LTR assumption 36 months after treatment initiation	[redacted]	[redacted]	£3,746
	Response 8: EAG's preferred bridging therapy costs for axi-cel and updated chemotherapy costs	[redacted]	[redacted]	−£1,007
	Response 7: Updated subsequent treatment assumptions	[redacted]	[redacted]	£6,174

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	Response 9: Updated 'low intensity' resource use assumptions	[redacted]	[redacted]	£6,205
	Base case analysis A (versus Pola + BR) following DGD response	[redacted]	[redacted]	£6,205
	Base case analysis B (epcoritamab versus axi-cel)			
	Company's base case following technical engagement (deterministic)	[redacted]	[redacted]	Epcoritamab is dominant
	Updates to base case following DGD response			
	Response 4: Inclusion of LTR assumption 36 months after treatment initiation	[redacted]	[redacted]	Epcoritamab is dominant
	Response 8: EAG's preferred monitoring costs and bridging therapy costs for axi-cel, and updated chemotherapy costs	[redacted]	[redacted]	Epcoritamab is dominant
	Response 7: Updated subsequent treatment assumptions	[redacted]	[redacted]	Epcoritamab is dominant
	Response 9: Updated 'low intensity' resource use assumptions	[redacted]	[redacted]	Epcoritamab is dominant
	Base case analysis B following DGD response	[redacted]	[redacted]	Epcoritamab is dominant
	Results for base case analysis A and base case analysis A.1 include a 1.2 severity modifier applied to the incremental QALYs.			

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	Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; R-based CIT: rituximab based chemoimmunotherapy; Pola + BR: polatuzumab with bendamustine plus rituximab. As highlighted by the Committee, the treatment landscape for patients with relapsing/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, is rapidly evolving (DGD Section 3.3), although Pola + BR may remain a treatment option for a minority of patients, AbbVie maintain that it is a less relevant comparator than axi-cel and R-based CIT. Due to the limitations associated with Sehn *et al.* as a source of efficacy data for Pola + BR (acknowledged by the EAG and Committee, technical engagement (TE) Issue 9 and DGD Section 3.8), scenario analyses in which the efficacy of Pola + BR is based on Northend *et al.* third-line and beyond (3L+) UK real-world data have also been conducted. UK clinical experts noted the limitations associated with Sehn *et al.* as well as comparing Northend *et al.*, real-world evidence, to clinical trial data, and concluded that the efficacy of Pola + BR in clinical practice is likely to fall somewhere between estimates from these sources. As such, cost-effectiveness results based on both Pola + BR data sources should be considered.
1	**AbbVie maintain that the MAICs in which prognostic/predictive baseline characteristics are adjusted for provide the most robust estimates of comparative efficacy, as supported by clinical experts and published literature. However, in response to the Committee's request, MAICs versus all comparators in which all available variables are adjusted for have been conducted and provided in the model as scenario analyses. Based on input from clinical experts, these MAICs are likely less clinically plausible as a result of over-adjustment.** As MAICs compare absolute treatment effects, they depend on the assumption that treatment effect modifiers and prognostic factors are homogeneous across the included populations. AbbVie acknowledge that, in theory, this balance may be achieved by adjusting for all available variables; however, in practice, the selection of variables to adjust for requires careful judgement, including consideration of factors such as the effective sample size, the clinical plausibility of MAIC results and issues associated with overfitting and multicollinearity.[1] When selecting the variables for adjustment in the MAICs informing the base case analyses, AbbVie considered such factors and therefore maintain that the MAICs in which prognostic/predictive variables are adjusted for, rather than all available variables, represent the most robust source of comparative efficacy estimates for

epcoritamab versus each comparator. This aligns with the input received by clinical experts who stated that the results of the MAICs when all available variables were adjusted were clinically implausible.[2]

During interviews conducted to support this appraisal, UK clinical experts stated that both disease stage and International Prognostic Index (IPI) score are prognostic factors; however, as disease stage informs IPI score, UK clinical experts also highlighted that these variables are correlated and adjustment for both variables is therefore not clinically necessary. The same was highlighted by UK clinical experts for refractoriness and number of prior lines of therapy; UK clinical experts noted that adjusting for both of these variables would be considered as double-counting.[2] Therefore, as supported by the published literature, issues associated with multicollinearity and over-adjustment must be considered when selecting the variables to adjust for in the MAICs in order to reduce concerns regarding bias and inefficiency.[3, 4] For example, as highlighted by Giacalone *et al.* (2018), multicollinearity can result in unstable estimates and inflated standard errors, thereby increasing the uncertainty associated with the estimates.[3] To avoid issues associated with multicollinearity, it is recommended to omit correlated variables from the analysis and this guidance has been followed when conducting the MAICs informing the base case analyses.

Nonetheless, in response to the Committee's request, MAICs versus all comparators in which the maximum reported variables are adjusted for have been conducted and incorporated in the model as scenario analyses. An overview of the additional scenario analyses conducted is presented in Table 2. Where feasible, all available variables were adjusted for. For the comparisons of epcoritamab versus R-based CIT (Neelapu *et al.* and Crump *et al.*) and Pola + BR (Northend *et al.*), the maximum reported variables were adjusted for, however it was not feasible to adjust for all available variables due to issues associated with convergence.

Table 2: Summary of scenario analyses in which the maximum reported variables are adjusted for[a]

Scenario	Epcoritamab population	Comparator (data source)	Number of variables adjusted for	Effective sample size
Ineligible for, or choose not to receive, intensive therapy				

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	Scenario analysis A	DLBCL no prior CAR-T therapy (N=[redacted])	R-Based CIT (SCHOLAR-1; Neelapu *et al.*)[5]	9	[redacted]
	Scenario analysis A.1	DLBCL no prior CAR-T therapy (N=[redacted])	Pola + BR (Sehn *et al.* 3L+)[6]	10	[redacted]
	Scenario analysis A.5	DLBCL no prior CAR-T therapy (N=[redacted])	Pola + BR (Northend *et al.* 3L+ RWE)[7]	13	[redacted]
	Scenario analysis A.6	LBCL, no prior CAR-T therapy (N=[redacted])	R-Based CIT (SCHOLAR-1; Crump *et al.*)[8]	11	[redacted]
	Eligible for intensive therapy				
	Scenario analysis B	DLBCL, no prior CAR-T, CAR-T eligible (N=[redacted])	Axi-cel (ZUMA-1; Locke *et al*)[9]	10	[redacted]
	Scenario analysis B.1	LBCL, no prior CAR-T, CAR-T eligible (N=[redacted])		11	[redacted]

[a] Where feasible, all available variables were adjusted for. For the comparisons of epcoritamab versus R-based CIT (Neelapu *et al.* and Crump *et al.*) and Pola + BR (Northend *et al.*), the maximum reported variables were adjusted for, however it was not feasible to adjust for *all* available variables due to issues associated with convergence.
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; LBCL: large B-cell lymphoma; Pola + BR: polatuzumab vedotin with bendamustine plus rituximab; R: rituximab.

Full details on MAICs in which the maximum reported variables were adjusted for were provided in the appendix to AbbVie's TE response. Details of the time-to-event analyses based on these MAICs are presented in Appendix D.

As highlighted in response to TE Issue 7, UK clinical experts questioned the clinical plausibility of the results of the MAICs in which the maximum reported variables were adjusted for, particularly highlighting how the MAIC versus SCHOLAR-1 produced a clinically implausible [redacted] and the MAICs versus axi-cel produce clinically implausible

	comparative efficacy estimates whereby epcoritamab improves OS by [redacted] compared with axi-cel (epcoritamab large B-cell lymphoma [LBCL] population). For the MAIC versus Pola + BR (based on Sehn *et al.*), UK clinical experts stated that this produces clinically implausible comparative efficacy estimates [redacted] of Pola + BR (although no statistically significant difference was identified; TE Appendix B.1.2.2). Due to the limitations associated with Sehn *et al.* regarding the overestimation of the efficacy of Pola + BR versus UK clinical practice (TE Issue 4 and 9, DGD Section 3.8), this is not unexpected. Moreover, considering the populations included in EPCORE™ NHL-1 and Sehn *et al.*, UK clinical experts stated that it is not clinically plausible that adjusting for more variables would decrease the relative treatment benefit of epcoritamab versus Pola + BR.[2] As such, AbbVie conducted additional MAICs for epcoritamab versus Pola + BR, in which the efficacy of Pola + BR is informed by Northend *et al.* 3L+ real-world data. After adjustment of the epcoritamab population, the results of this MAIC demonstrated a [redacted] treatment benefit for epcoritamab versus Pola + BR in terms of OS and PFS (OS: [redacted]; PFS: [redacted]; TE Appendix B.1.1.2). However, as highlighted during TE, it was not feasible to adjust for ECOG performance score due to differences between the populations; in order to address this, IPI score was adjusted for to indirectly address the imbalance and this approach was supported by UK clinical experts (TE Appendix B.1.1.2). When discussed during interviews, UK clinical experts stated that the MAIC based on Northend *et al.* 3L+, in which 11 variables are adjusted, produced results that are most representative of the expected comparative efficacy of epcoritamab versus Pola + BR. The MAIC informed by Sehn *et al.*in which all available variables were adjusted for was considered the least representative. Results of the scenario analyses are presented in Appendix A.5.
2	**To address the request from the EAG and Committee, MAICs of epcoritamab versus R-based CIT using data from the Crump *et al.* publication of SCHOLAR-1 have been conducted. However, AbbVie maintain that the SCHOLAR-1**

	publication by Neelapu *et al.* remains the most suitable source to derive efficacy estimates for R-based CIT for this decision problem. AbbVie recognise the limitations associated with Neelapu *et al.* (as discussed in response to TE Key Issue 3) as a source of efficacy data for R-based CIT (SCHOLAR-1), however, maintain that it is the most appropriate published source to derive efficacy estimates for R-based CIT because this population most closely aligns with the decision problem. Of the 636 patients included in the analysis presented by Crump *et al.* (2017), 28% of patients received only one prior line of therapy.[7] Whereas, although it is not explicitly stated within the paper to be exclusively a 3L+ population, the data reported in the secondary Neelapu *et al.* (2021) publication have been cited as representative for patients who have received two or more prior lines of therapy.[10] Nevertheless, to comply with the Committee's requests, MAICs of epcoritamab versus R-based CIT based on Crump *et al.* have been conducted. In these MAICs, the large B-cell lymphoma (LBCL), no prior CAR-T population from EPCORE™ NHL-1 was adjusted to match the R-based CIT population from Crump *et al.* Following feedback from the EAG and the Committee, AbbVie have conducted a primary MAIC in which 9 variables are adjusted for and a secondary MAIC in which 11 reported variables are adjusted for (Appendix C.1). Full details on the methodology and results are presented in Appendix C and Appendix D. When adjusting for 9 or 11 variables, the effective sample size for the epcoritamab population is decreased to just [redacted] patients in both analyses (from [redacted] patients). This substantial reduction in sample size for both MAICs reflects the incomparability of the epcoritamab population and R-based CIT population from Crump *et al.* (for example, there are large differences before adjustment in the proportion of patients with IPI score 3 or higher and the proportion of primary refractory patients). Regardless, the point estimate results of the MAICs of epcoritamab versus R-based CIT based on Crump *et al.* and Neelapu *et al.* (in which all prognostic/predictive variables are adjusted) are broadly consistent (Table 3). For the MAIC versus Crump *et al.* in which 11 variables are adjusted for, although the point estimate is consistent, the 95% CIs of the OS HR for epcoritamab

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versus R-based CIT [redacted]; UK clinical experts stated that it was clinically implausible for there to be no difference in OS between epcoritamab and R-based CIT.

Table 3: Unadjusted and adjusted outcomes for epcoritamab versus R-based CIT –no prior CAR-T therapy epcoritamab population adjusted to SCHOLAR-1 (Neelapu *et al.* and Crump *et al.*)

	Epcoritamab LBCL, no prior CAR-T			Epcoritamab DLBCL, no prior CAR-T		
	Unadjusted (N=[redacted])	Adjusted to SCHOLAR-1, Crump et al. – 9 variables adjusted (Neff=[redacted])	Adjusted to SCHOLAR-1, Crump et al. – 11 variables adjusted (Neff=[redacted])	Unadjusted (N=[redacted])	Adjusted SCHOLAR-1, Neelapu et al. – 7 variables adjusted (Neff=[redacted])	Adjusted SCHOLAR-1, Neelapu et al. – 9 variables adjusted (Neff=[redacted])
OS, HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma HR: hazard ratio; LBCL: large B-cell lymphoma; OS: overall survival.

The results of these MAICs have also been incorporated into the model as scenario analyses. All scenario analysis results are presented in Appendix A.5.

3	**Efficacy data and baseline characteristics for the DLBCL, ineligible for CAR-T population have been provided. However, AbbVie maintain that it is not appropriate for the epcoritamab population to be restricted to those ineligible for intensive therapies, without applying the same restriction to the comparator populations (which is not feasible due**

	to lack of individual patient data ([PD]). Thus, MAICs using this population have not been conducted or incorporated into the model. In response to the Committee's requests, the baseline characteristics and key efficacy outcomes for the DLBCL, ineligible for intensive therapies epcoritamab populations (DLBCL, ineligible for CAR-T [n=[redacted]] and DLBCL, no prior CAR-T, ineligible for CAR-T [n=[redacted]]) are provided in Appendix B. When compared with the overall DLBCL population, the DLBCL, no prior CAR-T, CAR-T ineligible population represents a less fit population; the median age of patients in the DLBCL, no prior CAR-T, CAR-T ineligible subgroup was [redacted] versus [redacted] for the overall DLBCL population, and the proportion of patients with IPI score 3 or higher was [redacted]% versus [redacted]%, respectively. Therefore, it is expected that outcomes for this population were slightly poorer when compared with the overall DLBCL population. As stated in the company submission (CS), Document B, Section B.2.8.2 and TE response to Key Issue 6, the epcoritamab population used for the MAICs versus R-based CIT and Pola + BR (Sehn *et al.* 3L+) was patients who had DLBCL and had received no prior CAR-T therapy (N=[redacted]). As the Sehn *et al.* and SCHOLAR-1 data sets were collected prior to the availability of CAR-T therapy, comparator data for an ineligible for CAR-T subgroup are not available; it was not a relevant subgroup at the time of data collection and publication.[6, 8] UK clinical experts stated that, if analysed retrospectively, the populations included in Sehn *et al.* and SCHOLAR-1 likely would include patients eligible for CAR-T therapy. For the Sehn *et al.* trial specifically, the clinical experts stated that although the trial included patients that had relapsed following autologous stem cell transplant (autoSCT), this population would include younger, fitter patients that would typically be eligible for CAR-T therapy (as well as older, less fit patients that would typically be ineligible for CAR-T therapy).[2] Furthermore, the clinical experts highlighted that if patients were eligible for inclusion in a clinical trial for Pola + BR, a T-cell engaging bispecific therapy, patients would most likely also be eligible for CAR-T therapy, another T-cell engaging therapy.[2] With this considered, it would be biased for the epcoritamab population to be restricted to patients ineligible for CAR-T therapy without applying the same restriction to the comparator populations, when a proportion of the comparator population would likely be eligible for CAR-T therapy also. As patients who are ineligible for CAR-T therapy are anticipated to have poorer outcomes, this would result in a comparison of a higher risk, less fit subgroup of the epcoritamab population with the full SCHOLAR-1 and Pola + BR populations. Furthermore, UK clinical experts highlighted that as clinical practice is likely moving

	away from determining treatment based on eligibility for intensive therapies and instead determining treatment based on time to relapse; it is less necessary for the epcoritamab population, and comparator populations, to be restricted to those ineligible for CAR-T therapy.[2, 11]
4	**As per the Committee's request, the LTR assumption has been included in the revised base case, in which patients that are progression-free 36 months after treatment initiation are considered to be in LTR. A scenario analysis has been conducted in which all patients entering LTR stop treatment with epcoritamab.** In line with feedback from UK clinical experts collected to support this DGD response, AbbVie have included the LTR assumption in the revised base case for all treatments whereby all patients that are progression-free 36 months after treatment initiation are considered to be in LTR, in line with Committee preferences during TA927.[12] In addition, UK clinical experts confirmed that it was reasonable for this assumption to begin after treatment initiation. As outlined previously, the cost-effectiveness model has been updated such that time to treatment discontinuation (TTD) is decoupled from LTR; this means that the LTR assumption only impacts PFS and OS, whilst TTD follows the extrapolated TTD curve. This allows patients receiving epcoritamab to remain on treatment, whilst still being considered to be in LTR. Furthermore, following feedback from UK clinical experts that some patients may discontinue treatment with epcoritamab after a prolonged period in complete response, an additional scenario analysis has been conducted in which epcoritamab patients discontinue treatment when entering LTR (36 months after treatment initiation).[2] Results of the scenario analysis is presented in Appendix A.5 and demonstrate minimal impact on the cost-effectiveness of epcoritamab versus all comparators.
5	**AbbVie have conducted a scenario analysis in which the HR between the epcoritamab OS and PFS KM curves is used to estimate a PFS curve for R-based CIT.** In the absence of published PFS data for R-based CIT from SCHOLAR-1, PFS for R-based CIT was modelled using the OS HR. In response to the Committee's request, a scenario analysis has been conducted in which the HR between the epcoritamab OS and PFS observed in EPCORE™ NHL-1 is applied to the R-based CIT OS curve to estimate PFS for R-based

CIT. For this scenario analysis, the HR between the OS and PFS KM curves for the DLBCL, no prior CAR-T epcoritamab population adjusted to SCHOLAR-1 (based on Neelapu *et al.*; 7 variables adjusted) is applied, presented in Table 4. By using this HR, it is assumed that the hazard of progression for patients receiving R-based CIT is approximately [redacted] that of the hazard of death. For completeness, the HR between OS and PFS for the unadjusted epcoritamab DLBCL population is also presented in Table 4.

Table 4: HR between OS and PFS for the population adjusted to R-based CIT and the unadjusted DLBCL, no prior CAR-T population

Population	OS/PFS HR (95% CI)
DLBCL, no prior CAR-T epcoritamab population unadjusted	[redacted]
DLBCL, no prior CAR-T epcoritamab population adjusted to SCHOLAR-1 (based on Neelapu *et al.*; 7 variables adjusted)	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; R-based CIT: rituximab based chemoimmunotherapy.

The results of this scenario analysis are presented in Appendix A.5, which demonstrate that using the EAG's preferred HR has minimal impact on the cost-effectiveness of epcoritamab versus R-based CIT.

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A scenario analyses have been conducted in which approximately 10% of patients discontinue treatment with R-based CIT and Pola + BR early, for reasons other than PFS.

As outlined in response to TE Key Issue 14, the assumption that TTD for R-based CIT and Pola + BR is equal to PFS for each treatment was adopted due to a lack of published data on the TTD of R-based CIT and Pola + BR in UK clinical practice.[13]

In response to the Committee's request, a scenario analysis is presented in which approximately 10% of patients receiving R-based CIT or Pola + BR discontinue earlier than the full six cycles. In the model, this scenario analysis is modelled via a HR

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<table>
<tr><td></td><td>applied to the TTD curves for R-based CIT and Pola + BR, resulting in approximately 10% of patients discontinuing early. The results of this scenario analysis are presented in Appendix A.5.</td></tr>
<tr><td>7</td><td>The original base case assumptions for subsequent treatments were informed by UK clinical expert feedback, however AbbVie have sought further input from UK clinical experts to inform the proportion of patients receiving each subsequent treatment. The revised base case has been updated in line with this feedback.

As part of the DGD, the Committee requested that subsequent treatment distributions that better reflect NHS clinical practice are incorporated into the model (DGD Section 3.17). In response to this request, AbbVie conducted additional interviews with four UK clinical experts to further understand the most likely subsequent treatments received by patients with R/R DLBCL after third-line treatment. During these interviews, experts were asked to complete the table below to provide their estimates for subsequent treatments in UK clinical practice. The outputs of the interviews are provided in Table 5, in which any estimates for oral chemotherapy were redistributed to the R-based CIT estimate and palliative care is assumed to include chemotherapy and steroids.

The revised based base incorporates these proportions and the additional quality-adjusted life year (QALY) adjustment for the epcoritamab arm has been removed, in alignment with the Committee’s request. The proportion of patients estimated by clinicians to receive palliative care are assumed to incur no costs associated with subsequent treatments. Full details of the revised base case cost-effectiveness results are presented in Appendix A.

Table 5: Revised base case assumption: Proportion of patients receiving subsequent treatments for each third-line treatment based on additional clinical validation[2]
<table>
<tr><th rowspan="2">Treatment at entry</th><th colspan="6">Percentage of patients receiving subsequent treatments</th></tr>
<tr><th>R-based CIT (includes Pola + BR)[a]</th><th>CAR-T therapy</th><th>Radiotherapy</th><th>AutoSCT</th><th>AlloSCT</th><th>Palliative care[b]</th></tr>
</table></td></tr>
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	Patients ineligible for, or choose not to receive, intensive therapies						
	Epcoritamab	40.6%	0.6%	12.5%	0.0%	0.3%	46.0%
	R-based CIT	19.4%	1.9%	15.0%	0.0%	0.0%	64.7%
	Pola + BR	23.0%	0.6%	13.8%	0.0%	0.0%	63.6%
	Patients eligible for intensive therapies						
	Epcoritamab	32.5%	8.1%	13.8%	1.9%	4.4%	40.4%
	Axi-cel	39.3%	0.0%	11.3%	1.3%	5.9%	43.4%

[a] R-based CIT includes oral chemotherapy; [b] Palliative care is assumed to incur no treatment costs.
Abbreviations: AlloSCT: allogenic stem cell transplant; autoSCT: autologous stem cell transplant; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; Pola + BR: Polatuzumab vedotin with rituximab and bendamustine; R: rituximab; SCT: stem cell transplant.

8	**The revised base case incorporates the Committee's preferred assumptions for the bridging and monitoring costs associated with axi-cel, as well as the preferred chemotherapy costs.** In response to feedback from the EAG and the Committee, AbbVie have updated the bridging costs for patients receiving axi-cel to align with the EAG's preferred assumptions (one-off cost of £23,850), based on information from the Cancer Drugs Fund's Clinical Lead. In addition, the one-time monitoring costs associated with axi-cel have been omitted. Furthermore, the Cancer Drugs Fund's Clinical Lead noted (DGD Section 3.18) that the chemotherapy costs used in the model were not up to date and provided some preferred chemotherapy costs based on the 2023/24 NHS payment scheme. These changes have all been incorporated into the revised base case.

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9

AbbVie have sought further validation to determine the follow-up costs used in the model for patients receiving epcoritamab who are in complete remission.

As outlined in the DGD, the Committee agreed that it was appropriate to reduce the intensity of follow up once patients receiving epcoritamab have achieved a complete response, as these patients who no longer require resource use such as routine PET or CT scans (DGD Section 3.19). In line with the recommendation from the Committee, AbbVie have conducted additional interviews with five UK clinical experts to further understand the expected resource use for these patients and the base case has been updated accordingly. In line with the clinical experts feedback the PFS off-treatment or PFS 'low intensity' resource use estimates have been updated to the inputs detailed in Table 6.

Table 6: Update to the PFS off-treatment resource use (per model cycle)

Resource use	Original base case	Revised DGD base case[a]	DGD scenario[a]
Residential care	0.75	0.75	**0.00**
Day care	0.28	0.28	**0.00**
Home care	1.17	1.17	**0.00**
Hospice	0.00	0.00	0.00
Oncologist	0.00	0.00	0.00
Haematologist	0.19	**0.50**	**0.50**
Radiologist	0.00	0.00	0.00
Nurse	1.00	1.00	1.00
Specialist nurse	0.17	**1.00**	**1.00**
GP	0.00	0.00	0.00
District nurse	0.38	0.38	0.38
CT scan	0.31	**0.00**	**0.00**
Full blood count	3.33	**1.00**	**1.00**

	LDH	2.00	**0.00**	**0.00**
	Liver function	3.33	**1.00**	**1.00**
	Renal function	1.00	1.00	1.00
	Immunoglobulin	0.67	**0.15**	**0.15**
	Calcium phosphate	0.15	**0.08**	**0.08**

[a] **Bold** values represent those that have been updated based on clinical validation as part of this DGD response.
Abbreviations: CT: computerised tomography; GP: general practitioner; LDH: lactate dehydrogenase; N/A: not applicable; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free.

10

The base case extrapolations have been selected based on feedback from UK clinical experts; as such, AbbVie maintain that the choice of extrapolations are appropriate and best reflect feedback from UK clinical experts. In combination with the LTR assumption, concerns regarding the extrapolations fitting the observed data are mitigated as patients no longer follow the extrapolated OS/PFS curves after 36 months.

The EAG questioned the base case extrapolations selected to model OS, PFS and TTD for epcoritamab and provided alternative preferred extrapolations (Section 3.12 to Section 3.16 of the DGD). AbbVie maintain that the base case extrapolations selected are reflective of feedback from UK clinical experts and the results of the MAICs. Of note, the preferred extrapolations selected to model OS and PFS for the comparison versus axi-cel is consistent with those used for decision making for Glofitamab appraisal (TA927). Furthermore, as the LTR assumption is now applied to all treatment arms for patients in PFS after 36 months (Response 4), concerns regarding the extrapolations fitting the observed data are mitigated as patients no longer follow the extrapolated OS/PFS curves after 36 months. Further details on the selected extrapolations for the base case analyses and scenario analyses are provided in Appendix D, with a summary provided in Table 7.

Table 7: Selected extrapolations for base case analysis and scenario analyses

	OS	PFS	TTD
Epcoritamab versus R-based CIT			
Base case analysis A	Lognormal	Generalised gamma	Exponential

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	Scenario analysis A	Lognormal	Gompertz	Exponential
	Scenario analysis A.6	Lognormal	Lognormal	9 variables adjusted: exponential 11 variables adjusted: Gamma
	Epcoritamab versus Pola + BR			
	Base case analysis A.1	Generalised gamma	Generalised gamma	Exponential
	Scenario analysis A.1	Generalised gamma	Generalised gamma	Gamma
	Scenario analysis A.5	Gompertz	Gompertz	Weibull
	Epcoritamab versus axi-cel			
	Base case analysis B	Gompertz	Gompertz	Exponential
	Scenario analysis B	Gompertz	Gompertz	Exponential
	Scenario analysis B.1	Gompertz	Gompertz	Exponential

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival; PFS; progression-free survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; R-Based CIT: rituximab based chemoimmunotherapy; TTD: time to treatment discontinuation.

AbbVie considered the EAG's preferred extrapolations, however these are not consistent with feedback received from UK clinical experts or the results of the MAICs. In particular, the EAG's preferred extrapolations for the comparison of epcoritamab versus axi-cel result in more QALYs predicted for axi-cel than epcoritamab ([redacted] versus [redacted]; based on the revised base case with the EAG's preferred extrapolations); this is however inconsistent with the EAG's preferred MAIC of epcoritamab versus axi-cel which demonstrates a treatment benefit for epcoritamab (adjusted OS HR: [redacted] [95% CIs: [redacted]]).

The EAG considered the extrapolated TTD of epcoritamab to be inconsistent with clinical expert opinion and the KM data from EPCORE™ NHL-1. However, AbbVie maintain that the selected base case TTD extrapolations are the most appropriate as UK clinical experts stated that they would expect very few patients to remain on treatment beyond five years. Based on AbbVie's base case TTD extrapolations, [redacted] to [redacted] of patients remain on treatment at five years, with [redacted] of patients remaining on treatment with epcoritamab at 10 years. The EAG also questioned TTD for R-based CIT and Pola + BR, stating that some

	patients would discontinue treatment for reasons other than progression. As outlined in Response 7, scenario analyses have been conducted to address this concern. For the comparison of epcoritamab versus Pola + BR, the EAG preferred the lognormal curve to model OS for epcoritamab and Pola + BR, the lognormal curve to model PFS for epcoritamab and the generalised gamma curve to model PFS for Pola + BR. When using the EAG's preferred PFS extrapolation for Pola + BR, approximately [redacted]% of patients in the Pola + BR treatment arm are in PFS at five years; this is inconsistent with real-world data published by Northend *et al.* which shows the same proportion of patients in PFS at one year, whilst the EAG's preferred extrapolation predicts approximately [redacted] of patients in PFS at one year. Overall, given the clinical inconsistencies described above, AbbVie maintain that their base case choice of extrapolations are the most appropriate.
11	**AbbVie have implemented scenario analyses using a piecewise approach in which the KM data for all treatments are used until 24 months (12 months for Pola + BR based on Northend *et al.*), after which the survival data are extrapolated based on standard parametric survival models and the LTR assumption is applied after 36 months. Considering the length of follow up of data from EPCORE™ NHL-1, the ability of other flexible survival models to robustly estimate survival curves for epcoritamab is uncertain.** For modelling epcoritamab and all comparators, the Committee requested that AbbVie explore more flexible survival models to see if they fit the observed data better (Section 3.12 to Section 3.16 of the DGD). The ability of many flexible survival models, such as mixture-cure models and flexible parametric models using cubic splines outlined in NICE DSU TSD 21, is uncertain due to the length of follow up of data from EPCORE™ NHL-1. However, AbbVie have implemented a more flexible piecewise approach in the model whereby the KM data for all treatments is used until 24 months (with 12 months used for Pola + BR based on Northend *et al.*), after which the survival data are modelled using the standard parametric functions. The LTR assumption is then applied to all patients in PFS after 36 months (Response 4). By doing so, any concerns regarding the extrapolations fitting the observed data are mitigated, as the observed data are used until 24 months in the majority of

	analyses. After this timepoint, the survival data are extrapolated using standard parametric models, but patients in LTR no longer follow these extrapolated OS/PFS curves after 36 months. Moreover, as highlighted in Response 10, the base case extrapolations have been carefully selected based on feedback from UK clinical experts. AbbVie acknowledge that alternative timepoints for switching from KM data to extrapolated data could be selected, however 24 months was selected across the majority of analyses for consistency. For the comparison of epcoritamab versus Pola + BR based on Northend *et al.*, 12 months was chosen as the study only provides 14 months of KM data. Considering other flexible models, robust estimation of mixture-cure models requires data with sufficient follow-up that exceeds the anticipated timepoint of cure, as noted in TA567, and sufficient patient numbers at the tail of the KM curves (median follow-up was [redacted] months in EPCORE™ NHL-1).[14] Nevertheless, AbbVie have explored the option of fitting mixture-cure models to the observed epcoritamab data (Appendix E) and the analyses demonstrate issues associated with convergence (i.e., problems with the computational estimation of the survival parameters), as well as variation in the estimated cure fractions and wide confidence intervals; this indicates that the mixture-cure models are uncertain and difficult to estimate reliably. As such, these mixture-cure models have not been incorporated into the model. For the same reasons, flexible parametric models using cubic splines were also deemed inappropriate. During an AbbVie-organised advisory board with four clinical and two health economic experts, all experts deemed flexible spline models inappropriate, with the health economic experts stating that they would not help when extrapolating the EPCORE™ NHL-1 data.[15] Particularly when considering the small effective sample sizes in the MAIC analyses, spline models would be associated with a high risk of overfitting to immature data, and the reliance of spline models on data in the tail of the KM curve where few patients are at risk would introduce additional uncertainty.

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Appendix A Updated base case cost-effectiveness results

A.1 Severity modifier calculations

In line with the method used in the original submission, the expected quality-adjusted life expectancy for the general population was calculated in line with the methods provided by Schneider *et al.* (2022).[16] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2017–2019.[17] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D, as reported by Hernandez Alava *et al.* (2022) through the NICE DSU.[18] A summary of the QALY shortfall calculations for each analysis is presented in Table 8, which demonstrates that base case A and base case A.1 are eligible for a 1.2x severity modifier.

Table 8: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with the condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Base case A: epcoritamab versus R-based CIT (based on SCHOLAR-1 [Neelapu *et al.*])			
[redacted]	0.88	[redacted]	0.94
Base case A.1: epcoritamab versus Pola + BR (based on Sehn *et al.* 3L+)			
[redacted]	1.73	[redacted]	0.85
Base case population B: epcoritamab versus axi-cel (based on ZUMA-1)			
[redacted]	5.86	[redacted]	0.59

Abbreviations: axi-cel: axicabtagene ciloleucel; QALY: quality-adjusted life year; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R-based CIT: rituximab-based chemoimmunotherapy.

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A.2 Updated base case following DGD response

A.2.1. Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

As outlined in Appendix A.1, based on the updated base case, the shortfall for base case population A meets the threshold for applying a severity modifier of 1.2 to the incremental QALYs. As such, this modifier is applied in the base case results for analyses considering the population of patients who are ineligible for, and choose not to receive, intensive therapy. Results of the base case analysis A without a severity modifier applied, and subsequently with the 1.2 severity modifier applied to the QALYs, are presented in the following sections.

With the severity modifier applied, the results of the base case cost-effectiveness analysis demonstrate that epcoritamab is a cost-effective use of NHS resources, when compared with R-based CIT and Pola + BR, especially when considered alongside the high level of unmet need in this patient population and innovative nature of epcoritamab. The results of the deterministic and probabilistic analyses demonstrate are a high degree of alignment.

A.2.1.1 No severity modifier applied

For patients ineligible for, or choose not to receive, intensive therapies, the results of the probabilistic analysis at epcoritamab patient access scheme (PAS) price are presented in Table 9. The probabilistic net health benefit (NHB) associated with epcoritamab at epcoritamab PAS price is presented in Table 10. The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Deterministic results are also provided in Table 11 (at epcoritamab PAS price). The deterministic NHB associated with epcoritamab is presented in Table 12 (at epcoritamab PAS price).

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Table 9: Base-case probabilistic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab versus R-based CIT							
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£39,369	[redacted]	0.885	[redacted]	[redacted]	[redacted]	£25,277
Epcoritamab versus Pola + BR							
Epcoritamab	[redacted]	[redacted]	[redacted]				
Pola + BR	£109,612	[redacted]	1.796	[redacted]	[redacted]	[redacted]	£12,230

The presented ICERs are pairwise comparisons versus epcoritamab.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years.

Table 10: Net health benefit (probabilistic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab versus R-based CIT						
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£39,369	0.885	[redacted]	[redacted]	[redacted]	[redacted]
Epcoritamab versus Pola + BR						
Epcoritamab	[redacted]	[redacted]				
Pola + BR	£109,612	1.796	[redacted]	[redacted]	[redacted]	[redacted]

The presented ICERs are pairwise comparisons versus epcoritamab.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

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Table 11: Base-case deterministic results (no severity modifier; epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab versus R-based CIT							
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£38,926.13	[redacted]	0.884	[redacted]	[redacted]	[redacted]	£24,230
Epcoritamab versus Pola + BR							
Epcoritamab	[redacted]	[redacted]	[redacted]				
Pola + BR	£109,955	[redacted]	1.729	[redacted]	[redacted]	[redacted]	£7,446

The presented ICERs are pairwise comparisons versus epcoritamab.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years.

Table 12: Net health benefit (deterministic; no severity modifier; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab versus R-based CIT						
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£38,926.13	0.884	[redacted]	[redacted]	[redacted]	[redacted]
Epcoritamab versus Pola + BR						
Epcoritamab	[redacted]	[redacted]				
Pola + BR	£109,955	1.729	[redacted]	[redacted]	[redacted]	[redacted]

The presented ICERs are pairwise comparisons versus epcoritamab.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

A.2.1.2 Severity modifier applied

Equivalent probabilistic and deterministic results cost-effectiveness results and NHB are presented in Table 13–Table 16 (at epcoritamab PAS price).

Table 13: Base-case probabilistic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab versus R-based CIT							
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£39,061	[redacted]	0.883	[redacted]	[redacted]	[redacted]	£20,912
Epcoritamab versus Pola + BR							
Epcoritamab	[redacted]	[redacted]	[redacted]				
Pola + BR	£109,803	[redacted]	1.803	[redacted]	[redacted]	[redacted]	£9,894

The presented ICERs are pairwise comparisons versus epcoritamab. These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years.

Table 14: Net health benefit (probabilistic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab versus R-based CIT						
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£39,061	0.883	[redacted]	[redacted]	[redacted]	[redacted]
Epcoritamab versus Pola + BR						
Epcoritamab	[redacted]	[redacted]				
Pola + BR	£109,803	1.803	[redacted]	[redacted]	[redacted]	[redacted]

The presented ICERs are pairwise comparisons versus epcoritamab. These results include a 1.2 severity modifier applied to the incremental QALYs.

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Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 15: Base-case deterministic results (epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab versus R-based CIT							
Epcoritamab	[redacted]	[redacted]	[redacted]				
R-based CIT	£38,926	[redacted]	0.884	[redacted]	[redacted]	[redacted]	£20,191
Epcoritamab versus Pola + BR							
Epcoritamab	[redacted]	[redacted]	[redacted]				
Pola + BR	£109,955	[redacted]	1.729	[redacted]	[redacted]	[redacted]	£6,205

The presented ICERs are pairwise comparisons versus epcoritamab. These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; R: rituximab; QALYs: quality-adjusted life years.

Table 16: Net health benefit (deterministic; at epcoritamab PAS price): ineligible for, or choose not to receive, intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab versus R-based CIT						
Epcoritamab	[redacted]	[redacted]				
R-based CIT	£38,926	0.884	[redacted]	[redacted]	[redacted]	[redacted]
Epcoritamab versus Pola + BR						
Epcoritamab	[redacted]	[redacted]				
Pola + BR	£109,955	1.729	[redacted]	[redacted]	[redacted]	[redacted]

The presented ICERs are pairwise comparisons versus epcoritamab. These results include a 1.2 severity modifier applied to the incremental QALYs.
Abbreviations: CIT: chemoimmunotherapy; PAS: patient access scheme; R: rituximab; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; QALYs: quality-adjusted life years; NHB: net health benefit.

A.2.2. Base case analysis B: Patients eligible for intensive therapies

For patients eligible for intensive therapies, the results of the probabilistic analysis are presented in Table 17 (at epcoritamab PAS price). The probabilistic NHB associated with epcoritamab is presented in Table 18 (at epcoritamab PAS price). The PSA was run for 1000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions.

Deterministic results are also provided in Table 19 (at epcoritamab PAS price). The deterministic NHB associated with epcoritamab is presented in Table 20 (at epcoritamab PAS price). The results of the base case cost-effectiveness analysis demonstrate that epcoritamab is a cost-effective use of NHS resources when compared with axi-cel, [redacted]. The results of the deterministic and probabilistic analyses demonstrate a high degree of alignment.

Table 17: Base-case probabilistic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
Axi-cel	£415,038	[redacted]	5.773	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 18: Net health benefit (probabilistic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
Axi-cel	£415,038	5.773	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Table 19: Base-case deterministic results (epcoritamab PAS price): eligible for intensive therapies

Technologies	Total			Incremental			ICER incremental (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Epcoritamab	[redacted]	[redacted]	[redacted]				
Axi-cel	£416,171	[redacted]	5.855	[redacted]	[redacted]	[redacted]	Epcoritamab is dominant

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 20: Net health benefit (deterministic; at epcoritamab PAS price): eligible for intensive therapies

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Epcoritamab	[redacted]	[redacted]				
Axi-cel	£416,171	5.855	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

A.3 Probabilistic sensitivity analysis

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for epcoritamab versus R-based CIT, epcoritamab versus Pola + BR and epcoritamab versus axi-cel are presented in Figure 1–Figure 6.

A.3.1. Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

Epcoritamab versus R-based CIT

Figure 1: Cost-effectiveness scatter plot for epcoritamab versus R-based CIT (epcoritamab PAS price; severity modifier applied)

Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

Figure 2: Cost-effectiveness acceptability curve for epcoritamab versus R-based CIT (epcoritamab PAS price; severity modifier applied))

Abbreviations: PAS: patient access scheme; R-based CIT: rituximab-based chemoimmunotherapy; QALY: quality-adjusted life year.

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Epcoritamab versus Pola + BR

Figure 3: Cost-effectiveness scatter plot for epcoritamab versus Pola + BR (epcoritamab PAS price; severity modifier applied)

Abbreviations: PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; QALY: quality-adjusted life year.

Figure 4: Cost-effectiveness acceptability curve for epcoritamab versus Pola + BR (epcoritamab PAS price; severity modifier applied)

Abbreviations: PAS: patient access scheme; Pola + BR: polatuzumab vedotin with bendamustine and rituximab; QALY: quality-adjusted life year.

A.3.2. Base case analysis B: Patients eligible for intensive therapies

Figure 5: Cost-effectiveness scatter plot for epcoritamab versus axi-cel (epcoritamab PAS price)

Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 6: Cost-effectiveness acceptability curve for epcoritamab versus axi-cel (epcoritamab PAS price)

Abbreviations: axi-cel: axicabtagene ciloleucel; PAS: patient access scheme; QALY: quality-adjusted life year.

A.4 Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis (DSA) was conducted. Where available, each parameter was varied by 95% CIs. For parameters where CIs were not available the input was varied by ±10% of their mean value. DSA tornado plots for epcoritamab versus R-based CIT, epcoritamab versus Pola + BR and epcoritamab versus axi-cel are presented in Figure 7–Figure 9.

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A.4.1. Base case analysis A: Patients ineligible for, or choose not to receive, intensive therapies

Epcoritamab versus R-based CIT

Figure 7: DSA tornado plot for epcoritamab versus R-based CIT (epcoritamab PAS price; severity modifier applied)

Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

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Epcoritamab versus Pola + BR

Figure 8: DSA tornado plot for epcoritamab versus Pola + BR (epcoritamab PAS price; severity modifier applied)

Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; epco: epcoritamab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; Pola + BR: Polatuzumab vedotin with rituximab and bendamustine.

A.4.2. Base case analysis B: Patients eligible for intensive therapies

Figure 9: DSA tornado plot for epcoritamab versus axi-cel (epcoritamab PAS price)

Abbreviations: BGM: background mortality; CAR-T: chimeric antigen receptor T-cell; DSA: deterministic sensitivity analysis; epco: epcoritamab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy; SC: subcutaneous.

A.5 Scenario analyses

A.5.1. Probabilistic results

A.5.1.1 No severity modifier

Probabilistic results at epcoritamab PAS price with no severity modifier applied for all scenario analyses run in response to the DGD are presented in Table 21.

Table 21: Scenario analyses probabilistic results (epcoritamab PAS price; no severity modifier)

Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT				[redacted]	[redacted]	£25,277	[redacted]	[redacted]
Scenario analysis A	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (9 variables adjusted)		[redacted]	[redacted]	£27,689	[redacted]	[redacted]
Scenario analysis A.6	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (9 variables adjusted)[a]		[redacted]	[redacted]	£22,004	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£23,851	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (9	R-based CIT OS extrapolation:	[redacted]	[redacted]	£21,486	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		variables adjusted)	generalised gamma					
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (11 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£23,625	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic		[redacted]	[redacted]	£24,820	[redacted]	[redacted]
PFS extrapolation for epcoritamab	Generalised gamma	Lognormal		[redacted]	[redacted]	£29,958	[redacted]	[redacted]
OS extrapolation for R-based CIT	lognormal	Loglogistic		[redacted]	[redacted]	£25,466	[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]	£23,322	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma		[redacted]	[redacted]	£26,665	[redacted]	[redacted]
PFS for R-based CIT	OS HR for R-based CIT used to estimate PFS for R-based CIT	HR between OS and PFS for epcoritamab used to estimate PFS for R-based CIT		[redacted]	[redacted]	£24,408	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£23,782	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Discontinuation	R-based CIT patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on R-based CIT discontinue before progression		[redacted]	[redacted]	£25,043	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£24,992	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£25,503	[redacted]	[redacted]
Base case population A versus Pola + BR				[redacted]	[redacted]	£12,230	[redacted]	[redacted]
Scenario analysis A.1	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (10 variables adjusted)		[redacted]	[redacted]	£13,688	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£6,631	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10	Epcoritamab TTD extrapolation: lognormal	[redacted]	[redacted]	£34,635	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		variables adjusted)						
Scenario analysis A.5	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£25,866	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (13 variables adjusted)[a]		[redacted]	[redacted]	£23,037	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£20,615	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab TTD extrapolation: generalised gamma	[redacted]	[redacted]	£35,750	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£9,554	[redacted]	[redacted]
Discontinuation	Pola + BR patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on Pola + BR discontinue before progression		[redacted]	[redacted]	£13,137	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£11,328	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£8,622	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]	Piecewise approach whereby KM data is used directly until 12 months, after which standard parametric extrapolations are used	[redacted]	[redacted]	£23,419	[redacted]	[redacted]
Base case population B versus axi-cel				[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario analysis B	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (10 variables adjusted)[a]		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
	Efficacy data from DLBCL, no	Efficacy data from DLBCL, no prior	Epcoritamab TTD	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (7 variables adjusted)	CAR-T-, CAR-T eligible adjusted to ZUMA-1 (10 variables adjusted)	extrapolation: Gamma					
Scenario analysis B.1	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (7 variables adjusted)	Efficacy data from LBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (10 variables adjusted)[a]		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (11 variables adjusted)[a]		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24		[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		months, after which standard parametric extrapolations are used					

[a] Extrapolations selected for use in these scenario analyses are detailed in Appendix D.
Abbreviations: Axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LTR: long-term remission; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy.

A.5.1.2 1.2x severity modifier

Probabilistic results at epcoritamab PAS price with a 1.2x severity modifier applied for base case analyses A and A.1 for all scenario analyses run in response to the DGD are presented in Table 22.

Table 22: Scenario analyses probabilistic results (epcoritamab PAS price; 1.2x severity modifier applied for base case analyses A and A.1)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT			[redacted]	[redacted]	£20,912	[redacted]	[redacted]
Scenario analysis A	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (9 variables adjusted)	[redacted]	[redacted]	£23,074	[redacted]	[redacted]
Scenario analysis A.6	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7	Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (9 variables adjusted)[a]	[redacted]	[redacted]	£18,336	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (11 variables adjusted)[a]	[redacted]	[redacted]	£19,876	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	variables adjusted)	Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (9 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£17,905	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (11 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£19,688	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic		[redacted]	[redacted]	£20,684	[redacted]	[redacted]
PFS extrapolation for epcoritamab	Generalised gamma	Lognormal		[redacted]	[redacted]	£24,965	[redacted]	[redacted]
OS extrapolation for R-based CIT	lognormal	Loglogistic		[redacted]	[redacted]	£21,221	[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]	£19,435	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma		[redacted]	[redacted]	£22,221	[redacted]	[redacted]
PFS for R-based CIT	OS HR for R-based CIT used to estimate PFS for R-based CIT	HR between OS and PFS for epcoritamab used to estimate PFS for R-based CIT		[redacted]	[redacted]	£20,340	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£19,819	[redacted]	[redacted]
Discontinuation	R-based CIT patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on R-based CIT discontinue before progression		[redacted]	[redacted]	£20,869	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£20,826	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£21,252	[redacted]	[redacted]
Base case population A versus Pola + BR				[redacted]	[redacted]	£9,894	[redacted]	[redacted]
Scenario analysis A.1	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (10 variables adjusted)		[redacted]	[redacted]	£11,407	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£5,526	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab TTD extrapolation: lognormal	[redacted]	[redacted]	£28,863	[redacted]	[redacted]
Scenario analysis A.5	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£21,555	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (13 variables adjusted)[a]		[redacted]	[redacted]	£19,197	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£17,179	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab TTD extrapolation: generalised gamma	[redacted]	[redacted]	£29,792	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£7,962	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Discontinuation	Pola + BR patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on Pola + BR discontinue before progression		[redacted]	[redacted]	£10,947	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£9,440	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£7,185	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]	Piecewise approach whereby KM data is used directly until 12 months, after which standard parametric extrapolations are used	[redacted]	[redacted]	£19,516	[redacted]	[redacted]

Results for base case analysis A and base case analysis A.1, include a 1.2 severity modifier applied to the incremental QALYs based on the evidence provided in Appendix A.1. The PSA was re-run for base case analysis A and base case analysis A.1, explaining the difference in incremental costs for each base case with and without the severity modifier applied; for each scenario analysis, a 1.2 severity modifier was applied to the incremental QALYs without re-running the PSA, hence there is no change in incremental costs for each scenario analysis with and without the severity modifier. [a] Extrapolations selected for use in these scenario analyses are detailed in Appendix D.
Abbreviations: Axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LTR: long-term remission; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy.

A.5.2. Deterministic results

A.5.2.1 No severity modifier

Deterministic results at epcoritamab PAS price with no severity modifier applied for all scenario analyses run in response to the DGD are presented in Table 23.

Table 23: Scenario analyses deterministic results (epcoritamab PAS price; no severity modifier)

Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT				[redacted]	[redacted]	£24,230	[redacted]	[redacted]
Scenario analysis A	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (9 variables adjusted)		[redacted]	[redacted]	£27,078	[redacted]	[redacted]
Scenario analysis A.6	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (9 variables adjusted)[a]		[redacted]	[redacted]	£22,012	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£23,937	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (9 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£21,483	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (11 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£23,596	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic		[redacted]	[redacted]	£24,149	[redacted]	[redacted]
PFS extrapolation for epcoritamab	Generalised gamma	Lognormal		[redacted]	[redacted]	£30,292	[redacted]	[redacted]
OS extrapolation for R-based CIT	lognormal	Loglogistic		[redacted]	[redacted]	£24,552	[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]	£21,292	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma		[redacted]	[redacted]	£26,030	[redacted]	[redacted]
PFS for R-based CIT	OS HR for R-based CIT used to estimate PFS for R-based CIT	HR between OS and PFS for epcoritamab used to estimate PFS for R-based CIT		[redacted]	[redacted]	£23,124	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£23,123	[redacted]	[redacted]
Discontinuation	R-based CIT patients discontinue only	10% of patients on R-based CIT discontinue before progression		[redacted]	[redacted]	£24,260	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	due to progression (TTD is equal to PFS)							
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£23,739	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£23,398	[redacted]	[redacted]
Base case population A versus Pola + BR				[redacted]	[redacted]	£7,446	[redacted]	[redacted]
Scenario analysis A.1	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (10 variables adjusted)		[redacted]	[redacted]	£11,489	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£10,960	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab TTD extrapolation: lognormal	[redacted]	[redacted]	£47,134	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Scenario analysis A.5	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£25,339	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (13 variables adjusted)[a]		[redacted]	[redacted]	£23,208	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£19,902	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab TTD extrapolation: generalised gamma	[redacted]	[redacted]	£33,594	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£4,988	[redacted]	[redacted]
Discontinuation	Pola + BR patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on Pola + BR discontinue before progression		[redacted]	[redacted]	£8,676	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£7,242	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£5,238	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]	Piecewise approach whereby KM data is used directly until 12 months, after which standard parametric extrapolations are used	[redacted]	[redacted]	£23,016	[redacted]	[redacted]
Base case population B versus axi-cel				[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario analysis B	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (10 variables adjusted)[a]		[redacted]	[redacted]	Dominant	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (10 variables adjusted)	Epcoritamab TTD extrapolation: Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario analysis B.1	Efficacy data from DLBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (7 variables adjusted)	Efficacy data from LBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (10 variables adjusted)[a]		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T-, CAR-T eligible adjusted to ZUMA-1 (11 variables adjusted)[a]		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

[a] Extrapolations selected for use in these scenario analyses are detailed in Appendix D.
Abbreviations: Axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LTR: long-term remission; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy.

A.5.2.2 1.2x severity modifier

Deterministic results at epcoritamab PAS price with a 1.2x severity modifier applied for base case analyses A and A.1 for all scenario analyses run in response to the DGD are presented in Table 24.

Table 24: Scenario analyses deterministic results (epcoritamab PAS price; 1.2x severity modifier applied to base case analyses A and A.1)

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case population A versus R-based CIT			[redacted]	[redacted]	£20,191	[redacted]	[redacted]
Scenario analysis A	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to SCHOLAR-1 (9 variables adjusted)	[redacted]	[redacted]	£22,565	[redacted]	[redacted]
Scenario analysis A.6	Efficacy data from DLBCL, no prior CAR-T	Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (9 variables adjusted)[a]	[redacted]	[redacted]	£18,343	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	adjusted to SCHOLAR-1 (7 variables adjusted)	Efficacy data from LBCL, no prior CAR-T adjusted to Crump *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£19,948	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (9 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£17,903	[redacted]	[redacted]
		Efficacy data from LBCL, no prior CAR-T adjusted to Crump et al. (11 variables adjusted)	R-based CIT OS extrapolation: generalised gamma	[redacted]	[redacted]	£19,663	[redacted]	[redacted]
OS extrapolation for epcoritamab	Lognormal	Loglogistic		[redacted]	[redacted]	£20,124	[redacted]	[redacted]
PFS extrapolation for epcoritamab	Generalised gamma	Lognormal		[redacted]	[redacted]	£25,243	[redacted]	[redacted]
OS extrapolation for R-based CIT	lognormal	Loglogistic		[redacted]	[redacted]	£20,460	[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]	£17,743	[redacted]	[redacted]
TTD extrapolation for epcoritamab	Exponential	Gamma		[redacted]	[redacted]	£21,692	[redacted]	[redacted]

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Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
PFS for R-based CIT	OS HR for R-based CIT used to estimate PFS for R-based CIT	HR between OS and PFS for epcoritamab used to estimate PFS for R-based CIT	[redacted]	[redacted]	£19,270	[redacted]	[redacted]
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR	[redacted]	[redacted]	£19,269	[redacted]	[redacted]
Discontinuation	R-based CIT patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on R-based CIT discontinue before progression	[redacted]	[redacted]	£20,217	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care	[redacted]	[redacted]	£19,783	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used	[redacted]	[redacted]	£19,498	[redacted]	[redacted]
Base case population A versus Pola + BR			[redacted]	[redacted]	£6,205	[redacted]	[redacted]
Scenario analysis A.1	Efficacy data from DLBCL, no prior CAR-T	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (10 variables adjusted)	[redacted]	[redacted]	£9,574	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£9,133	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn et al. (10 variables adjusted)	Epcoritamab TTD extrapolation: lognormal	[redacted]	[redacted]	£39,279	[redacted]	[redacted]
Scenario analysis A.5	Efficacy data from DLBCL, no prior CAR-T adjusted to Sehn *et al.* (6 variables adjusted)	Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]		[redacted]	[redacted]	£21,116	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (13 variables adjusted)[a]		[redacted]	[redacted]	£19,340	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab OS extrapolation: lognormal	[redacted]	[redacted]	£16,585	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend et al. (13 variables adjusted)	Epcoritamab TTD extrapolation: generalised gamma	[redacted]	[redacted]	£27,995	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
LTR	LTR at 36 months following treatment initiation	LTR at 36 months following treatment initiation and patients discontinue treatment with epcoritamab when entering LTR		[redacted]	[redacted]	£4,157	[redacted]	[redacted]
Discontinuation	Pola + BR patients discontinue only due to progression (TTD is equal to PFS)	10% of patients on Pola + BR discontinue before progression		[redacted]	[redacted]	£7,230	[redacted]	[redacted]
Resource use	PFS off-treatment resource use based on clinical expert input	PFS off-treatment resource use based on clinical expert input, including further removal of residential care, day care and home care		[redacted]	[redacted]	£6,035	[redacted]	[redacted]
Survival extrapolations	Standard parametric extrapolations	Piecewise approach whereby KM data is used directly until 24 months, after which standard parametric extrapolations are used		[redacted]	[redacted]	£4,365	[redacted]	[redacted]
		Efficacy data from DLBCL, no prior CAR-T adjusted to Northend *et al.* (11 variables adjusted)[a]	Piecewise approach whereby KM data is used directly until 12 months, after which standard parametric	[redacted]	[redacted]	£19,180	[redacted]	[redacted]

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Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
			extrapolations are used					

Results for base case analysis A and base case analysis A.1, include a 1.2 severity modifier applied to the incremental QALYs based on the evidence provided in Appendix A.1. The PSA was re-run for base case analysis A and base case analysis A.1, explaining the difference in incremental costs for each base case with and without the severity modifier applied; for each scenario analysis, a 1.2 severity modifier was applied to the incremental QALYs without re-running the PSA, hence there is no change in incremental costs for each scenario analysis with and without the severity modifier. [a] Extrapolations selected for use in these scenario analyses are detailed in Appendix D.
Abbreviations: Axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio; LTR: long-term remission; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; R-based CIT: rituximab based chemoimmunotherapy.

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Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

[ID4045]

Draft Guidance Document Response Appendix

November 2023

File name	Version	Contains confidential information	Date
ID4045_Epcoritamab_ NICE DGD Response Appendix [Fully Redacted]_28Nov23	Final	Yes	28th November 2023

Contents

Tables

Figures

Appendix B Clinical data from EPCORE™ NHL-1 – DLBCL, ineligible for intensive therapies

B.1 Baseline characteristics

Demographic characteristics

In response to the request from the Committee, the demographic characteristics for the subgroups of patients with DLBCL who are ineligible for CAR-T therapies in the EPCORE™ NHL-1 trial are summarised in Table 1.

[redacted] of all patients in the CAR-T ineligible subgroups were reported as White; [redacted] and [redacted], for the all DLBCL and DLBCL, no prior CAR-T subgroups, respectively. Patients in the DLBCL, no prior CAR-T, CAR-T ineligible subgroup were [redacted] than patients in the DLBCL, CAR-T ineligible subgroup (median: [redacted] years versus [redacted] years, respectively). However, there were similarities in the proportion of patients who were male ([redacted]% versus [redacted]%, respectively) and the median BMI at study baseline ([redacted] kg/m^2 versus [redacted] kg/m^2, respectively).

Table 1: Key demographic characteristics (DLBCL, CAR-T ineligible subgroups)

Number of treated patients, n (%)	DLBCL, CAR-T ineligible subgroups	
	All DLBCL (N=[redacted])	DLBCL, no prior CAR-T (N=[redacted])
Age (years)		
Median (range: min, max)	[redacted]	[redacted]
Age category (years)		
<65 years	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]
Sex (at birth)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported[a]	[redacted]	[redacted]
BMI (kg/m^2) at baseline		
Median (range: min, max)	[redacted]	[redacted]
ECOG performance status		
0	[redacted]	[redacted]
1	[redacted]	[redacted]

Number of treated patients, n (%)	DLBCL, CAR-T ineligible subgroups	
	All DLBCL (N=[redacted])	DLBCL, no prior CAR-T (N=[redacted])
2	[redacted]	[redacted]

[a] Not reported in non-US countries.
Abbreviations: BMI: body mass index; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; max: maximum; min: minimum; US: United States.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Baseline disease characteristics

The baseline disease characteristics for the subgroups of patients with DLBCL who are ineligible for CAR-T therapies in the EPCORE™ NHL-1 trial are summarised in Table 2 below.

The baseline disease characteristics for both subgroups of patients were broadly similar. [redacted] of patients were considered to have had *de novo* disease (All DLBCL, CAR-T ineligible: [redacted]%; DLBCL, no prior CAR-T, CAR-T ineligible: [redacted]%) and an IPI classification ≥3 at the study baseline (All DLBCL, CAR-T ineligible: [redacted]%; DLBCL, no prior CAR-T, CAR-T ineligible: [redacted]%). The [redacted] of patients in either subgroup also presented with Ann Arbor Stage IV disease at the time of screening (All DLBCL, CAR-T ineligible: [redacted]%; DLBCL, no prior CAR-T, CAR-T ineligible: [redacted]%).

Table 2: Baseline disease characteristics (DLBCL, CAR-T ineligible subgroups)

Number of treated patients, n (%)	DLBCL, CAR-T ineligible subgroups	
	All DLBCL (N=[redacted])	DLBCL, no prior CAR-T (N=[redacted])
Disease type at trial entry		
DLBCL	[redacted]	[redacted]
DLBCL type		
De novo	[redacted]	[redacted]
Transformed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Ann Arbor Stage at Screening		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
IPI (at study entry)		
0–2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; IPI: International Prognostic Index.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Prior medications and procedures

An overview of the prior cancer therapies received by patients in the CAR-T ineligible subgroups of the EPCORE™ NHL-1 trial is shown in Table 3.

A [redacted] of patients ([redacted] [redacted%]) in the DLBCL, CAR-T ineligible subgroup had a history of receiving previous CAR-T and, of these, [redacted] were refractory to CAR T-cell therapy (defined as disease that either progressed during therapy or progressed <6 months after completion of therapy).

The median number of prior anti-lymphoma therapies received by these patients were [redacted] (range [min, max]: [redacted], [redacted]), however within this subgroup, a [redacted] of patients received three or more than three prior anti-lymphoma therapies ([redacted]% and [redacted]% respectively). The median time from the end of the last-line anti-lymphoma therapy to the first dose of epcoritamab in patients was [redacted] months (range [min, max]: [redacted], [redacted]).

[redacted] of the patients ([redacted]) had primary refractory disease and [redacted] were refractory to ≥2 consecutive prior lines of anti-lymphoma therapy. [redacted] patients [redacted] were refractory to the last line of systemic antineoplastic therapy. Finally, only [redacted] ([redacted]% of patients had received prior ASCT.

For the DLBCL, no prior CAR-T, CAR-T ineligible subgroup, the baseline medical history shared similar trends with the overall DLBCL, CAR-T ineligible patient population. However, notably, the [redacted]([redacted]%) had received between 2–3 prior lines of therapy before receiving epcoritamab, and the proportion of patients with either primary refractory disease ([redacted] [redacted%]) or who were refractory to ≥2 consecutive prior lines of anti-lymphoma therapy ([redacted] [redacted%]) was [redacted] than in the overall DLBCL, CAR-T ineligible population.

Table 3: Prior anticancer therapies (DLBCL, CAR-T ineligible subgroups)

Number of treated patients, n (%)	DLBCL, CAR-T ineligible subgroups	
	All DLBCL (N=[redacted])	DLBCL, no prior CAR-T (N=[redacted])
Prior ASCT	[redacted]	[redacted]
Prior CAR-T therapy	[redacted]	[redacted]
Refractory to CAR-T therapy		
No	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Prior anti-lymphoma therapy		
Median number (min, max) of prior lines of anti-lymphoma therapy	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥4	[redacted]	[redacted]

Number of treated patients, n (%)	DLBCL, CAR-T ineligible subgroups	
	All DLBCL (N=[redacted])	DLBCL, no prior CAR-T (N=[redacted])
Median time (min, max) from end of last-line anti lymphoma therapy to first dose of epcoritamab (months)	[redacted]	[redacted]
Patients with primary refractory disease[a]	[redacted]	[redacted]
Patients refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[b]	[redacted]	[redacted]
Last-line systemic antineoplastic therapy		
Refractory[b]	[redacted]	[redacted]
Relapsed[c]	[redacted]	[redacted]

[a] Patient was considered primary refractory if the patient is refractory to frontline anti-lymphoma therapy; [b] Patient was considered refractory if the patient experienced disease progression or stable disease as best response or disease progression within six months after therapy completion; [c] Patient was considered relapsed if the patient experienced disease progression >6 months after last treatment.
Abbreviations: ASCT: autologous stem cell transplantation; CAR-T: chimeric antigen receptor T-cells; DLBCL: diffuse large B-cell lymphoma; max: maximum; min: minimum.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

B.2 Efficacy endpoints

PFS based on IRC assessment, Lugano Criteria (DLBCL, CAR-T ineligible subgroups)

In the DLBCL, CAR-T ineligible subgroup, [redacted] patients experienced a PFS event (disease progression or death) as assessed by IRC. The median PFS was [redacted]). The estimated percentage of patients remaining progression-free at six and 12 months was [redacted] and [redacted], respectively.

For the DLBCL, no prior CAR-T, CAR-T ineligible subgroup, [redacted] patients experienced a PFS event (disease progression or death) as assessed by IRC. The median PFS was [redacted]). The estimated percentage of patients remaining progression-free at six and twelve months was [redacted] and [redacted], respectively.

The PFS based on IRC assessment (Lugano criteria) are presented in Table 4 and a KM plot of PFS based on IRC assessment for patients in the CAR-T ineligible subgroups is presented in Figure 1.

Figure 1: KM plot of PFS based on IRC assessment, Lugano Criteria (DLBCL, CAR-T ineligible subgroups; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor-T cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; IRC: independent review committee; KM: Kaplan–Meier.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Table 4: PFS based on IRC assessment Lugano Criteria (DLBCL, CAR-T ineligible subgroups; [redacted] data cut-off)

	All DLBCL ([redacted])	DLBCL, No prior CAR-T (N=[redacted])
Number of events	[redacted]	[redacted]
Number of censored	[redacted]	[redacted]
PFS (months)		
Median (95% CI)[a]	[redacted]	[redacted]
Estimated percentage of patients remaining progression-free (95% CI)[a]		
6-month	[redacted]	[redacted]
12-month	[redacted]	[redacted]
18-month	[redacted]	[redacted]

[a] Based on KM estimate.
Abbreviations: CI: confidence interval; CAR-T: chimeric antigen receptor T cell; DLBCL: diffuse large B-cell lymphoma; IRC: independent review committee; PFS: progression-free survival.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Figure 2: KM plot of PFS based on IRC assessment, Lugano Criteria (DLBCL, CAR-T ineligible subgroups; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor-T cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; IRC: independent review committee; KM: Kaplan–Meier.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

OS (DLBCL, CAR-T ineligible subgroups)

Among all patients who were CAR-T ineligible, [redacted] had died and [redacted] were still alive. Median OS was [redacted](95% CI: [redacted]). The estimated percentage of CAR-T ineligible DLBCL patients who remained alive at 6, 12, and 18 months was [redacted], [redacted], and [redacted], respectively.

For patients within the DLBCL, no prior CAR-T, CAR-T ineligible subgroup, [redacted] had died and [redacted] were still alive. Median OS was [redacted](95% CI: [redacted]). The estimated percentage of patients who remained alive at 6, 12, and 18 months was [redacted], [redacted], and [redacted], respectively.

These results are presented below in Table 5 and a KM plot of OS for DLBCL CAR-T ineligible subgroups are shown in Figure 3.

Figure 3: KM plot of OS (DLBCL, CAR-T ineligible subgroups; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; KM: Kaplan–Meier; OS: overall survival; NE: not estimable.

Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Table 5: OS (DLBCL, CAR-T ineligible subgroups; [redacted] data cut-off)

	All DLBCL ([redacted])	DLBCL, No prior CAR-T (N=[redacted])
Number of events	[redacted]	[redacted]
Number of censored	[redacted]	[redacted]
OS (months)		
Median (95% CI)[a]	[redacted]	[redacted]
Estimated percentage of patients alive (95% CI)[a]		
6-month	[redacted]	[redacted]
12-month	[redacted]	[redacted]
18-month	[redacted]	[redacted]

[a] Based on Kaplan–Meier estimate.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; NE: not estimable; OS: overall survival.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Figure 4: KM plot of OS (DLBCL, CAR-T ineligible subgroups; [redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T cell; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HR: hazard ratio; KM: Kaplan–Meier; OS: overall survival; NE: not estimable.
Source: AbbVie (Data on File), EPCORE™ NHL-1 Data Files, April 2023.

Appendix C Indirect treatment comparisons

MAICs of epcoritamab versus R-based CIT, based on Crump *et al.*, have been conducted; results for these MAICs are presented in the following sections.

C.1 Adjusted baseline characteristics

Scenario analysis A.6 – epcoritamab LBCL, no prior CAR-T adjusted to Crump et al. (9 variables adjusted)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, no prior CAR-T therapy population). As outlined above, this EPCORE™ NHL-1 population was adjusted to match the CIT arm of the SCHOLAR-1 population from Crump *et al*. (2017). Following adjustment the effective sample size (N_{eff}) for the EPCORE™ NHL-1 population was [redacted].

An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 6. After generation of the adjustment weights, they were not truncated. The distribution of weights for this MAIC are presented in Figure 5.

Table 6: Baseline characteristics for scenario analysis A.6 (epcoritamab LBCL, no prior CAR-T population adjusted to Crump et al. – 9 variables adjusted)

	Unadjusted epcoritamab LBCL, no CAR-T ([redacted])	Adjusted epcoritamab LBCL, no CAR-T ([redacted])*	Crump *et al.* (2017) CIT (SCHOLAR-1) (N=636)
Age			
Median (years)	[redacted]	[redacted]	55.0
≥ 55 years	[redacted]	[redacted]	**50.0%**
≥ 65 years	[redacted]	[redacted]	**13.8%**
Male	[redacted]	[redacted]	**64.0%**
Patients with DLBCL (including TFL)	[redacted]	[redacted]	**97.8%†**
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]	**83.9%†**
Disease stage III-IV	[redacted]	[redacted]	**72.0%**
IPI score ≥3	[redacted]	[redacted]	33.0%
IPI score unknown/missing/NA	[redacted]	[redacted]	18.0%
Number of prior lines			
2-3 lines of chemo and ASCT, all patients	[redacted]	[redacted]	NA
>3 lines of chemo and ASCT, all patients	[redacted]	[redacted]	NA
2-3 lines of chemo and ASCT, excluding patients relapsed within 12 months of ASCT	[redacted]	[redacted]	49.0%
>3 lines of chemo and ASCT, excluding patients relapsed within 12 months of ASCT	[redacted]	[redacted]	<1.0%
Primary refractory	[redacted]	[redacted]	**28.0%**
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]	**50.0%**
Relapse within 12 months of ASCT	[redacted]	[redacted]	**22.0%**

* Values adjusted for: age (≥55 years), age (≥65 years), male, ECOG PS, disease stage, primary refractory, refractory to ≥2 consecutive lines of therapy, and relapse within 12 months of ASCT. †Out of patients with known values for these variables

Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESS: effective sample size; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; NA: not applicable; N_{eff}: effective sample size; TFL: transformed follicular lymphoma.

Figure 5: Adjustment weights distribution for scenario analysis A.6 (epcoritamab LBCL, no prior CAR-T population adjusted to Crump et al. – 9 variables adjusted)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B-Cell lymphoma.

Scenario analysis A.6 – epcoritamab LBCL, no prior CAR-T adjusted to Crump et al. (11 variables adjusted)

A total of [redacted] were included from the EPCORE™ NHL-1 trial (LBCL, no prior CAR-T therapy population). Following adjustment, the N_{eff} for the EPCORE™ NHL-1 population was [redacted] An overview of the EPCORE™ NHL-1 baseline characteristics prior to and after adjustment, alongside the baseline characteristics of the comparator populations included in the analysis is presented in Table 7. After generation of the adjustment weights, they were not truncated. The distribution of weights for this MAIC are presented in Figure 6.

Table 7: Baseline characteristics for scenario analysis A.6 (epcoritamab LBCL, no prior CAR-T population adjusted to Crump et al. – 11 variables adjusted)

	Unadjusted epcoritamab LBCL, no CAR-T ([redacted])	Adjusted epcoritamab LBCL, no CAR-T ([redacted])*	Crump *et al.* (2017) CIT (SCHOLAR-1) (N=636)
Age			
Median (years)	[redacted]	[redacted]	**55.0**
≥ 55 years	[redacted]	[redacted]	**50.0%**
≥ 65 years	[redacted]	[redacted]	**13.8%**
Male	[redacted]	[redacted]	**64.0%**
Patients with DLBCL (including TFL)	[redacted]	[redacted]	**97.8%†**
ECOG PS 0-1 (vs 2)	[redacted]	[redacted]	**83.9%†**
Disease stage III-IV	[redacted]	[redacted]	**72.0%**
IPI score ≥3	[redacted]	[redacted]	**33.0%**
IPI score unknown/missing/NA	[redacted]	[redacted]	**18.0%**
Number of prior lines			
2-3 lines of chemo and ASCT, all patients	[redacted]	[redacted]	NA

>3 lines of chemo and ASCT	[redacted]	[redacted]	NA
2-3 lines of chemo and ASCT, excluding patients relapsed within 12 months of ASCT	[redacted]	[redacted]	49.0%
>3 lines of chemo and ASCT, excluding patients relapsed within 12 months of ASCT	[redacted]	[redacted]	<1.0%
Primary refractory	[redacted]	[redacted]	**28.0%**
Refractory to ≥2 consecutive lines of therapy	[redacted]	[redacted]	**50.0%**
Relapse within 12 months of ASCT	[redacted]	[redacted]	**22.0%**

***** Values adjusted for: age (≥55 years, age (≥65 years), male, ECOG PS, disease stage, IPI (high, unknown/missing), primary refractory, refractory to ≥2 consecutive lines of therapy, and relapse within 12 months of ASCT. † Out of patients with known values for these variables
Abbreviations: ASCT: autologous stem cell transplant; CAR-T: chimeric antigen receptor T-cell therapy; CIT: chemoimmunotherapy; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; LBCL: large B-cell lymphoma; NA: not applicable; N_{eff}: effective sample size; TFL: transformed follicular lymphoma.

Figure 6: Adjustment weights distribution for scenario analysis A.6 (epcoritamab LBCL, no prior CAR-T population adjusted to Crump et al. – 11 variables adjusted)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B-Cell lymphoma.

C.2 Efficacy results

Scenario analysis A.6 – epcoritamab LBCL, no prior CAR-T adjusted to Crump et al. (9 variables adjusted)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus CIT from SCHOLAR-1 is presented in Table 8, alongside the unadjusted and adjusted KM curves for OS in Figure 7. PFS for CIT from SCHOLAR-1 was not available and therefore a comparison for PFS was not conducted.

The adjusted OS HR for epcoritamab versus CIT is [redacted]
This demonstrates [redacted] in favour of epcoritamab versus CIT, which was [redacted]

[redacted]. There was also [redacted] in CR rate and ORR between epcoritamab and CIT.

Table 8: Unadjusted and adjusted outcomes for epcoritamab (LBCL, no prior CAR-T) versus CIT (SCHOLAR-1, Crump *et al.* [2017]) – 9 variables adjusted

	Epcoritamab LBCL, no prior CAR-T unadjusted (N=[redacted])	Epcoritamab LBCL, no prior CAR-T adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)[a]		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; HR: hazard ratio; LBCL: large B-cell lymphoma; ORR: overall response rate; OS: overall survival.

Figure 7: Unadjusted and adjusted OS KM curves for epcoritamab (LBCL, no prior CAR-T) versus CIT (SCHOLAR-1, Crump *et al.* [2017]) – 9 variables adjusted

[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival.

Scenario analysis A.6 – epcoritamab LBCL, no prior CAR-T adjusted to Crump et al. (11 variables adjusted)

A summary of the unadjusted and adjusted outcomes for epcoritamab versus CIT from SCHOLAR-1 is presented in Table 9, alongside the unadjusted and adjusted KM curves for OS in Figure 8. PFS for CIT from SCHOLAR-1 was not available and therefore a comparison for PFS was not conducted.

The adjusted OS HR for epcoritamab versus CIT is [redacted] This demonstrates [redacted] in favour of epcoritamab versus CIT, which was, however, [redacted]. Additionally, there was [redacted] in CR rate and ORR between epcoritamab and CIT.

Table 9: Unadjusted and adjusted outcomes for epcoritamab (LBCL, no prior CAR-T) versus CIT (SCHOLAR-1, Crump *et al.* [2017]) – 11 variables adjusted

	Epcoritamab LBCL, no prior CAR-T unadjusted (N=[redacted])	Epcoritamab LBCL, no prior CAR-T adjusted (N_{eff}=[redacted])
Survival, HR (95% CI)[a]		
OS	[redacted]	[redacted]
Response rates, %		
CR (epcoritamab vs CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]
ORR (epcoritamab vs CIT)	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence interval; CIT: chemoimmunotherapy; CR: complete response; HR: hazard ratio; LBCL: large B-cell lymphoma; ORR: overall response rate; OS: overall survival.

Figure 8: Unadjusted and adjusted OS KM curves for epcoritamab (LBCL, no prior CAR-T) versus CIT (SCHOLAR-1, Crump *et al.* [2017]) – 11 variables adjusted

Abbreviations: CAR-T: chimeric antigen receptor T-cell; CIT: chemoimmunotherapy; Kaplan–Meier; LBCL: large B-cell lymphoma; OS: overall survival.

Appendix D Time-to-event analyses (standard parametric models)

D.1 Overview

As outlined in the CS (Document B, Section B.3.2.2) parametric models for PFS, OS and ToT were fitted to the KM curves from the EPCORE™ NHL-1 trial (Appendix C.2) and the comparator data (Appendix C.4) in line with NICE DSU TSD14.[7] The parametric distributions were selected based on statistical goodness of visual fit to the observed data, feedback form UK clinicians and comparison with long-term data in the published literature where available. When goodness of fit statistics did not provide clear differentiation for models, clinical plausibility (and alignment to MAIC outcomes) was prioritised when selecting extrapolation.

D.2 Epcoritamab

D.2.1. Scenario analysis A.1 – DLBCL, no prior CAR-T adjusted to Sehn *et al.* (10 variables adjusted)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 adjusted to the Sehn *et al*. population (10 variables adjusted) is provided in Figure 9.

Figure 9: KM plot of PFS, OS and TTD used in scenario analysis A.1 ([redacted] data cut-off)

Abbreviations: KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Sehn *et al.* (10 variables adjusted), and evaluated based on AIC and BIC values, which are presented in Table 10.

The log-normal distribution and exponential model performs best in terms of AIC and BIC, respectively. However, all distributions could be considered viable on the basis of goodness of fit statistics due to minimal differences in the AIC/BIC values.

Table 10: Goodness of fit statistics for OS (AIC and BIC; scenario analysis A.1)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 10. The corresponding survival estimates at several landmarks are presented in Table 11. The generalised gamma extrapolation was selected to model OS for epcoritamab in scenario analysis A.1. This is in line with feedback from UK clinical experts who stated that the long-term OS outcomes predicted by the generalised gamma extrapolation are the most clinically plausible, followed by the loglogistic and lognormal models. A scenario analysis in which epcoritamab OS is extrapolated using the lognormal model was conducted.

Figure 10: Long-term OS extrapolations for epcoritamab (scenario analysis A.1)

Abbreviations: OS: overall survival.

Table 11: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model OS for epcoritamab in scenario analysis A.1.
Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Sehn *et al.* (10 variables adjusted). These were evaluated based on AIC and BIC values, which are presented in Table 12. Based on AIC and BIC criteria, the log-normal extrapolation demonstrates the best statistical fit.

Table 12: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.1)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 11. The corresponding survival estimates at several landmarks are presented in Table 13. The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1. This is in line with feedback from UK clinical experts, who statedthat During interviews with UK clinical experts, the experts stated that the generalised gamma extrapolation produces the most clinically plausible long-term estimates, with the Gompertz model also being considered clinically plausible.

Figure 11: Long-term PFS extrapolations for epcoritamab (scenario analysis A.1)

Abbreviations: PFS: progression-free survival.

Table 13: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The generalised gamma extrapolation was selected to model PFS for epcoritamab in scenario analysis A.1.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Sehn *et al.* (10 variables adjusted) are presented in Table 14. Based on AIC and BIC, the log-normal and log-logistic distributions show the best statistical fit to the observed data, however there are minimal differences in the statistical fit of all extrapolations.

Table 14: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis A.1)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The gamma extrapolation was selected to model TTD for epcoritamab in scenario analysis A.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 12. The corresponding TTD estimates at several landmarks are presented in Table 15. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years, with experts estimating a range of 0% to 25% of patients remaining on treatment at 10 years. As such, in line

with feedback from UK clinical experts, the gamma extrapolation was selected to model TTD for epcoritamab in scenario analysis A.1, with the lognormal extrapolation explored in a scenario analysis.

Figure 12: Long-term TTD extrapolations for epcoritamab (scenario analysis A.1)

Abbreviations: TTD: time to treatment discontinuation.

Table 15: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis A.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The gamma extrapolation was selected to model TTD for epcoritamab in in scenario analysis A.1.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

D.2.2. Scenario analysis A.5 – DLBCL, no prior CAR-T adjusted to Northend *et al.* (13 variables adjusted)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the Northend *et al*. population (13 variables adjusted) is provided in Figure 13.

Figure 13: KM plot of PFS, OS and TTD used in scenario analysis A.5 ([redacted] data cut-off)

Abbreviations: KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to the Northend *et al*. population (13 variables adjusted), and evaluated based on AIC and BIC values, which are presented in Table 16.

The exponential and log-normal distribution performs best in terms of AIC and BIC. However, Gompertz, generalised gamma, and log-logistic models could be considered viable on the basis of goodness of fit statistics due to minimal differences in the AIC/BIC values.

Table 16: Goodness of fit statistics for OS (AIC and BIC; scenario analysis A.5)

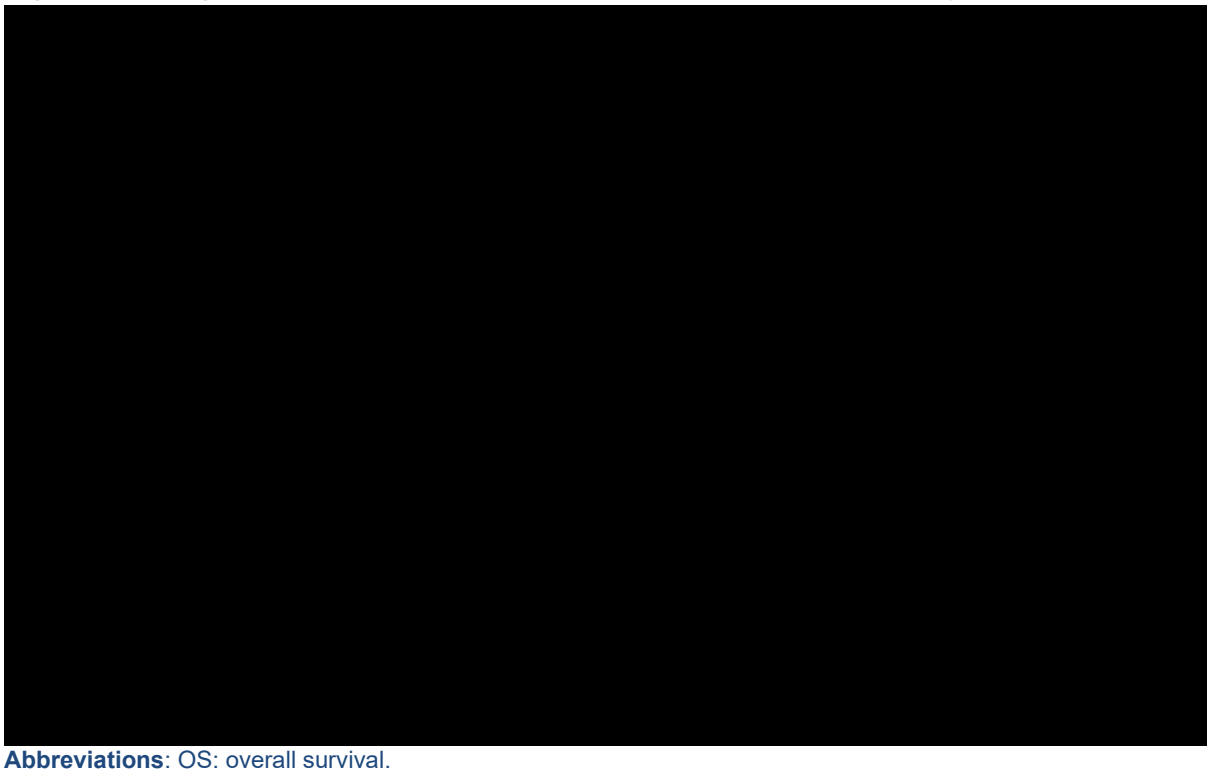
Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis A.5.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 14. The corresponding survival estimates at several landmarks are presented in Table 17. During interviews with UK clinical experts, clinical experts stated that the Gompertz extrapolation provides the most clinically plausible long-term estimates of OS for epcoritamab. As such, in line with feedback from UK clinical experts the Gompertz model was selected to model OS for epcoritamab in scenario analysis A.5. A scenario analysis lognormal extrapolation to model OS for epcoritamab was also conducted.

Figure 14: Long-term OS extrapolations for epcoritamab (scenario analysis A.5)



Abbreviations: OS: overall survival.

Table 17: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.5)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis A.5.
Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Northend *et al*. (13 variables adjusted). These were evaluated based on AIC and BIC values, which are presented in Table 18. Based on AIC and BIC criteria, the log-normal extrapolation demonstrates the best statistical fit.

Table 18: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.5)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis A.5.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 15. The corresponding survival estimates at several landmarks are presented in Table 19. During interviews with UK clinical experts, clinical experts stated that the Gompertz extrapolation provides the most clinically plausible long-term estimates of PFS for epcoritamab, with one clinical expert noting that the estimates from the Gompertz extrapolation

are pessimistic compared to their expectations. As such, in line with this feedback, the Gompertz model was selected to model PFS for epcoritamab in scenario analysis A.5.

Figure 15: Long-term PFS extrapolations for epcoritamab (scenario analysis A.5)

Abbreviations: PFS: progression-free survival.

Table 19: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.5)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis A.5.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Northend *et al*. (13 variables adjusted) are presented in Table 20. Based on AIC and BIC, the log-normal distribution shows the best statistical fit to the observed data, however there are minimal differences in the statistical fit of the Gompertz, log-logistic, and generalised gamma extrapolations.

Table 20: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis A.5)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Weibull extrapolation was selected to model TTD for epcoritamab in scenario analysis A.5.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 16. The corresponding TTD estimates at several landmarks are presented in Table 21. In line with the clinical expert feedback outlined in Appendix D.2.1, the Weibull extrapolation was selected to model TTD for epcoritamab in scenario analysis A.5.

Figure 16: Long-term TTD extrapolations for epcoritamab (scenario analysis A.5)

Abbreviations: TTD: time to treatment discontinuation.

Table 21: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis A.5)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Weibull extrapolation was selected to model TTD for epcoritamab in scenario analysis A.5.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

D.2.3. Scenario analysis A.6 – LBCL, no prior CAR-T adjusted to Crump *et al.* (9 variables adjusted)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the LBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the SCHOLAR-1 population from Crump *et al.* (9 variables adjusted) is provided in Figure 17.

Figure 17: KM plot of PFS, OS and TTD used in scenario analysis A.6 ([redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; KM: Kaplan–Meier; LBCL: large B cell lymphoma; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial, adjusted to Crump *et al.* (SCHOLAR-1; 9 variables adjusted), and evaluated based on AIC and BIC values, which are presented in Table 22.

The exponential distribution performs best in terms of AIC and BIC. With the exception of generalised gamma, the statistical goodness of fit of the remaining parametric distributions were similar. However, it should be noted that, due to the small effective sample size (N_{eff}=[redacted]) the results of the goodness-of-fit statistics are not considered to be reliable and should be interpreted with caution.

Table 22: Goodness of fit statistics for OS (AIC and BIC; scenario analysis A.6 (LBCL, no prior CAR-T adjusted to Crump *et al.* [9 variables adjusted])

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.6.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 18. The corresponding survival estimates at several landmarks are presented in Table 23. In line with the extrapolation selected for epcoritamab in base case analysis A, the lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.6.

Figure 18: Long-term OS extrapolations for epcoritamab (scenario analysis A.6)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; OS: overall survival.

Table 23: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.6)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.6.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence intervals; LBCL: large B cell lymphoma; NA: not applicable; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial, adjusted to Crump *et al.* (SCHOLAR-1; 9 variables adjusted). These were evaluated based on AIC and BIC values, which are presented in Table 24. Based on AIC and BIC criteria, the exponential extrapolation demonstrates the best statistical fit.

Table 24: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.6)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis A.6.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; PFS: progression free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 19. The corresponding survival estimates at several landmarks are presented in Table 25. UK clinical experts estimated that approximately 20% to 30% of patients would be progression-free at five years, with a similar proportion at 10 years. As such, the lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis A.6.

Figure 19: Long-term PFS extrapolations for epcoritamab (scenario analysis A.6)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; PFS: progression free survival.

Table 25: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.6)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis A.6.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence intervals; LBCL: large B cell lymphoma; NA: not applicable; PFS: progression free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial, adjusted to Crump *et al.*

(SCHOLAR-1; 9 variables adjusted), are presented in Table 26. Based on AIC and BIC, the exponential distribution shows the best statistical fit to the observed data, however there are minimal differences in the statistical fit of all extrapolations.

Table 26: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis A.6)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.6.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 20. The corresponding TTD estimates at several landmarks are presented in Table 27. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years, with experts estimating a range of 0% to 25% of patients remaining on treatment at 10 years. As such, in line with feedback from UK clinical experts, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.6.

Figure 20: Long-term TTD extrapolations for epcoritamab (scenario analysis A.6)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; TTD: time to treatment discontinuation.

Table 27: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis A.6)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis A.6.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence intervals; LBCL: large B cell lymphoma; NA: not applicable; TTD: time to treatment discontinuation.

D.2.4. Scenario analysis A.6 – LBCL, no prior CAR-T adjusted to Crump *et al.* (11 variables adjusted)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the LBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the SCHOLAR-1 population from Crump *et al.* (11 variables adjusted) is provided in Figure 21.

Figure 21: KM plot of PFS, OS and TTD used in scenario analysis A.6 ([redacted] data cut-off)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; KM: Kaplan–Meier; LBCL: large B cell lymphoma; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Crump *et al.* (SCHOLAR-1; 11 variables adjusted), and evaluated based on AIC and BIC values, which are presented in Table 28.

The exponential distribution performs best in terms of AIC and BIC. With the exception of generalised gamma, the statistical goodness of fit of the remaining parametric distributions were similar. However, it should be noted that, due to the small effective sample size (N_{eff}=[redacted]) the results of the goodness of fit measures are not considered to be reliable.

Table 28: Goodness of fit statistics for OS (AIC and BIC; scenario analysis A.6)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.6.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 22. The corresponding survival estimates at several landmarks are presented in Table 29. In line with the reasoning outlined in Appendix D.2.4, the lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.6.

Figure 22: Long-term OS extrapolations for epcoritamab (scenario analysis A.6)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; OS: overall survival.

Table 29: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.6)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for epcoritamab in scenario analysis A.6.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence intervals; LBCL: large B cell lymphoma; NA: not applicable; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Crump *et al.* (SCHOLAR-1; 11 variables adjusted). These were evaluated based on AIC and BIC values, which are presented in Table 30. Based on AIC and BIC criteria, the exponential extrapolation demonstrates the best statistical fit.

Table 30: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis A.6)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis A.6.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; PFS: progression free survival.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 23. The corresponding survival estimates at several landmarks are presented in Table 31. In line with the reasoning outlined in Appendix D.2.3, the lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis A.6.

Figure 23: Long-term PFS extrapolations for epcoritamab (scenario analysis A.6)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; PFS: progression free survival.

Table 31: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis A.6)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model PFS for epcoritamab in scenario analysis A.6.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence intervals; LBCL: large B cell lymphoma; NA: not applicable; PFS: progression free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to Crump *et al.* (SCHOLAR-1; 11

variables adjusted), are presented in Table 32. Based on AIC and BIC, the exponential distribution shows the best statistical fit to the observed data. Given the small Neff, there were minimal differences observed for the goodness of fit criteria between the remaining extrapolations.

Table 32: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis A.6)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

The gamma extrapolation was selected to model TTD for epcoritamab in scenario analysis A.6.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 24. The corresponding TTD estimates at several landmarks are presented in Table 33. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years, with experts estimating a range of 0% to 25% of patients remaining on treatment at 10 years. As such, in line with feedback from UK clinical experts, the gamma extrapolation was selected to model TTD for epcoritamab in scenario analysis A.6.

Figure 24: Long-term TTD extrapolations for epcoritamab (scenario analysis A.6)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; TTD: time to treatment discontinuation.

Table 33: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis A.6)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The gamma extrapolation was selected to model TTD for epcoritamab in scenario analysis A.6.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; CI: confidence intervals; LBCL: large B cell lymphoma; NA: not applicable; TTD: time to treatment discontinuation.

D.2.5. Scenario analysis B – DLBCL, no prior CAR-T adjusted to ZUMA-1 (10 variables adjusted)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the DLBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the ZUMA-1 population (all available variables adjusted) is provided in Figure 25.

Figure 25: KM plot of PFS, OS and TTD used in scenario analysis B ([redacted] data cut-off)

Abbreviations: KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to ZUMA-1 (all available variables adjusted), and evaluated based on AIC and BIC values, which are presented in Table 34.

The generalised gamma distribution performs best in terms of AIC and BIC. However, the exponential, log-normal and Gompertz distributions could be considered viable on the basis of goodness of fit statistics due to minimal differences in the BIC values.

Table 34: Goodness of fit statistics for OS (AIC and BIC; scenario analysis B)

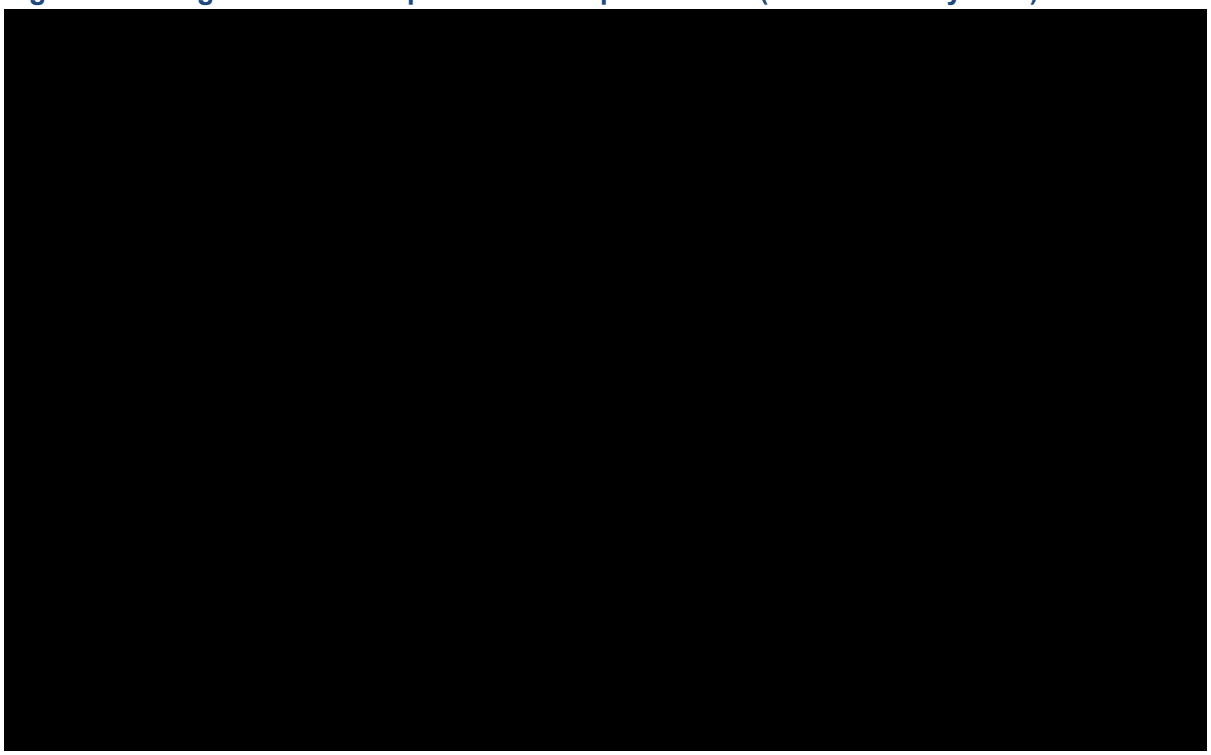
Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Distribution	AIC	BIC
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 26. The corresponding survival estimates at several landmarks are presented in Table 35. Based on feedback from UK clinical experts and to ensure the selected extrapolations reflect the results of the MAIC of epcoritamab versus axi-cel when considered alongside the axi-cel extrapolations, the Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.

Figure 26: Long-term OS extrapolations for epcoritamab (scenario analysis B)



Abbreviations: OS: overall survival.

Table 35: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis B)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.
Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the DLBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to ZUMA-1 (all available variables adjusted). These were evaluated based on AIC and BIC values, which are presented in Table 36. Based on AIC and BIC criteria, the generalised gamma extrapolation demonstrates the best statistical fit.

Table 36: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis B)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 27. The corresponding survival estimates at several landmarks are presented in Table 37. When considered in comparison with the axi-cel selected extrapolations and to ensure the extrapolations reflect the results of the MAIC of epcoritamab versus axi-cel, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.

Figure 27: Long-term PFS extrapolations for epcoritamab (scenario analysis B)

Abbreviations: PFS: progression-free survival.

Table 37: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis B)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the DLBCL, no prior CAR-T, CAR-t eligible population from EPCORE™ NHL-1 adjusted to ZUMA-1 (all available variables adjusted) are presented in Table 38. Based on AIC and BIC, the

log-normal and exponential distributions show the best statistical fit to the observed data, however there are minimal differences in the statistical fit of all extrapolations.

Table 38: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis B)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis B.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 28. The corresponding TTD estimates at several landmarks are presented in Table 21. During interviews with UK clinical experts, the experts stated that they would expect very few patients to remain on treatment with epcoritamab beyond 5 years. As such, in line with feedback from UK clinical experts, the exponential extrapolation was selected to model TTD for epcoritamab in updated base case analysis B, with the gamma extrapolation explored in a scenario analysis.

Figure 28: Long-term TTD extrapolations for epcoritamab (scenario analysis B)

Abbreviations: TTD: time to treatment discontinuation.

Table 39: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis B)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis B.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

D.2.6. Scenario analysis B.1 – LBCL, no prior CAR-T adjusted to ZUMA-1 (11 variables adjusted)

Epcoritamab efficacy

A KM plot of PFS, OS and TTD for the LBCL, no prior CAR-T EPCORE™ NHL-1 population adjusted to the ZUMA-1 population (all available variables adjusted) is provided in Figure 29.

Figure 29: KM plot of PFS, OS and TTD used in scenario analysis B.1 (data cut-off)

Abbreviations: KM: Kaplan–Meier; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Overall survival: extrapolation selection

The same seven parametric distributions explored in the original submission were also fitted to the OS KM data of the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to ZUMA-1 (all available variables adjusted), and evaluated based on AIC and BIC values, which are presented in Table 40.

The generalised gamma exponential and log-normal distribution performs best in terms of AIC and BIC. However, all distributions could be considered viable on the basis of goodness of fit statistics due to minimal differences in the AIC/BIC values.

Table 40: Goodness of fit statistics for OS (AIC and BIC; scenario analysis B.1)

Distribution	AIC	BIC
Exponential		
Log-normal		
Gompertz		
Log-logistic		
Weibull		
Gamma		
Generalised gamma		

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 30. The corresponding survival estimates at several landmarks are presented in Table 41. As outlined in Appendix D.2.5, based on feedback from UK clinical experts and to ensure the selected extrapolations reflect the results of the MAIC of epcoritamab versus axi-cel, the Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.1.

Figure 30: Long-term OS extrapolations for epcoritamab (scenario analysis B.1)

Abbreviations: OS: overall survival.

Table 41: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model OS for epcoritamab in scenario analysis B.1.

Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival

Seven parametric distributions were fitted to the PFS KM data of the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to ZUMA-1 (all available variables adjusted). These were evaluated based on AIC and BIC values, which are presented in Table 42. Based on AIC and BIC criteria, the generalised gamma and exponential extrapolations demonstrate the best statistical fit.

Table 42: Goodness of fit statistics for PFS (AIC and BIC; scenario analysis B.1)

Distribution	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for PFS, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 31. The corresponding survival estimates at several landmarks are presented in Table 43. As outlined in Appendix D.2.5, when considered in comparison with the axi-cel selected extrapolations and to ensure the extrapolations reflect the results of the MAIC of epcoritamab versus axi-cel, the Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.

Figure 31: Long-term PFS extrapolations for epcoritamab (scenario analysis B.1)

Abbreviations: PFS: progression-free survival.

Table 43: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The Gompertz extrapolation was selected to model PFS for epcoritamab in scenario analysis B.1.
Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The AIC and BIC values based on the seven parametric distributions fitted to the TTD KM data from the LBCL, no prior CAR-T population from EPCORE™ NHL-1 trial adjusted to ZUMA-1 (all available variables adjusted) are presented in Table 44. Based on AIC and BIC, the exponential

distribution shows the best statistical fit to the observed data, however there are minimal differences in the statistical fit of all extrapolations in terms of the AIC.

Table 44: Goodness of fit statistics for TTD (AIC and BIC; scenario analysis B.1)

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis B.1.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

The long-term extrapolations for TTD, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 32. The corresponding TTD estimates at several landmarks are presented in Table 45. In line with the justification outlined in Appendix D.2.5, the exponential extrapolation was selected to model TTD for epcoritamab in scenario analysis B.1.

Figure 32: Long-term TTD extrapolations for epcoritamab (scenario analysis B.1)

Abbreviations: TTD: time to treatment discontinuation.

Table 45: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (scenario analysis B.1)

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The exponential extrapolation was selected to model TTD for epcoritamab in the scenario analysis B.1.
Abbreviations: CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

D.3 Comparators (proportional hazards approach)

An overview of the assessment of the PH assumption, and the HRs and CIs that can be applied to the epcoritamab curves to derive the time-to-event outcomes for the comparators arms in the cost-effectiveness model are provided in the following section for all additional scenario analyses conducted.

D.3.1. Scenario analysis A.1 – DLBCL, no prior CAR-T adjusted to Sehn *et al*. (10 variables)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus Pola + BR are presented in Figure 33 and Figure 34, respectively. The log-cumulative hazard plot shows crossing of the curves [redacted] ([redacted] on the natural log scale). They then run roughly parallel from [redacted] ([redacted] on the natural log scale) before the cumulative hazards of epcoritamab start to [redacted] towards Pola + BR. In the Schoenfeld residual curve, a pattern over time cannot be observed, suggesting the covariate is time independent and so the proportional hazard assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p-value >0.05) indicating that the proportional hazard assumption cannot be rejected. Despite this, there is some evidence that the proportional hazard assumption is violated.

Figure 33: Log-cumulative hazard curve – OS (epcoritamab versus Pola +BR)

Abbreviations: OS: overall survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 34: Schoenfeld residual curve – OS (epcoritamab versus Pola +BR)

Abbreviations: overall survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

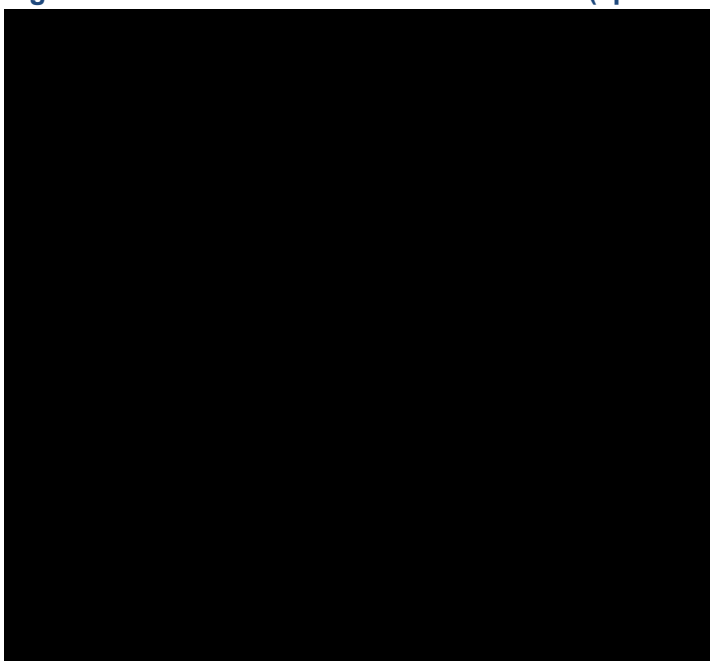
Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus Pola + BR are presented in Figure 35 and Figure 36. The log-cumulative hazard plot shows that both treatment arms cross multiple times [redacted]. This suggests potential non-proportionality of the hazard curves for PFS. The Schoenfeld residual curves do not show a pattern overtime, which suggests the covariate is time independent. Additionally, the Grambsch and Therneau test of PFS had a p-> 0.05, which combined with the crossing of the log-cumulative hazard curves, indicated the proportional hazards assumption can be rejected.

Figure 35: Log-cumulative hazard curve – PFS (epcoritamab versus Pola +BR)

Abbreviations: PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Figure 36: Schoenfeld residual curve – PFS (epcoritamab versus Pola +BR)



Abbreviations: PFS: progression-free survival; Pola +BR: Polatuzumab vedotin with rituximab and bendamustine.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the Pola + BR arm in the cost-effectiveness model is presented in Table 46.

Table 46: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (scenario analysis A.1)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	Sehn *et al.* 3L+

[a] As Pola + BR is administered for a fixed number of doses of cycles and there is a lack of published data for ToT, ToT for Pola + BR is assumed equal to PFS, based on feedback from UK clinical experts.
Abbreviations: OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; HR: hazard ratio.

D.3.2. Scenario analysis A.5 – DLBCL, no prior CAR-T adjusted to Northend *et al.* (13 variables adjusted)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus Northend *et al*. population are presented in Figure 37 and Figure 38, respectively. The log-cumulative hazard plot shows crossing of both treatment arms cross near [redacted], which then remains parallel, suggesting potential non-proportionality of the hazard curves for OS based on the log-cumulative hazard curves. In the Schoenfeld residual curve, a pattern over time can be observed, suggesting the covariate is not time independent. Hence, proportional hazards may be violated. This is consistent with the Grambsch and Therneau test of OS ($p < 0.05$), which indicated that the proportional hazards assumption can be rejected. As such, there is some evidence proportional hazards assumption is violated.

Figure 37: Log-cumulative hazard curve – OS (epcoritamab versus the Northend *et al*. population)

Abbreviations: OS: overall survival.

Figure 38: Schoenfeld residual curve – OS (epcoritamab versus the Northend *et al*. population)

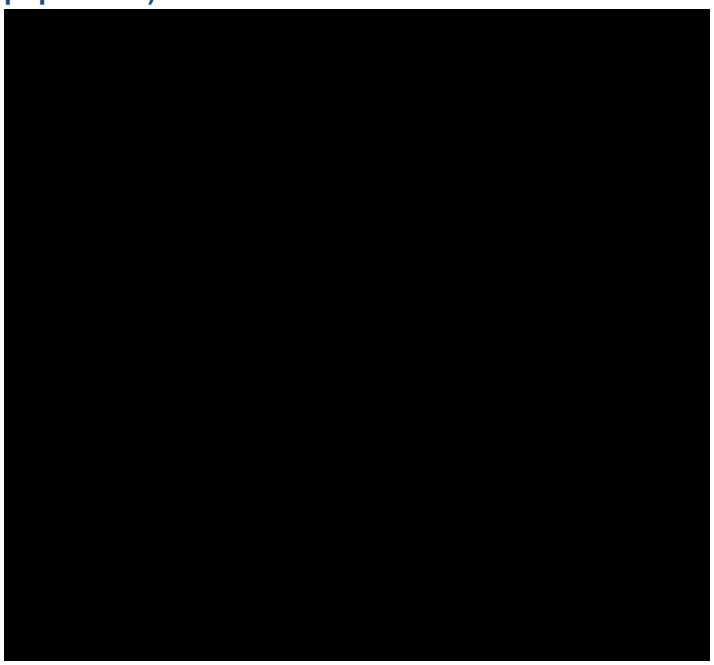
Abbreviations: OS: overall survival.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus Northend *et al*. population are presented in Figure 39 and Figure 40, respectively. The log-cumulative hazard plot shows that both treatment arms cross multiple times throughout [redacted], suggesting non-proportionality of the hazard curves for PFS. The Schoenfeld residual curve does not show a pattern over time, which suggests the covariate is time

independent. Hence, proportional hazards may not be violated. This is not consistent with the Grambsch and Therneau test of PFS (p>0.05), which indicates that the proportional hazards assumption can be seen to be violated.

Figure 39: Log-cumulative hazard curve – PFS (epcoritamab versus the Northend *et al*. population)



Abbreviations: PFS: progression-free survival.

Figure 40: Schoenfeld residual curve – PFS (epcoritamab versus the Northend *et al*. population)

Abbreviations: PFS: progression-free survival.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the Northend *et al*. population arm in the cost-effectiveness model is presented in Table 47.

Table 47: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (scenario analysis A.5)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	Northend *et al*.+

[a] As Pola + BR is administered for a fixed number of doses of cycles and there is a lack of published data for ToT, ToT for Pola + BR is assumed equal to PFS, based on feedback from UK clinical experts.
Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; OS: overall survival; PFS: progression-free survival; Pola + BR: polatuzumab vedotin plus rituximab with or without bendamustine; HR: hazard ratio.

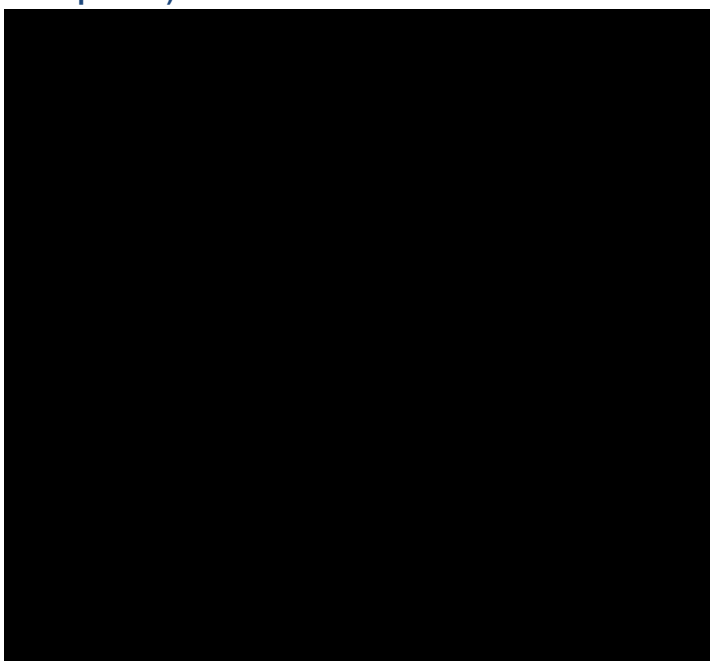
D.3.3. Scenario analysis A.6 – LBCL, no prior CAR-T adjusted to Crump *et al.* (9 variables adjusted)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab adjusted to the CIT arm of Crump *et al.* are presented in Figure 41 and Figure 42. The log-cumulative hazard plot shows crossing of both treatment arms near the start of the observation period, then remaining parallel throughout. This suggests potential non-proportionality of the hazard curves for OS based on the log-cumulative hazard curves. In the Schoenfeld residual curve, no pattern over time can-be observed, suggesting the covariate is time independent. Hence, the proportional hazard assumption may be violated. However this is not consistent with the Grambsch and Therneau test of OS as the p-value <0.05 indicating that the proportional hazards assumption could not be rejected. Due to the small sample size, and crossing of the smoothed hazard curve, it is likely the proportional hazards assumption is violated.

Figure 41: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT, based on Crump et al.)



Abbreviations: CAR-T: chimeric antigen receptor T-cell; Epcoritam: epcoritamab; LBCL: large B cell lymphoma; OS: overall survival.

Figure 42: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT, based on Crump et al.)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; OS: overall survival.

Progression-free survival

PFS for CIT from Crump *et al.* (SCHOLAR-1) was not available and therefore a comparison of proportional hazards for PFS was not conducted.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the CIT arm (Crump *et al.* [SCHOLAR-1]) in the cost-effectiveness model is presented in Table 48.

Table 48: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (scenario analysis A.6)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	NA[a]
ToT	NA[b]
Source of comparator efficacy	Crump *et al.* (SCHOLAR-1) CIT arm

[a] PFS for CIT from Crump *et al.* (SCHOLAR-1) was not available and therefore a comparison for PFS was not conducted. [a] As R-based CIT is administered for a fixed number of doses of cycles and there is a lack of published data for ToT, ToT for R-based CIT is assumed equal to PFS, based on feedback from UK clinical experts.
Abbreviations: CI: confidence interval; CIT: chemoimmunotherapy; LBCL: large B-cell lymphoma; N/A: not applicable; OS: overall survival; PFS: progression-free survival; HR: hazard ratio.

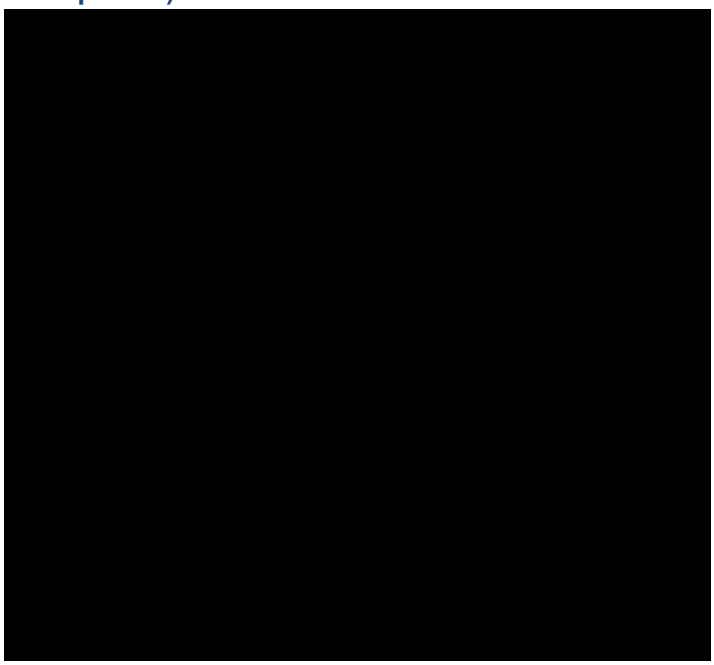
D.3.4. Scenario analysis A.6 – LBCL, no prior CAR-T adjusted to Crump *et al.* (11 variables adjusted)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab fully adjusted to Crump et al. are presented in Figure 43 and Figure 44. The log-cumulative hazard plot of both treatment arms cross near the start of the observation period, then remain parallel throughout. This suggests potential non-proportionality of the hazard curves for OS based on the log-cumulative hazard curves. In the Schoenfeld residual curve, no pattern over time can-be observed, although the value for beta remains very large throughout, suggesting the covariate is time independent. Hence, the proportional hazard assumption may be violated, which is consistent with the Grambsch and Therneau test of OS as the p-value <0.05 indicating that the proportional hazards assumption could be rejected. Based on the evidence it is likely that the proportional hazards assumption may have been violated.

Figure 43: Log-cumulative hazard curve – OS (epcoritamab versus R-based CIT, based on Crump et al.)



Abbreviations: CAR-T: chimeric antigen receptor T-cell; Epcoritam: epcoritamab; LBCL: large B cell lymphoma; OS: overall survival.

Figure 44: Schoenfeld residual curve – OS (epcoritamab versus R-based CIT, based on Crump et al.)

Abbreviations: CAR-T: chimeric antigen receptor T-cell; LBCL: large B cell lymphoma; OS: overall survival.

Progression-free survival

PFS for CIT from Crump *et al.* (SCHOLAR-1) was not available and therefore a comparison of proportional hazards for PFS was not conducted.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the CIT arm (Crump *et al.* [SCHOLAR-1]) in the cost-effectiveness model is presented in Table 49.

Table 49: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (scenario analysis A.6)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	NA[a]
ToT	NA[b]
Source of comparator efficacy	Crump *et al.* (SCHOLAR-1) CIT arm

[a] PFS for CIT from Crump *et al.* (SCHOLAR-1) was not available and therefore a comparison for PFS was not conducted. [a] As R-based CIT is administered for a fixed number of doses of cycles and there is a lack of published data for ToT, ToT for R-based CIT is assumed equal to PFS, based on feedback from UK clinical experts.
Abbreviations: CI: confidence interval; CIT: chemoimmunotherapy; LBCL: large B-cell lymphoma; N/A: not applicable; OS: overall survival; PFS: progression-free survival; HR: hazard ratio.

D.3.5. Scenario analysis B – DLBCL, no prior CAR-T adjusted to ZUMA-1 (10 variables adjusted)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus axi-cel are presented in Figure 45 and Figure 46, respectively. The log-cumulative hazard plot shows crossing of both treatment arms several times from the middle to the end of the observation period, suggesting potential non-proportionality of the hazard curves for OS. In the Schoenfeld residual curve, a pattern over time can be observed, suggesting the covariate is not time independent. However, this is not consistent with the Grambsch and Therneau test of OS (p >0.05) indicating that the proportional hazards assumption cannot be rejected. As such, there is some evidence to suggest the proportional hazards assumption is violated.

Figure 45: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Figure 46: Schoenfeld residual curve – OS (epcoritamab versus axi-cel)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus axi-cel are presented in Figure 47 and Figure 48, respectively. The log-cumulative hazard plot shows that both treatment arms cross multiple times throughout the trial, suggesting non-proportionality of the hazard curves for PFS. The Schoenfeld residual curve shows a pattern over time, which suggests the covariate is time independent. This is also consistent with the Grambsch and Therneau test of PFS ($p>0.05$), however, combined with the cross of the log-cumulative hazard curves, this suggests the proportional hazards assumption can be violated.

Figure 47: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Figure 48: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the Pola + BR arm in the cost-effectiveness model is presented in Table 50.

Table 50: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (scenario analysis B)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	ZUMA-1[10]

[a] ToT is not applicable for axi-cel as it is administered as a single-dose.
Abbreviations: axi-cel: axicabtagene ciloleucel; CI: confidence interval; PFS: progression-free survival; HR: hazard ratio.

D.3.6. Scenario analysis B.1 – LBCL, no prior CAR-T adjusted to ZUMA-1 (11 variables adjusted)

Assessment of the PH assumption

Overall survival

The log-cumulative hazard curve and Schoenfeld residual curve for OS for epcoritamab versus Pola + BR are presented in Figure 49 and Figure 50,respectively. The log-cumulative hazard plot shows crossing of both treatment arms several times [redacted], suggesting non-proportionality of the hazard curves for OS. In the Schoenfeld residual curve, a pattern over time can be observed, suggesting the covariate is not time independent. Hence, proportional hazard assumption may be violated. However, this is not consistent with the Grambsch and Therneau test of OS (p >0.05), which indicates that the proportional hazards assumption cannot be rejected. Despite this, based what is presented in the log-cumulative hazard curve and Schoenfeld residual curve, there is some evidence that proportional hazards assumption is violated.

Figure 49: Log-cumulative hazard curve – OS (epcoritamab versus axi-cel)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Figure 50: Schoenfeld residual curve – OS (epcoritamab versus axi-cel)

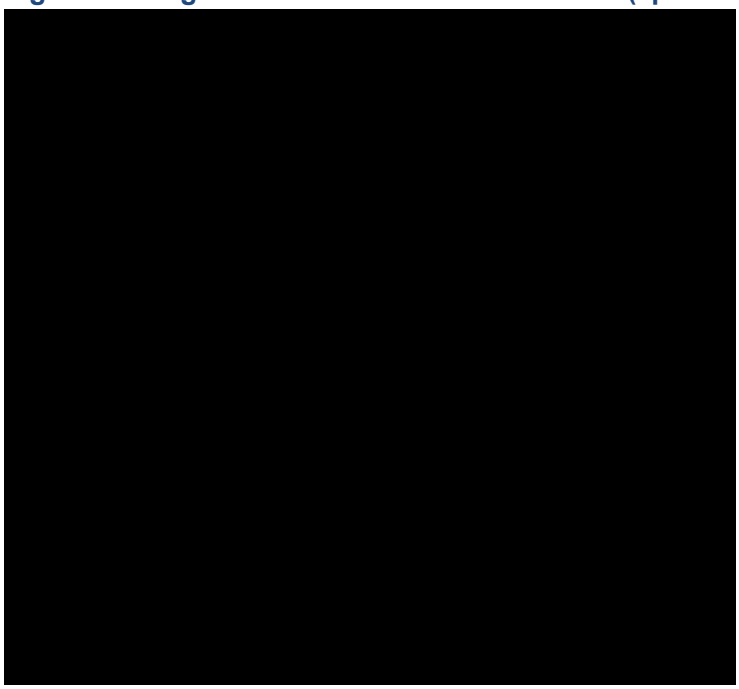
Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Progression-free survival

The log-cumulative hazard curve and Schoenfeld residual curve for PFS for epcoritamab versus Pola + BR are presented in Figure 51 and Figure 52, respectively. The log-cumulative hazard plot shows that both treatment arms cross multiple times , suggesting potential non-proportionality of the hazard curves for PFS.

The Schoenfeld residual curve shows a pattern over time, which suggests the covariate is time independent. Additionally, the Grambsch and Therneau test of PFS p-value was >0.05. Due to the crossing of the log-cumulative hazard curves and the Schoenfeld residuals, there is evidence that the PHA can be seen to be violated.

Figure 51: Log-cumulative hazard curve – PFS (epcoritamab versus axi-cel)



Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Figure 52: Schoenfeld residual curve – PFS (epcoritamab versus axi-cel)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival.

Comparator efficacy

A summary of the HRs applied to the epcoritamab arm to derive the time-to-event outcomes for the Pola + BR arm in the cost-effectiveness model is presented in Table 51.

Table 51: Summary of HRs applied to the epcoritamab arm to derive the time-to-event outcomes for comparator arms in the cost-effectiveness model (scenario analysis B.1)

Outcome	Hazard ratio (95% CI)
OS	[redacted]
PFS	[redacted]
ToT	N/A[a]
Source of comparator efficacy	ZUMA-1[10]

[a] ToT is not applicable for axi-cel as it is administered as a single-dose.
Abbreviations: axi-cel: axicabtagene ciloleucel; CI: confidence interval; PFS: progression-free survival; HR: hazard ratio.

D.4 Comparators (independent modelling approach)

In line with the approach taken during Technical Engagement, AbbVie have conducted additional analyses for R-based CIT based on Crump et al. to allow R-based CIT to be modelled via independent extrapolation of the survival data.

The time-to-event analyses for R-based CIT based on Crump *et al.* are provided in the following section. R-based CIT is independently modelled based on the below time-to-event analyses in scenario analyses A.6.

D.4.1. R-based CIT based on Crump *et al.*

Overview

The results presented in this section are for the R-based CIT comparator based on individual patient level data from Crump *et al*. (2017, SCHOLAR-1). The KM curve of the OS endpoint for these data are presented in Figure 53. PFS for CIT from Crump *et al.* (SCHOLAR-1) was not available and therefore R-based CIT analyses based on Crump *et al.* were not conducted for PFS.

Figure 53: KM plot of OS for R-based CIT based on Crump *et al.* (SCHOLAR-1) IPD data

Abbreviations: CIT: chemoimmunotherapy; IPD: individual patient data; KM: Kaplan–Meier; OS: overall survival.

Overall survival

Extrapolation selection

The seven parametric distributions explored in the original submission were also fitted to the OS KM data for CIT from Crump *et al.* (SCHOLAR-1), and evaluated based on AIC and BIC values, which are presented in Table 52. The generalised gamma distribution performs best in terms of AIC and BIC. The rest of the distributions have a higher AIC and BIC values as compared to the generalised gamma distribution

Table 52: Goodness of fit statistics for OS (AIC and BIC; R-based CIT based on Crump *et al.* [SCHOLAR-1] IPD data)

Distribution	AIC	BIC
Generalized gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for R-based CIT based on Crump *et al*. (SCHOLAR-1). The Gompertz extrapolation was explored but did not converge.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CIT: chemoimmunotherapy; IPD: individual patient data; OS: overall survival

The long-term extrapolations for OS for R-based CIT, alongside the KM data from EPCORE™ NHL-1, are presented in Figure 54. The corresponding survival estimates at several landmarks

are presented in Table 53. UK clinical experts estimated that approximately 5% to 10% of patients receiving R-based CIT would be alive at five years. However, data from Crump *et al.* shows that 15% of patients are alive at five years, with Neelapu *et al.* showing 20% of patients alive at two years. Based on published data combined with UK clinical expert feedback, the lognormal extrapolation was selected to model OS for R-based CIT.

Figure 54: Long-term OS extrapolations for R-based CIT based on Crump *et al.* (SCHOLAR-1) IPD data

Abbreviations: CIT: chemoimmunotherapy; IPD: individual patient data; OS: overall survival.

Table 53: Predicted and observed OS for R-based CIT based on Crump *et al.* (SCHOLAR-1) IPD data at several landmarks for each extrapolation

Distribution	Month					
	12	24	48	60	120	180
Observed (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The lognormal extrapolation was selected to model OS for R-based CIT based on Crump *et al.* (SCHOLAR-1).
Abbreviations: CI: confidence intervals; IPD: individual patient data; NR: not reached; OS: overall survival.

Appendix E Mixture-cure models

E.1 Epcoritamab versus R-based CIT (based on SCHOLAR-1, Neelapu *et al.*)

Overall survival: extrapolation selection

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 66. Based on AIC and BIC criteria, the exponential/cure extrapolation demonstrates the best statistical fit. However, there is minimal difference between the extrapolations.

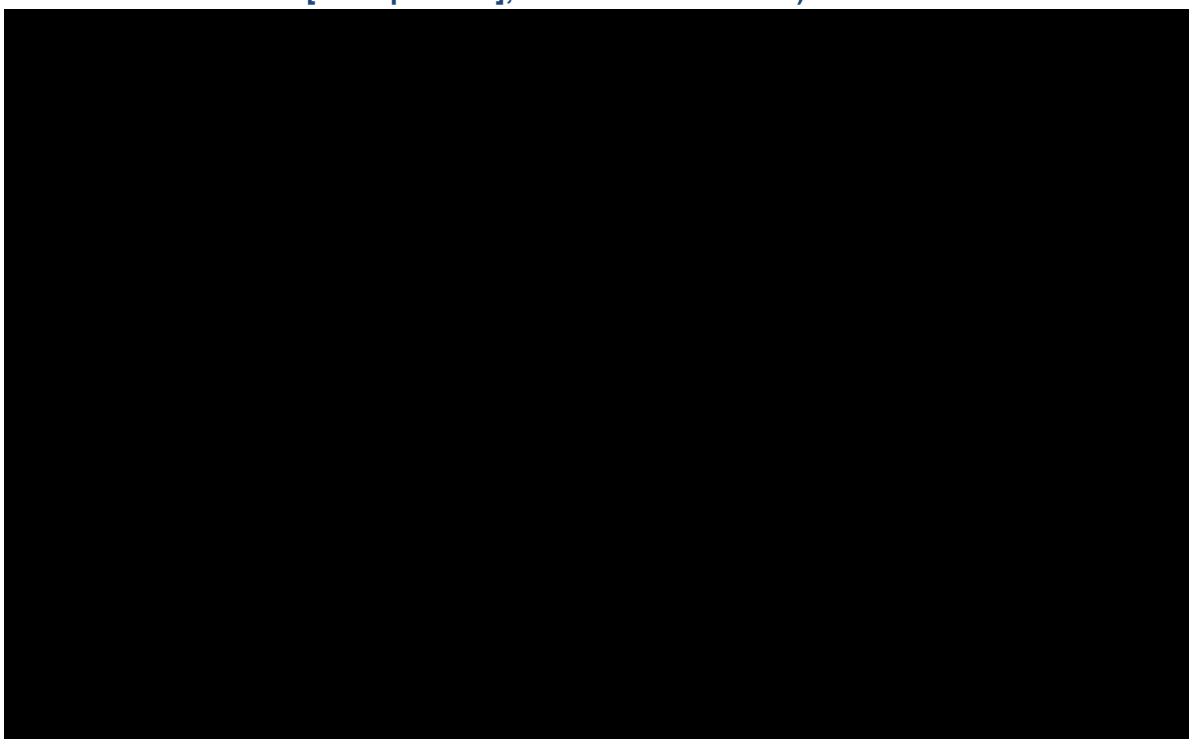
Table 54: Goodness of fit statistics for OS (AIC and BIC; Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models])

Distribution	AIC	BIC
Exponential/cure	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; R-based CIT: rituximab-based chemoimmunotherapy.

The long-term extrapolations for OS applied to the KM data for EPCORE™ NHL-1 data adjusted to SCHOLAR-1 are presented in Figure 55. The corresponding survival estimates at several landmarks are presented in Table 55.

Figure 55: Long-term OS extrapolations for epcoritamab (DLBCL, adjusted to R-based CIT based on SCHOLAR-1 [Neelapu et al.]; mixture cure models)



Abbreviations: OS: overall survival; R-based CIT: rituximab-based chemoimmunotherapy.

Table 55: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; OS: overall survival; R-based CIT: rituximab-based chemoimmunotherapy.

Progression-free survival

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 68. Based on AIC and BIC criteria, the lognormal/cure extrapolation demonstrates the best statistical fit.

Table 56: Goodness of fit statistics for PFS (AIC and BIC; Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)

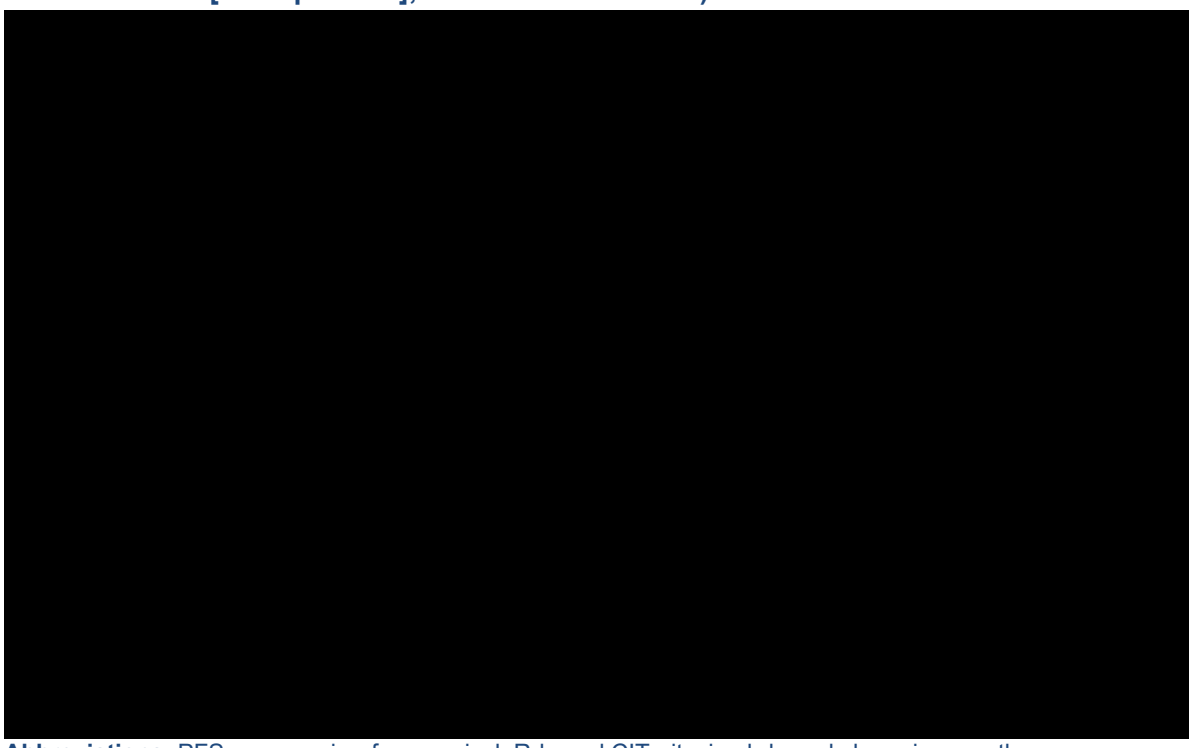
Distribution	AIC	BIC
Log-normal/cure	[redacted]	[redacted]

Distribution	AIC	BIC
Exponential/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

The long-term extrapolations for PFS, alongside the KM data for EPCORE™ NHL-1 data adjusted to SCHOLAR-1, are presented in Figure 56. The corresponding survival estimates at several landmarks are presented in Table 69.

Figure 56: Long-term PFS extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)



Abbreviations: PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

Table 57: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; PFS: progression-free survival; R-based CIT: rituximab-based chemoimmunotherapy.

TTD

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 70. Based on AIC and BIC criteria, the lognormal/cure extrapolation demonstrates the best statistical fit. However, there is minimal difference between all extrapolations.

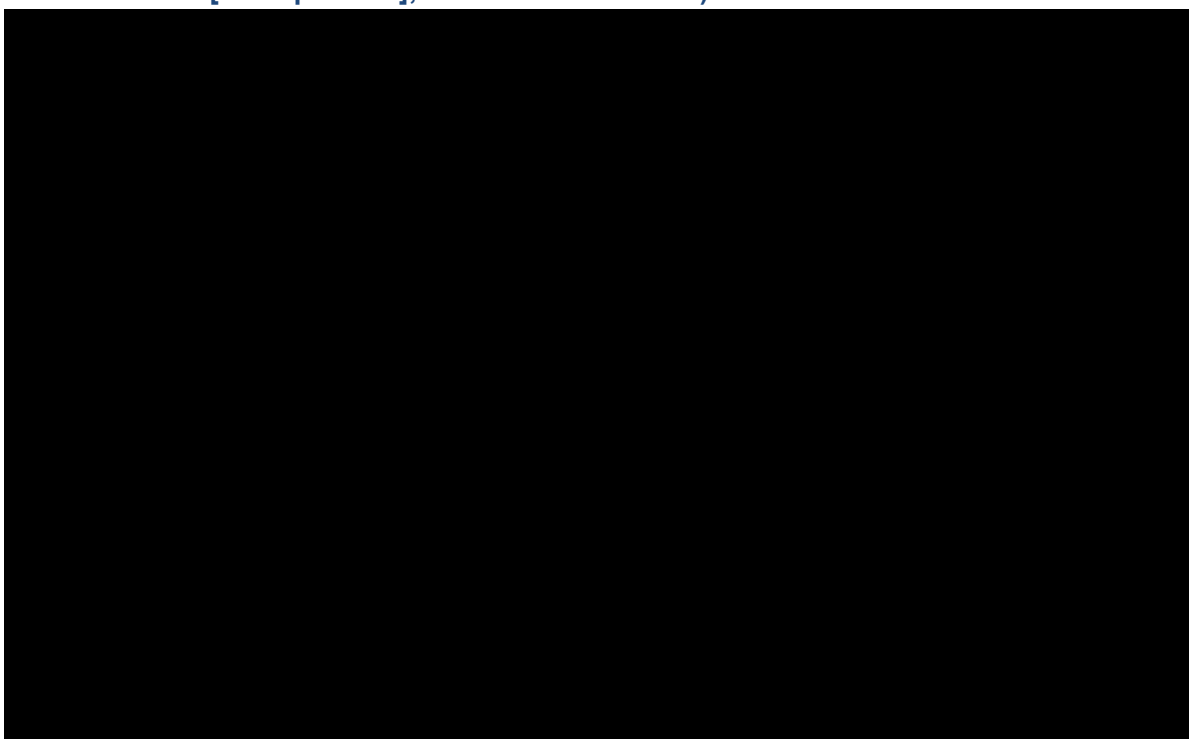
Table 58: Goodness of fit statistics for TTD (Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)

Distribution	AIC	BIC
Log-normal/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Exponential/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; R-based CIT: rituximab-based chemoimmunotherapy; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data for EPCORE™ NHL-1 data adjusted to SCHOLAR-1, are presented in Figure 57. The corresponding TTD estimates at several landmarks are presented in Table 71.

Figure 57: Long-term TTD extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)



Abbreviations: R-based CIT: rituximab-based chemoimmunotherapy; TTD: time to treatment discontinuation.

Table 59: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to SCHOLAR-1 [Neelapu et al.]; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; R-based CIT: rituximab-based chemoimmunotherapy; TTD: time to treatment discontinuation.

E.2 Pola + BR based on Sehn *et al.* 3L+

Overall survival: extrapolation selection

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 60. Based on AIC and BIC criteria, the exponential/cure extrapolation demonstrates the best statistical fit. However, there is minimal difference between all extrapolations.

Table 60: Goodness of fit statistics for OS (AIC and BIC; Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Distribution	AIC	BIC
Exponential/cure	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

The long-term extrapolations for OS, alongside the KM data for EPCORE™ NHL-1 data adjusted to Sehn *et al.* 3L+, are presented in Figure 58. The corresponding survival estimates at several landmarks are presented in Table 61.

Figure 58: Long-term OS extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Abbreviations: OS: overall survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

Table 61: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Month					
	12	24	48	60	120	180
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; NA: not applicable; OS: overall survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

Progression-free survival

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 62. Based on AIC and BIC criteria, the lognormal/cure extrapolation demonstrates the best statistical fit. However, loglogistic also demonstrates a reasonable fit.

Table 62: Goodness of fit statistics for PFS (AIC and BIC; Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Distribution	AIC	BIC
Log-normal/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Exponential/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

The long-term extrapolations for PFS, alongside the KM data for EPCORE™ NHL-1 data adjusted to Sehn et al. 3L+, are presented in Figure 59. The corresponding survival estimates at several landmarks are presented in Table 63.

Figure 59: Long-term PFS extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Abbreviations: PFS: progression-free survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

Table 63: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; NA: not applicable; PFS: progression-free survival; Pola + BR: polatuzumab vedotin with rituximab and bendamustine.

TTD

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 64. Based on AIC and BIC criteria, the lognormal/cure extrapolation demonstrates the best statistical fit. However, log-logistic/cure also demonstrates a reasonable fit.

Table 64: Goodness of fit statistics for TTD (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Distribution	AIC	BIC
Log-normal/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]
Exponential/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data for EPCORE™ NHL-1 data adjusted to Sehn *et al.* 3L+, are presented in Figure 60. The corresponding TTD estimates at several landmarks are presented in Table 65.

Figure 60: Long-term TTD extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Abbreviations: Pola + BR: polatuzumab vedotin with rituximab and bendamustine; TTD: time to treatment discontinuation.

Table 65: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to Sehn et al 3L+; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; NA: not applicable; Pola + BR: polatuzumab vedotin with rituximab and bendamustine; TTD: time to treatment discontinuation.

E.3 Axi-cel based on ZUMA-1

Overall survival: extrapolation selection

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 66. Based on AIC and BIC criteria, the all extrapolations demonstrate a reasonable statistical fit.

Table 66: Goodness of fit statistics for OS (AIC and BIC; Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Distribution	AIC	BIC
Exponential/cure	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; axi-cel: axicabtagene ciloleucel; BIC: Bayesian information criterion; OS: overall survival.

The long-term extrapolations for OS, alongside the KM data for EPCORE™ NHL-1 data adjusted to ZUMA-1, are presented in Figure 61. The corresponding survival estimates at several landmarks are presented in Table 67.

Figure 61: Long-term OS extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Abbreviations: OS: overall survival.

Table 67: Predicted and observed OS for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CI: confidence intervals; NA: not applicable; OS: overall survival.

Progression-free survival

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 68. Based on AIC and BIC criteria, the log-normal/cure extrapolation demonstrates the best statistical fit.

Table 68: Goodness of fit statistics for PFS (AIC and BIC; Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Distribution	AIC	BIC
Log-normal/cure	[redacted]	[redacted]
Exponential/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]

Distribution	AIC	BIC
Gamma/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; axi-cel: axicabtagene ciloleucel; BIC: Bayesian information criterion; PFS: progression-free survival.

The long-term extrapolations for PFS, alongside the KM data for EPCORE™ NHL-1 data adjusted to ZUMA-1, are presented in Figure 62. The corresponding survival estimates at several landmarks are presented in Table 69.

Figure 62: Long-term PFS extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Abbreviations: axi-cel: axicabtagene ciloleucel; PFS: progression-free survival.

Table 69: Predicted and observed PFS for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CI: confidence intervals; NA: not applicable; PFS: progression-free survival.

TTD

The seven parametric distributions were evaluated based on AIC and BIC values, which are presented in Table 70. Based on AIC and BIC criteria, all extrapolations demonstrate a reasonable statistical fit with the lognormal/cure extrapolation demonstrating the best fit.

Table 70: Goodness of fit statistics for TTD (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Distribution	AIC	BIC
Log-normal/cure	[redacted]	[redacted]
Exponential/cure	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; axi-cel: axicabtagene ciloleucel; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

The long-term extrapolations for TTD, alongside the KM data for EPCORE™ NHL-1 data adjusted to ZUMA-1, are presented in Figure 63. The corresponding TTD estimates at several landmarks are presented in Table 71.

Figure 63: Long-term TTD extrapolations for epcoritamab (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Abbreviations: axi-cel: axicabtagene ciloleucel; TTD: time to treatment discontinuation.

Table 71: Predicted and observed TTD for epcoritamab at several landmarks for each extrapolation (Epcoritamab DLBCL, adjusted to ZUMA-1; mixture cure models)

Distribution	Month					
	12	24	48	60	120	180
Exponential/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal/cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axi-cel: axicabtagene ciloleucel; CI: confidence intervals; NA: not applicable; TTD: time to treatment discontinuation.

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Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Blood Cancer UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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1	Blood Cancer UK are disappointed by the draft negative decision for the use of Epcoritamab in the relapsed/refractory diffuse large B-cell lymphoma population. We reiterate the following key messages from our initial submission and would ask these be reconsidered before the final decision is reached: • A significant proportion of patients will fail to respond to first two lines of therapy or will relapse after an initial response. These patients with highly refractory / relapsed disease live with the challenges associated with the disease itself combined with treatment toxicities, as well as the psychological impacts of ineffective and harsh treatments. This has significant effects on the quality of life of both patients and carers. • Current treatment options do not offer everyone with refractory / relapsed diffuse large B-cell lymphoma a cure or produce durable remissions for everyone. This highlights a significant unmet need for effective therapies. • A treatment's ability to improve a patient's quality and length of life is hugely important to them and their loved ones. • Epcoritamab is relatively easy to administer, well tolerated, is more readily available than options like CAR-T therapy and has the potential to provide durable benefit. • Epcoritamab offers a good option for patients who have exhausted other options. Even if not curative, additional life years gained through this treatment is hugely valuable for patients and their loved ones. This has been emphasised directly by them.
2	Whilst we acknowledge the difficulties in determining a reliable cost effectiveness estimate for Epcoritamab, we would like to remind and highlight that patients should continue to remain to be at the heart of decision making when deciding on new therapies.
3	There is an apparent heavy burden that relapsed/refractory diffuse large B-cell lymphoma patients and their carers bear in both symptom management and toxicities from current standard of care. Both the disease itself and its treatments can significantly affect quality of life with patients having varying treatment experiences. Although patients are grateful for the available options, existing treatments can be hard to tolerate, bringing a range of side effects and late effects. There is, therefore, a need for kinder treatments such as Epcoritamab.
4	At the third line and beyond, there is no widely accessible standard of care. This means a significant number of patients are waiting for and would benefit from options like Epcoritamab. To deny them a treatment with proven potential to produce durable remissions can be very difficult for patients and their loved ones to comprehend. We are concerned the significance of this is not being considered enough. Furthermore, when comparatively reviewing outcomes of existing therapies, we request for appropriate consideration to account for the nuances seen in controlled clinical trials

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	versus in clinical practice. This is because the true value of therapies may differ between the two.
5	The tolerability of Epcoritamab, its potential clinical benefit coupled with its superior subcutaneous administration are all valuable benefits to both patients and the NHS. The method of administration is an important consideration for patients as it affects both convenience of receiving treatment but also the additional disruptions that would impact their day-to-day lives.
6	It is important not to lose sight of the potential of Epcoritamab in changing the course of both individual and a collective group of patients' lives. Patients this far down the treatment line are heavily anxious with substantial physical and mental burdens and are desperate for hope in the form of new, innovative treatments. At the third line and beyond, this hope is restricted by their eligibility (and preference) for intensive therapies. This is further narrowed when considering access barriers to existing comparator treatments, such as CAR-T, which mean the real-world numbers of people for whom CAR-T is a real option is even smaller than the eligible population. The value of providing an innovative alternative treatment as an option is therefore immense and cannot be overlooked.
7	Epcoritamab offers heavily pretreated patients with very limited options a transformative choice. We therefore hope the issues can be addressed and an agreement can be reached with the company in a way that does not impede access to this treatment for patients who eagerly await new treatments.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	RCP-ACP-RCR

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The RCP-ACP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	Our experts are disappointed by NICE's decision not to recommend epcoritamab as a treatment option for patients with relapsed/refractory diffuse large B cell lymphoma after 2 prior treatment lines. It is a highly effective therapy for patients that have few other

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	treatment options and is easily deliverable in a day case setting. It would be an excellent treatment option for those patients that opt for treatment at their local centre and its subcutaneous method of administration makes it very attractive for some patients. Furthermore, our experts note that glofitamab has been recommended in the same indication, which has an identical response rate and similar adverse event profile according to the Phase 2 study data. It may become clear in the future that the real world data suggest that one bispecific is superior to the other, and our experts are concerned that if NICE does not approve epcoritamab as well as glofitamab, NHS patients could be denied access to the superior product. It is clinically implausible based on our experts' experience that epcoritamab will not have an advantage over R-chemo in this setting. Our experts would not expect patients having R-chemotherapy to survive long term in the third line and further setting. With regards to cross trial comparisons used in the MAIC, our experts believe it is important to consider the very heavily pretreated nature of patients in the GEN-01 study, including 40% of patients with prior CAR-T therapy. None of the other studies used for comparison will have had such a poor risk, heavily pretreated group. Furthermore, our experts note that the GEN-01 study was conducted in the COVID-19 era, which had a negative impact on all studies done at this time. Therefore, it is difficult to account for in cross trial comparisons.

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- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gilead Sciences Ltd

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	On page 15 (section 3.9), please remove the statement "They also advised that axicabtagene ciloleucel needs a period of bridging therapy before it is administered". This statement implies that bridging therapy is mandatory, whereas this is not the case. While bridging therapy is often given between the time of apheresis and CAR T-cell infusion to reduce disease bulk and reduce the risk of disease progression while the CAR T-cells are being manufactured, its use and composition is variable and not a requirement prior to

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	CAR T-cell therapy. According to a real-world study, approximately 11% of patients treated with CAR T-cell therapy in the UK between 2020-2022 received no bridging therapy or corticosteroids only (Boyle et al., BJ Haem, 2023).
2	This comment is in relation to the following statement on page 15 (section 3.9): "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 explanation supporting this statement in the document provides inadequate substantiation, and we believe this is not a reasonable interpretation of the clinical evidence and it cannot be reasonably assumed that the axicabtagene ciloleucel population in ZUMA-1 was likely to be healthier than the epcoritamab population in EPCORE NHL-1.Considering the baseline characteristics of patients in the two distinct pivotal clinical trials, it cannot be reasonably assumed that the axicabtagene ciloleucel population were healthier than the epcoritamab population. For example, in ZUMA-1, 85% (n=86/101) of patients who received axicabtagene ciloleucel had stage III or IV disease. In contrast, in EPCORE NHL-1, only 73% (n=102/139) of patients with DLBCL who were enrolled had stage III or IV disease. [Source: Yescarta (axicabtagene ciloleucel) GB SmPC, Tepkinly (epcoritamab) EMA SmPC].
3	On page 24 (section 3.18), the costs associated with axicabtagene ciloleucel treatment should be reviewed. Within the NICE Single Technology Appraisal TA895, NHS England explained that the tariff includes all costs of care from the decision for the person to have CAR T-cell therapy to 100 days after infusion, which may include bridging therapy. Due to this, any costs related to axicabtagene ciloleucel use should be reviewed to ensure that components are not included in multiple instances.
4	We agree with the EAG that the MAICs need to be fully adjusted rather than partially adjusted. With only a partial adjustment, the populations may not be comparable enough for a valid indirect comparison, rendering results unreliable and potentially misleading. Specifically, we believe that the number of prior lines of therapy is a highly important prognostic factor in DLBCL, and appropriate adjustments must be made for a valid comparison. Limitations of conclusions drawn from inadequately matched comparisons in the Company's base case analysis should be clearly highlighted throughout the document. Specifically, on page 28 (section 3.22), please include additional text to provide context regarding the limitations of the company's base case when presenting the results of their analysis compared to axicabtagene ciloleucel. For example, text from section 3.9 should be replicated here (i.e. "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"), along with a statement clarifying that several limitations were associated with the company's base case analysis.
5	We request that the EAG reconsiders the appropriateness of conducting separate analyses for people who cannot have or choose not to have autologous stem cell

Epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID4045]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments **5pm on Tuesday 21 November 2023**. Please submit via NICE Docs.

	transplant or CAR T therapy ('population A') and those who can have autologous stem cell transplant or CAR T therapy ('population B'). Given axicabtagene ciloleucel's positive NICE recommendation for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies, we question the rationale for splitting the population in two as proposed by the company. If this approach is deemed appropriate, we request that the methodology used to define each population is clearly defined in the document, and that NICE recommended criteria are used rather than clinical trial eligibility criteria. For example, patients with ECOG 2 may be considered candidates for CAR T in the UK, representing ~17% of CAR T patients treated from 2020-2022 (Boyle et al., BJ Haem, 2023). It would therefore be inappropriate to delineate between these two populations based on ECOG status.
6	Company is not considering the full evidence base vs axicabtagene ciloleucel, as it is only comparing vs ZUMA-1 without taking the robust body of real-world evidence into account. A recent UK study (Boyle et al., BJ Haem, 2023) has demonstrated strong real-world efficacy and safety of axicabtagene ciloleucel, which should be taken into consideration when conducting a comparison.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

NICE National Institute for Health and Care Excellence

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

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18/11/2023 Dr Wendy Osborne NICE epcoritamab clinical expert

I would be keen for NICE to consider the points below when making the final decision about approval for epcoritamb for patients with relapsed refractory DLBCL in a 3rd line and beyond setting.

1) **Comparison with Rituximab bendamustine polatuzumab (RBP)** – none of the patients in the RBP study had received prior CAR T because it wasn't available as a treatment option when this trial was performed. This is in comparison to 40% of patients having had prior CAR T in the EPCORE NHL 1 study. The patients receiving epcoritamab were significantly higher risk in view of not only the number of prior lines of therapy between the 2 studies (30% or patients had had only 1 prior line in the RBP study) but also the intensity and efficacy of those treatments. The historical era of the RBP study meant that less efficacious treatments were available). The patients who have been failed by more efficacious treatment such as CAR T will be of higher risk and therefore achieving a 39% complete response rate in these heavily pretreated patients in a more recent era when more effective treatment options were available compared to the historical rituximab bendamustine polatuzumab data is important. There was concern from the committee about indirect comparisons with these RBP data. The RBP study with patients who had fewer prior lines of treatments as well as less exposure to more effective treatments leads to bias against epcoritamab who had more patients who had been failed by more lines of more effective treatment.

2) **Comparison with Rituximab bendamustine polatuzumab -** this combination will now be very infrequently used for our patients with relapsed refractory large cell lymphoma and is clinically not a useful comparison.
   This is for two reasons, firstly patients have all now receive polatuzumab in a first line setting and we will therefore not want to reuse when a patient relapses.
   The 2nd reason is that we are keen to avoid the use of bendamustine now that we have T-cell engagers available. There are data that bendamustine causes T cell depletion for years. Bendamustine reduces efficacy of car T and now that 3rd line bispecific T-cell engaging therapy is available we will not be wanting to give bendamustine to patients. It may be possible that we consider RBP after they have been failed by CAR T and bispecifics ie 4th or 5th line and not had first line polatuzumab but this will be a very rare patient as polatuzumab first line is standard of care now. I am also not clear of the efficacy of RBP in 4th or 5th line as the study included a good risk group of patients with no prior CAR T and 30% 2nd line only. Clinically the statement made ("Usual treatment for DLBCL after 2 or more treatments is rituximab-based chemoimmunotherapy, polatuzumab vedotin with bendamustine plus rituximab (polatuzumab-BR)") is therefore now not clinically accurate. The increased data (Iacobi et al) about the toxicity of bendamustine on T cell has made us reluctant as lymphoma clinicians to use any bendamustine containing combination.

3) **Efficacy** – The effectiveness of epcoritamab is identical to glofitamab which has been NICE approved. There were 40% post CAR T patients in the EPCORE NHL 1 study compared to the glofitamab study which had 33%. It is possible that the epcore patients are a higher risk patient group and it may be more effective, but we will need to collect real world data. In the past it is been helpful that 2 similar technologies were approved for example Axi-cel and Tisa-cel even though the trial data looked as if the efficacy was the same. However the real

world data and propensity score matching (Bachy et al Nature) suggested that axi-cel was superior in efficacy and now the UK is only using this product. I am concerned that if a similar outcome occurs with the 2 current bispecifics the UK patients may be at a disadvantage if different efficacy is demonstrated between products in this real world data. Epcoritamab and glofitamab are identical at present in terms of efficacy and both would be used in practice until the real world data guides us about patient selection as it has done in the other current T cell engager, CAR T.

4) **Patient fitness -** there is a lot of discussion about treatment intensity. A patient must be very fit for high-dose chemotherapy and an autologous stem cell transplant and it is unusual for us to do this for patients over the age of 70 years because of the toxicity of treatment and risk of dying from the procedure. A patient does not have to be very fit to tolerate car T and we deliver this to people into their 80s. In my experience patients are of similar fitness to tolerate car T and bispecific antibodies which is a similar fitness as to tolerate rituximab bendamustine polatuzumab or other intravenous chemotherapy. Intensive treatment is therefore autologous stem cell transplant and less intensive treatment is all other treatment including T-cell engages such as car T and bispecifics and chemotherapy. It should also be noted that intensive treatment (ie auto transplant) is less effective than the less intensive T cell engaging treatment (CAR T and bispecific) which give patients a 40 % chance of complete remission.

5) **Treatment pathway** - comparison is made with 3rd line Axi-cel but 75% of patients will now be receiving Axi-cel in a second line setting because they have relapsed within 12 months of treatment and are now eligible for Axi-cel (ZUMA 7 study).
Patients would therefore receive epcoritamab
    a. 3rd line post 2nd line CAR T,
    b. 4th line if they were a later (post 12 months) relapse and therefore could not have second-line car T and could only have it in the 3rd line setting
    c. Third line instead of CAR T because the disease kinetics did not allow us to wait for apheresis and manufacturing or because of patient choice not wanting to travel to a CAR T centre.

6) Intention to treat data – When comparing to 3rd line Axi-cel, Zuma 1 is only assessing infused patients and not the patients who did not reach infusion (drop out post apheresis UK data published Kuhnl et al). There is also the unknown number of patients not referred because of rapidly progressive lymphoma which could not be held for the 6-8 weeks before CAR T infusion possible or not referred because of distance from a CAR T centre. The EPCORE NHL1 is all intention to treat data and must be considered when comparing efficacy of cellular therapy vs “off the shelf bispecifics”

7) **Delivery –** Many district general hospitals are already experienced in delivering bispecific antibodies particularly those hospitals that are a long way from CAR T centres as patients are choosing to have effective treatment options closer to home. Bispecifics offer an improvement in access for patients independent of geography unlike CAR T. The numerous district general Hospitals that are already using these treatments demonstrate that this is possible and will improve equity of access for efficacious drugs. Epcoritamab is delivered

subcutaneously and is off the shelf and hospitals which can manage neutropenic sepsis can manage the low grade predictable CRS associated with bispecifics.

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EAG response to Company draft guidance comments

December 2023

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1 Introduction

This document provides the External Assessment Group (EAG)'s critique of the Company's response to the draft guidance (DG) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments (ID4045).[1]

Section 2 presents the EAG's critique of the comments made by the Company in response to the DG, the Company's updated results are presented in Section 2 and Section 3 presents the results of the EAG's preferred assumptions and scenarios. Comments by the Company are discussed according to comment number as per the Company's response document to DG. Table 1 below summarises these comments, including which area of the DG they relate to and EAG response, as well as reference to which section they are discussed in more detail.

All analyses presented in this document include the patient access scheme (PAS) price of [redacted] for epcoritamab. The EAG notes that PAS discounts are available for comparator treatments and has produced a confidential appendix to this document with these discounts included. Analyses presented in the confidential appendix include the Company's revised base case results and scenario analyses, as well as EAG exploratory analyses and preferred base case.

Table 2 and Table 3 below summarise the Committee's preferences/comments outlined following appraisal Committee meeting 1 (ACM1), revised Company base case assumptions and the EAG's preferred assumptions following DG.

Regarding the clinical evidence, the EAG notes that the Company has either performed all of the requests by Committee or provided information that reduces the EAG's concerns about them being performed. Additional data and matching-adjusted indirect comparisons (MAICs) provided have not led to any changes in the EAG's preferences; it still retains a preference for fully adjusted MAICs (or 9/10 variables adjusted for rituximab-based chemoimmunotherapy [R-based CIT]) outlined in Section 2.7 of its technical engagement (TE) critique. The EAG no longer has concerns about using Crump *et al.* as an alternative to Neelapu *et al.* for SCHOLAR-1 in the comparison vs R-based CIT and agrees with the Company that limiting the EPCORE™ NHL-1 population analysed for comparisons vs R-based CIT and polatuzumab vedotin with rituximab and bendamustine (Pola + BR) would be less appropriate.[2, 3] The EAG also reiterates its concerns about Northend *et al.* as an alternative to Sehn *et al.* for the Pola + BR data source and considers analyses using Northend *et al.* to be associated

with more limitations.[4-7] Overall, the EAG considers that the Company has explored the clinical analyses as requested and does not consider anything further would improve the uncertainty that remains. While the EAG is not requesting any further analyses, it notes that this does not mean the uncertainty is completely resolved and considers it important that even the results of the fully adjusted MAICs are considered with this uncertainty in mind. Areas of uncertainty that remain are included in Section 5, all of which were already raised before ACM1.

In terms of the economic analysis, the Company has aimed to address all of the Committee's preferred assumptions and requests for additional analyses and also tried to align the key assumption of long-term remission (LTR) with recommendations in the appraisal of glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments (TA927).[8] However, the EAG remains concerned that the application of the LTR assumption may only relate to treatments that have a fixed duration as opposed to epcoritamab, which is given until disease progression or unacceptable toxicity. Additionally, the EAG considers there is still uncertainty around the long-term survival extrapolations for epcoritamab, but acknowledges that the inclusion of the EAG-preferred MAICs and also exploration of piecewise survival models that use Kaplan-Meier (KM) data from the MAIC analyses allows the EAG to put forward its preferred assumptions and base case for the comparisons with R-based CIT, Pola + BR and axicabtagene ciloleucel (axi-cel).

Table 1. Summary of issues covered in Company's response to draft guidance

Comment in Company DG response	Relevant DG section	Company response	EAG comment	Key issue number in EAG TE report (resolved?)
1	3.5, 3.14, 3.15, 3.16, 3.23, 3.24	Maintain that partially adjusted MAICs most appropriate. Has provided ability for scenarios using fully adjusted MAICs for all comparators in the economic model.	Maintains its preference for MAICs that are adjusted for as many variables as possible. See Section 2.1 for more detail.	Key issue 7 in the EAG's TE critique. Partially resolved – now have the ability to use as scenarios in the model but Company and EAG still differ with regards to preferences.
2	3.7, 3.24	Provides additional MAIC using Crump *et al.* paper as requested for R-based CIT. Retains its preference for using Neelapu *et al.* for SCHOLAR-1 data.	Considers the new MAIC using Crump *et al.* to be more limited and agrees that Neelapu *et al.* may be the best source available for R-based CIT. See Section 2.2 for more detail.	Key issue 2 in the EAG's TE critique. Resolved – the EAG is satisfied that the use of this paper has been explored but that it is less appropriate than the Neelapu *et al.* paper for SCHOLAR-1.
3	3.6, 3.21, 3.24	Provides baseline characteristics and efficacy data for the subgroup from EPCORE™ NHL-1 that were ineligible for CAR-T, as requested, but does not provide MAICs using this subgroup.	Considers the subgroup requested may be a higher risk group and survival outcomes appear substantially worse than the group analysed in the MAICs. Considers that the additional rationale put forward by the Company reduces its concerns and accepts that limiting the EPCORE™ NHL-1 to those ineligible for CAR-T/intensive treatments is unlikely to be appropriate. See Section 2.3 for more detail.	Key issue 6 in the EAG's TE critique. Partially resolved – the EAG agrees with the Company regarding not limiting to those patients ineligible for CAR-T/intensive treatments but considers there may be some uncertainty about the applicability to "population A" as outlined in the CS.
4	3.11, 3.23	Has included the LTR assumption in its revised base case, which now involves a time-point of 36 months after treatment initiation. A scenario where all patients entering LTR stop treatment with epcoritamab has been included.	The Company has aligned their assumption with that accepted in the appraisal of glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments (TA927).[8] However, the EAG notes glofitamab is a fixed length	Key issue 11 in the EAG's TE critique. Partially resolved – the LTR assumption is included for all treatments, but uncertainty around the timepoint of the assumption for epcoritamab remains.

			treatment and so the assumption of LTR after 36 months may not be appropriate for epcoritamab, which is given until progression or unacceptable toxicity. See Section 2.4 for more detail.	
5	3.14, 3.24	Provides a scenario analysis for R-based CIT where the HR between epcoritamab OS and PFS KM curves is used to estimate the PFS curve, as requested.	The Company has provided OS to PFS hazard ratios based on unadjusted KM data from EPCORE-TM NHL-1 and also their preferred MAIC analysis. See Section 2.5 for more detail. However, the Company maintains their base case assumption using the OS HR from the MAIC analysis to estimate a PFS curve for R-based CIT.	Key issue 13 of the EAG's TE critique. Partially resolved. The EAG has included the OS to PFS HR based on unadjusted KM data from EPCORE-TM NHL-1 in its preferred base case.
6	3.14, 3.15, 3.24	Provides scenario analyses where ~10% of patients discontinue treatment with R-based CIT and Pola + BR for reasons other than progression, as requested.	The Company has provided the requested scenario analysis. See Section 2.6 for more detail.	Key issue 14 in the EAG's TE critique. Partially resolved – the Company maintains their base case assumption of TTD equal to PFS. However, the EAG has included the Company's scenario in its preferred base case.
7	3.17, 3.24	Revised base case in terms of subsequent treatment assumptions following further clinical expert feedback.	The EAG considers that the Company's revised subsequent treatment distribution does not reflect the subsequent treatment pathway that would be seen in clinical practice, as outlined in the EAG's critique of the Company's TE response. See Section 2.7 for more detail.	Key issue 17 in the EAG's TE critique. Partially resolved – the EAG maintains its preferred subsequent treatment distribution, as presented in the EAG's critique of the Company's TE response, for its base case.
8	3.9, 3.18, 3.23	The Company has revised its base case to incorporate the Committee's preferred assumption of bridging cost for axi-cel (£23,850) and updated chemotherapy	Appropriate.	Resolved.

		administration costs as per advice received from the Cancer Drugs Fund Lead.		
9	3.19, 3.23	Sought further validation from its clinical experts to determine follow-up costs used in the model for patients receiving epcoritamab and are in complete remission. The Company has updated its base case to incorporate the additional clinical expert feedback.	Compared with the Company's original PFS off-treatment resource use estimates, the Company's revised estimates reduce the usage of blood, liver, immunoglobin and calcium phosphate tests, but increase the usage of specialist nurse and haematologist time The EAG considers that the deviations from the Company's original resource assumptions have not been justified. See Section 2.8 for more detail.	Key issue 18 in the EAG's TE critique. Partially resolved – the EAG prefers to use the Company's original assumptions of the follow-up costs patients receiving epcoritamab and are in complete remission in its base case.
10 and 11	3.12 to 3.16, 3.24	Maintains that its choice of extrapolations are appropriate for OS, PFS and TTD for epcoritamab. The Company provided piecewise models which use KM data from the MAIC analyses up to a certain cut point and then the remainder of the survival curve is informed by an extrapolation of the entire KM curve.	The EAG considers that the Company's piecewise models are not implemented correctly as per guidance in the NICE DSU TSD 21.[9] The EAG is unable to predict what the impact on the cost-effectiveness results would be if the Company provided appropriate piecewise models. See Section 2.9 for more detail.	Key issues 12-14 in the EAG's TE critique. Partially resolved – even though there are issues with the Company's piecewise models, the EAG acknowledges that the direct use of the KM data from the MAIC analyses does mitigate many of the EAG's issues around capturing the points at which KM curves crossed or overlapped based on the MAIC analyses. As such, piecewise models, with the EAG's preferred long-term extrapolations have been included in its base case.
Additional comment	3.3, 3.8, 3.23	Maintains that Pola + BR is not an appropriate comparator and reiterates limitations associated with the Sehn *et al.* trial.	Maintains its preference for Pola + BR to be included as a comparator, as agreed by Committee in the DG. Reiterates its arguments regarding additional limitations of using Northend *et al.* instead of Sehn *et al.* for Pola + BR.	Key issue 9 in the EAG's TE critique. Partially resolved. Committee's preference at ACM1 was for Pola + BR to be included as a comparator. The EAG does not consider Northend *et al.* to be a more

			See Section 2.10 for more detail.	appropriate source of Pola + BR data than Sehn *et al.* for use in MAICs.

Abbreviations: ACM1, appraisal Committee meeting 1; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CS, company submission; DG, draft guidance; DSU, Decision Support Unit; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TE, technical engagement; TSD, Technical Support Document; TTD, time to treatment discontinuation.

Table 2. List of assumptions and preferences following draft guidance

Committee preference / comments at ACM1	Revised Company base case assumptions	EAG-preferred assumptions
R-based CIT		
MAIC adjusted for 9 of 10 reported variables.	Unchanged. The Company maintains the use of the following MAIC: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 7 variables adjusted to SCHOLAR-1)	As per Committee preferences. Company scenario analysis A: ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 9 variables adjusted to SCHOLAR-1)
Re-introduce the LTR assumption for all comparators.	The Company has applied a LTR assumption for all treatments 36 months after treatment initiation, as per Committee preferences from TA927.[8]	Scenario exploring no LTR assumption for epcoritamab provided.
Use of subsequent treatment distributions that better reflect NHS clinical practice.	The Company explored subsequent treatment proportions with 15 clinical experts and has used the distribution, presented in Section 2.7. The Company has also removed the QALY adjustment for subsequent axi-cel for epcoritamab patients.	EAG maintains its preferred distribution of subsequent treatment proportions based on advice from its clinical experts, outlined in the EAG report, Section 4.2.6.4 and the EAG's critique of the Company's TE response, Section 2.19.
Include updated chemotherapy administration costs based on advice from CDF lead.	Aligned with Committee preferred assumptions.	N/A.
Reduced follow up intensity for patients on epcoritamab.	The Company has provided updated PFS off-treatment resource use estimates based on additional interviews with clinical experts. Reduced PFS off-treatment resource use estimates are applied from [redacted], based on the Company's original approach in the CS. The Company's timepoint is based on median PFS from the [redacted] data cut for DLBCL patients in EPCORE™ NHL-1 and it is assumed that this timepoint reflects the when the majority of PFS patients will have complete response.	Company's original PFS off treatment resource use assumptions, presented in Section 2.8, applied in line with the timepoint used for the LTR assumption for epcoritamab.
Pola + BR		
Included as comparator	Base case analysis provided	N/A.
Scenario exploring fully adjusted MAIC.	Unchanged. The Company maintains the use of the following MAIC: ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 6 variables adjusted to Sehn *et al.*).	Company scenario analysis A.1: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior

	Scenarios provided exploring fully adjusted MAIC.	CAR-T, 10 variables adjusted to Sehn *et al.*).
Re-introduce the LTR assumption for all comparators.	The Company has applied a LTR assumption for all treatments 36 months after treatment initiation, as per Committee preferences from TA927.[8]	Scenario exploring no LTR assumption for epcoritamab provided.
Use of subsequent treatment distributions that better reflect NHS clinical practice.	The Company explored subsequent treatment proportions with 15 clinical experts and had used the distribution, presented in Section 2.7. The Company has also removed the QALY adjustment for subsequent axi-cel for epcoritamab patients.	EAG maintains its preferred distribution of subsequent treatment proportions based on advice from its clinical experts, outlined in the EAG report, Section 4.2.6.4 and the EAG's critique of the Company's TE response, Section 2.19.
Include updated chemotherapy administration costs based on advice from CDF lead.	Aligned with Committee preferred assumptions.	N/A.
Reduced follow up intensity for patients on epcoritamab.	The Company has provided updated PFS off-treatment resource use estimates based on additional interviews with clinical experts. Reduced PFS off-treatment resource use estimates are applied from [redacted], based on the Company's original approach in the CS. The Company's timepoint is based on median PFS from the [redacted] data cut for DLBCL patients in EPCORE™ NHL-1 and it is assumed that this timepoint reflects the when the majority of PFS patients will have complete response.	Company's original PFS off treatment resource use assumptions, presented in Section 2.8, applied in line with the timepoint used for the LTR assumption for epcoritamab.
Axi-cel		
Scenario exploring fully adjusted MAIC.	Unchanged. The Company maintains the use of the following MAIC: eligible for intensive therapy (DLBCL, no prior CAR-T, CAR-T eligible, 7 variables adjusted to ZUMA-1)	Company scenario analysis B.1: Eligible for intensive therapy (LBCL, no prior CAR-T, CAR-T eligible, 11 variables adjusted to ZUMA-1).
Re-introduce the LTR assumption for all comparators.	The Company has applied a LTR assumption for all treatments 36 months after treatment initiation, as per Committee preferences from TA927.[8]	Scenario exploring no LTR assumption for epcoritamab provided.
Use of subsequent treatment distributions that better reflect NHS clinical practice.	The Company explored subsequent treatment proportions with 15 clinical experts and had used the distribution, presented in Section 2.7. The Company has also removed the QALY	EAG maintains its preferred distribution of subsequent treatment proportions based on advice from its clinical experts, outlined in the EAG report, Section 4.2.6.4 and the

	adjustment for subsequent axi-cel for epcoritamab patients.	EAG's critique of the Company's TE response, Section 2.19.
Exclude additional monitoring costs for axi-cel, use EAG preferred bridging costs (£23,850) and include updated chemotherapy administration costs based on advice from CDF lead.	Aligned with Committee preferred assumptions.	N/A.
Reduced follow up intensity for patients on epcoritamab.	The Company has provided updated PFS off-treatment resource use estimates based on additional interviews with clinical experts. Reduced PFS off-treatment resource use estimates are applied from [redacted], based on the Company's original approach in the CS. The Company's timepoint is based on median PFS from the [redacted] data cut for DLBCL patients in EPCORE™ NHL-1 and it is assumed that this timepoint reflects the when the majority of PFS patients will have complete response.	Company's original PFS off treatment resource use assumptions, presented in Section 2.8, applied in line with the timepoint used for the LTR assumption for epcoritamab.

Abbreviations: ACM1, appraisal Committee meeting 1; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; CS, company submission; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; LBCL, large B-cell lymphoma; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; N/A, not applicable; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TE, technical engagement..

2 EAG's critique of Company response to draft guidance

2.1 Company comment 1 – Fully vs partially adjusted MAICs and incorporation in the economic model

The Company has provided the ability to use fully adjusted matching-adjusted indirect comparisons (MAICs) for polatuzumab vedotin with rituximab and bendamustine (Pola + BR) and axicabtagene ciloleucel (axi-cel) in the economic model by providing extrapolated curves based on these MAIC analyses (Appendix D.2.1 and D.2.6 of the response to draft guidance [DG]) and allowing their use in the economic model, as requested in Section 3.24 of the DG. The External Assessment Group (EAG)'s preferred MAIC for rituximab-based chemoimmunotherapy (R-based CIT; 9/10 factors adjusted for) could already be implemented by the EAG in the model following technical engagement (TE).

However, the Company reiterates its opinion that the partially adjusted analyses that it prefers for comparisons against R-based CIT, Pola + BR and axi-cel are the most appropriate and that fully adjusted MAICs are not necessary. In support of its preferences, the Company outlines the following:

- It cites a publication linked to guidance from the NICE Decision Support Unit (DSU),[10, 11] which suggests that factors adjusted for in MAICs should be balanced with the impact on effective sample size (ESS) and should be carefully considered, even for unanchored comparisons;
- Reiterates its concerns about multicollinearity and not adjusting for multiple factors that may be linked to one another, based on feedback from its clinical experts and published literature;[12, 13]
- Considers that its preferred analyses include adjustment for all prognostic/predictive variables;
- Notes that feedback from its clinical experts was that fully adjusted MAIC results for all comparators were not clinically plausible, as discussed in response to TE – this includes an implausible [redacted] for epcoritamab and it being implausible that such a large benefit of epcoritamab over axi-cel [redacted] would be observed or that comparative efficacy estimates would [redacted] Pola + BR (albeit a non-significant difference) based on their expectations in clinical practice. The Company considers it is implausible that epcoritamab could have estimates that are similar to both axi-cel and Pola + BR or that adjusting for more variables would reduce the relative benefit of epcoritamab vs Pola + BR when Sehn *et al.* is used;[5-7]

- Reiterates the limitations associated with Sehn *et al.* and highlights that MAICs using Northend *et al.* should also be considered,[4-7] given feedback from its clinical experts that relative estimate obtained from this MAIC with adjustment for 11 variables is the most representative of the expected comparative efficacy (the EAG discusses this in Section 2.10 below).

2.1.1 EAG comment

The EAG notes that this issue is related to Company comments 10 and 11, which are discussed in Section 2.9 below and concern extrapolations used in the economic model. The EAG confirms that the Company has now provided the ability for fully adjusted MAICs for Pola + BR and axi-cel comparators to be included in the economic model, given extrapolated epcoritamab curves have now been provided for these analyses. While the Company reiterates its arguments against using fully adjusted MAICs, the EAG does not consider these to change its own position on this issue and retains a preference for extrapolated curves based on fully adjusted MAICs (or 9/10 factors adjusted for vs R-based CIT) to be used in the economic model. The EAG responds to the Company's arguments in the text that follows and its response at TE can be found in Section 2.7 of its TE critique.

The Company states that its preferred MAICs include adjustment for all prognostic/predictive variables; however, the EAG notes that those omitted from partially adjusted analyses were originally identified by the Company as being prognostic factors (e.g. line of treatment, International Prognostic Index [IPI] and various treatment refractory groupings). In response to clarification question A6b, the Company explained the rationale for this, which included concerns about multicollinearity and similar variables already being adjusted for (or variables already being well-matched) as well as variation in terms of prior lines of treatment (i.e. variability in the number of prior lines of therapy in each trial, exact regimens administered and corresponding sequence of administration).

While the EAG accepts that it is possible that there could be some overlap or association between different measures of refractoriness, it considers adjustment for all of those reported to be appropriate given that adjustment for those selected has not resolved the imbalance for others omitted from the adjustment. With regards to prior lines of treatment, the EAG considers that regardless of what prior treatment involved for patients in the different trials and the sequence,

number of lines of treatment failed is still likely to be an important prognostic factor and does not agree with the rationale provided for its omission from partially adjusted analyses.

While the Company argues that analyses do not need to adjust for IPI given individual components of this measure (age, disease stage and Eastern Cooperative Oncology Group [ECOG] score) are already adjusted for, the EAG is not convinced by this argument given that in the Company's preferred results for axi-cel, adjustment for these factors has not improved the imbalance between proportions with IPI score ≥3. Given it was originally highlighted as a prognostic factor, the EAG, therefore, considers its inclusion important. The EAG accepts that IPI is already fairly well-balanced in the Company's preferred analyses for R-based CIT and Pola + BR but notes that this is not the case for the analysis vs axi-cel. Furthermore, for R-based CIT and Pola + BR comparisons, the EAG considers there are important imbalances for line of therapy and/or variables related to refractoriness not adjusted for in the Company's preferred MAICs; while IPI may be well balanced for these comparators in the Company's preferred MAICs, this may not remain the case were additional adjustments solely for line of therapy and refractoriness variables included, as considered important by the EAG for these comparators. For example, were updated analyses with adjustment for line of therapy and refractoriness variables added, it may be that IPI becomes more imbalanced if it is not included in the adjustment.

The EAG acknowledges that the publication cited by the Company in relation to NICE DSU guidance highlights that trade-offs between ESS and number of variables adjusted for may be required even for unanchored MAICs given the potential number of prognostic variables may be large. However, the publication also highlights that the estimates will remain biased unless all prognostic factors and effect modifiers are included in the adjustment. It further highlights that the individual factors adjusted for that reduce ESS the most will be those that are most imbalanced between studies and, therefore, more important to adjust for than others that lead to less of a reduction in ESS.[10, 11] It is the EAG's opinion that the fully adjusted MAICs (or 9/10 adjustments for R-based CIT) in this appraisal are most appropriate given partially adjusted ones preferred by the Company do not adjust for some prognostic factors that remain in considerable imbalance. Concerns about reducing ESS and precision are noted but the EAG reiterates that this may highlight issues with the overlap of EPCORE™ NHL-1 and the comparator studies and is not a reason to omit variables from adjustment, particularly if they have been noted as being potentially prognostic. In this particular case, the EAG considers that the inclusion of additional variables in its preferred MAICs at the expense of ESS and precision is warranted given its concerns about the comparability of the pairs of trials and that the

increased uncertainty is preferable to more precise results that may be misleading given imbalances in patient characteristics that could be important prognostically remain.

With regards to comments from the Company's clinical experts that results of fully adjusted MAICs are implausible, the EAG agreed with the Company's concerns about the fully adjusted MAIC vs SCHOLAR-1 (using Neelapu *et al.*) given the [redacted] and instead favoured the analysis where 9/10 variables were adjusted for, which still differs from the Company's preferred analysis (7/10 variables adjusted for; see Section 2.7 of the EAG's TE critique).[3] This is despite the analysis having quite a large imbalance for proportion with "SCT (stem cell transplant) any time after refractory disease" remaining, which the EAG considers to be a limitation but is unsure of the potential impact and how prognostic this factor is. For fully adjusted MAICs against Pola + BR and axi-cel, the Company states that clinical experts considered the relative efficacy estimates to be implausible in terms of the [redacted] for epcoritamab vs axi-cel and the estimates [redacted] Pola + BR, and that it is unlikely that epcoritamab would be similar to both axi-cel and Pola + BR. While the EAG considers this input to be valid and useful, it notes that there is a lack of comparative evidence for epcoritamab vs any of the included comparators either in the form of randomised or non-randomised trials and so it is unclear how outcomes for treatments would compare were they all to be assessed in groups of patients with similar baseline characteristics within the same trial. The purpose of a MAIC with adjustment is to improve the comparability of patient populations between trials so that more robust comparisons can be made and the EAG considers that its preferred MAICs with full or additional adjustment are more appropriate than those preferred by the Company, as outlined above.

In terms of the comment that fully adjusting vs Sehn *et al.* would not be expected to reduce the relative efficacy of epcoritamab vs Pola + BR compared to the partially adjusted analysis preferred by the Company,[5-7] the EAG does not consider it possible to anticipate the direction of impact given some factors associated with higher risk were present in more patients for epcoritamab (IPI score ≥3) and others were higher for Sehn *et al.* (≥3 lines of chemotherapy and autologous stem cell transplant, and refractory to last prior anti-lymphoma treatment) before they were also included in the adjustment.

2.2 Company comment 2 – SCHOLAR-1 comparison for R-based CIT MAIC using Crump *et al.* rather than Neelapu *et al.*

The Company has performed the additional MAIC requested by the EAG and as part of the DG for SCHOLAR-1 using Crump *et al.* rather than Neelapu *et al.* (Section 3.24).[2, 3] In its response to TE, the Company outlines that when adjusted for 9 or 11 variables, the ESS reduces to just n=[redacted] patients in both cases (from n=[redacted] originally included in the large B-cell lymphoma [LBCL] no prior chimeric antigen receptor T-cell [CAR-T] population from EPCORE™ NHL-1). It notes that the point estimates of these MAICs is not too dissimilar to its preferred analysis using Neelapu *et al.* with partial adjustment.

2.2.1 EAG comment

The EAG acknowledges that the requested scenario using Crump *et al.* has now been performed by the Company.[2] The rationale for this request by the EAG was to potentially reduce the uncertainty associated with the comparison vs R-based CIT (outlined in Section 2.2 of the EAG's TE critique) given it was not clear what the impact of using this study would be; however, on reviewing the additional MAICs performed, the EAG considers that the Crump *et al.* study may be even less comparable to EPCORE™ NHL-1 than Neelapu *et al.* This is indicated by the fact that an adjustment for 9 variables has a bigger impact on the ESS when Crump *et al.* is used and that even when variables have been included in the adjustment, they are not all well-matched after adjustment.[2, 3] For this reason, the EAG accepts that Neelapu *et al.* may be the best available source for R-based CIT but notes that it has a preference for the analysis with 9/10 variables adjusted for, which differs to the Company's preference for 7/10 variables included. While the concern about not using Crump *et al.* is resolved, the EAG considers that limitations of the EAG's preferred analysis remain including it being unclear whether Neelapu *et al.* includes some non-diffuse large B-cell lymphoma (DLBCL) patients that cannot be adjusted for, the fact that there is a large imbalance remaining for one reported baseline factor (discussed above in Section 2.1.1) and other limitations noted for SCHOLAR-1 in Section 2.3 of the EAG's TE critique.

2.3 Company comment 3 – Additional data for the DLBCL, no prior CAR-T, ineligible for CAR-T subgroup from the EPCORE™ NHL-1 trial

The Company has provided additional information (including baseline characteristics and efficacy data; see Appendix B of the Company's response to DG) for the DLBCL ineligible for intensive treatments (defined by the Company here as ineligible for CAR-T) and no prior CAR-T subgroup from

EPCORE™ NHL-1, as requested by Committee in Section 3.24 of the DG. However, MAICs vs R-based CIT and Pola + BR have not been conducted using this smaller subgroup from EPCORE™ NHL-1, which was also requested in Section 3.24 of the DG.

The Company provides baseline characteristics and efficacy data for two different subgroups; the DLBCL ineligible for CAR-T subgroup ([redacted]) and a smaller subgroup of those with DLBCL that are ineligible for CAR-T and have also not had prior CAR-T treatment ([redacted]). It is the latter that the EAG was interested in in terms of aligning the analysed EPCORE™ NHL-1 population with the population that R-based CIT and Pola + BR were outlined by the Company in the CS as being relevant for (those patients ineligible for intensive treatments, with those with prior CAR-T excluded given the comparator trials did not include these patients). The Company outlines that this subgroup from EPCORE™ NHL-1 was a less fit population compared to the overall DLBCL population (for example, median age was higher [[redacted] vs [redacted] years] as was the proportion with IPI score ≥3 [[redacted]% vs [redacted]%]). Based on this, the Company expects that outcomes for this subgroup would be slightly poorer compared with the overall DLBCL population, which is confirmed when comparing Kaplan-Meier (KM) curves in Figures 1 and 3 of Appendix B of the Company's DG response with the equivalent curves for the overall DLBCL population (see Figure 1 vs Figure 2 below for progression-free survival [PFS] and Figure 3 vs Figure 4 below for OS).

To support its argument that MAICs using the DLBCL no prior CAR-T and ineligible for intensive treatments subgroup (defined by the Company as ineligible for CAR-T) from EPCORE™ NHL-1 would not be appropriate, it reiterates that the same would need to be done for comparator studies to avoid potentially introducing bias against epcoritamab, which is not possible given individual patient data is not available for SCHOLAR-1 or Sehn *et al.* studies.[2, 3, 5-7] The Company outlines that SCHOLAR-1 and Sehn *et al.* data were collected prior to the availability of CAR-T treatment, meaning ineligibility for CAR-T was not a relevant subgroup at the time these data were collected and published; however, feedback from clinical experts consulted by the Company suggests that SCHOLAR-1 and Sehn *et al.* studies would likely have included patients eligible for CAR-T treatment. They also noted that if patients were eligible for inclusion in a clinical trial for Pola + BR, patients would most likely also be eligible for CAR-T therapy, which is another T-cell engaging therapy. The Company also highlights feedback from its clinical experts that clinical practice is likely moving away from determining treatment based on eligibility for intensive therapies and instead determining treatment based on time to relapse, meaning it is less necessary for the analysed populations to be restricted to those patients ineligible for CAR-T treatment.

Figure 1. KM plot of PFS based on IRC assessment (Lugano Criteria) – DLBCL CAR-T ineligible subgroups ([redacted] data cut-off) – reproduced from Figure 1 of the Company's DG response appendix

[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DG, draft guidance; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; IRC, independent review Committee; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 2. KM plot of PFS based on IRC assessment (Lugano Criteria) – overall DLBCL population ([redacted] data cut-off) – reproduced from Figure 3 of the Company's TE response appendix

[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; IRC, independent review Committee; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; PFS, progression-free survival; TE, technical engagement.

Figure 3. KM plot of OS – DLBCL CAR-T ineligible subgroups ([redacted] data cut-off) – reproduced from Figure 3 of the Company's DG response appendix

[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DG, draft guidance; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival.

Figure 4. KM plot of OS – overall DLBCL population ([redacted] data cut-off) – reproduced from Figure 5 of the Company's TE response appendix

[redacted]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; OS, overall survival; TE, technical engagement.

2.3.1 EAG comment

Based on the additional baseline characteristics and survival outcomes provided for the DLBCL no prior CAR-T and CAR-T ineligible subgroup from EPCORE™ NHL-1 ([redacted]), the EAG agrees with the Company's comments that this may represent a subgroup with reduced fitness and subsequently poorer survival outcomes compared to the overall DLBCL population. The EAG considers the same to be true for baseline characteristics and survival outcomes in this subgroup when compared to the population already analysed in the MAICs for R-based CIT and Pola + BR (DLBCL, no prior CAR-T; n=[redacted]; red curves Figure 1 and Figure 3 above vs unadjusted EPCORE™ NHL-1 curves in Figures 5-7 of the EAG's TE critique).

The EAG notes that the Company has defined "ineligible for intensive treatments" as "ineligible for CAR-T" when providing this subgroup data, which it considers to be reasonable. The EAG notes that no detail on how ineligibility for CAR-T was determined in EPCORE™ NHL-1 has been provided as part of this response but that it appears to be in line with ECOG 0-2 (as patients with ECOG 2 have not been excluded from the subgroup), which was outlined by Gilead Sciences Ltd. (manufacturer of axi-cel, a CAR-T treatment) in its stakeholder response to this DG.

The EAG considers the clinical expert feedback sought by the Company on the SCHOLAR-1 and Sehn *et al.* trial populations to be useful,[2, 3, 5-7] particularly the point that these data were collected before CAR-T treatments were available. The feedback the Company received about patients eligible for inclusion in a clinical trial for Pola + BR likely also being eligible for CAR-T was supported by feedback from a clinical expert commenting as a stakeholder on the DG. One of the EAG's concerns about not limiting the EPCORE™ NHL-1 population in the MAICs vs R-based CIT and Pola + BR (population A, defined by the Company as ineligible for intensive treatments) to those ineligible for intensive treatments was that it would be unlikely for patients to receive R-based CIT or Pola + BR were they to be eligible for intensive treatments (such as CAR-T; see Section 2.6.2 of the EAG's TE critique); however, given the point that these trials were performed and published before CAR-T treatments were available, the EAG considers its concerns about this to be reduced and agrees with the Company that it is likely that SCHOLAR-1 and Pola + BR did include some patients that would be considered eligible for CAR-T/intensive treatments had they been classified according to this at the

time. For this reason, the EAG agrees that it would not be appropriate to limit the EPCORE™ NHL-1 MAIC populations for analyses vs R-based CIT and Pola + BR further. Furthermore, it considers that MAICs using the small n=[redacted] subgroup would be difficult given adjustment for even a few variables may reduce the ESS to very small numbers.

The EAG notes that some concerns about how applicable these MAIC analyses are to the population outlined in the company submission (CS) for comparisons vs R-based CIT and Pola + BR remain (population A, ineligible for intensive treatments) given that EPCORE™ NHL-1 and comparator studies include some that would be eligible for intensive treatments such as CAR-T. However, in the interest of improving the comparability of the trials being compared, it would not be appropriate to narrow the population in one trial and not the other and the EAG considers that this may be a minor issue. Furthermore, the Company highlights that clinical expert feedback suggests there may be a move away from determining treatment choice on eligibility for intensive treatments and towards basing decisions on time to relapse, which the EAG notes was also raised during appraisal Committee meeting 1 (ACM1; Section 3.3 of DG). The Company suggest that this means it is less important for these analyses to be specific to those patients that are ineligible for intensive treatments; the EAG agrees that this is a reasonable conclusion to make if it is agreed that this is likely to be the move in clinical practice.

2.4 Company comment 4 – Inclusion of the LTR assumption in the revised Company base case

In the DG, the Committee preferred to include the assumption of long-term remission (LTR) in the analysis. In Section 3.11 of the DG, it was noted that the clinical experts at the appraisal Committee meeting considered it was reasonable to assume a person's cancer is in LTR if it has not progressed two years after treatment ends.

In their response to the DG, the Company revised their base case to include the LTR assumption for all treatments in the model, and applied the assumption 36 months after treatment initiation. The Company explained that it assumed LTR begins 36 months after treatment initiation to be consistent with the Committee preferences for the appraisal of glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments (TA927).[8]

2.4.1 EAG comment

In TA927, the Committee concluded that, "*there is uncertainty about the exact point at which people would no longer have a higher risk of cancer progression, but that assuming a cure point of 3 years was reasonable*".[8] However, it is important to consider that glofitamab is a fixed duration treatment, which is given for a maximum of 12 cycles or until disease progression or unmanageable toxicity, with each cycle lasting 21 days.[14] Conversely, epcoritamab is given until disease progression or unacceptable toxicity; i.e. it is not provided for a fixed duration.[15] As such, for glofitamab and comparators (which included R-based CIT, Pola + BR and axi-cel and which are also provided for a fixed duration), including the LTR assumption after treatment initiation could be considered appropriate, as patients are all off treatment by 36 months.

In the EAG report and the EAG's critique of the Company's TE response, the EAG considered that, based on advice from its clinical experts, patients on epcoritamab would not be considered to enter LTR while on treatment, nor would they be discharged from follow-up in the NHS while on treatment. The Company's current approach does not address the EAG's or Committee's concerns, as it still assumes that epcoritamab patients enter LTR and are discharged from any follow-up while still on treatment (although still incurring the costs of treatment), which is considered clinically implausible.

Nonetheless, the EAG acknowledges that in TA927 the Committee did consider long-term remission three years after treatment was reasonable. Therefore, in addition to the Company's revised base case approach, the EAG considers a scenario where no LTR assumption is applied to epcoritamab patients and the LTR assumption for comparators begins after 36 months is important for the Committee to consider and has included it in its preferred base case presented in Section 4.

2.5 Company comment 5 – Hazard ratio used to estimate a PFS curve for R-based CIT

As mentioned in the EAG report and the EAG's critique of the Company TE response, SCHOLAR-1 did not report PFS data, so the Company used the OS hazard ratio (HR) derived from the 7/10 adjusted MAIC of epcoritamab vs R-based CIT to generate a PFS curve for R-based CIT and this is still maintained for the Company's revised base case. However, in the DG the Committee requested that the Company explore a scenario in which the HR between the epcoritamab OS and PFS KM curves for is used to estimate a PFS curve for R-based CIT.

The Company supplied two HRs, one using KM data for epcoritamab from EPCORE™ NHL-1 based on the unadjusted, DLBCL population, no prior CAR-T (HR [redacted], 95% CI: [redacted]), which was preferred by the EAG and another HR based on KM data for the epcoritamab population adjusted to SCHOLAR-1 using Neelapu *et al.*, with 7/10 variables matched (HR [redacted], 95% CI: [redacted]). The Company included the adjusted OS to PFS HR ([redacted]) in a scenario and results are presented in Section A.5 of the Company's response to the DG. However, the EAG notes that in the Company's scenario, the OS to PFS HR is applied to the Company's OS curve for R-based CIT estimated using the proportional hazards (PH) approach, rather than the independently fit OS curve that is used for the rest of the analysis.

2.5.1 EAG comment

The EAG has corrected the Company's scenario exploring the OS to PFS HR to estimate a PFS curve for R-based CIT to apply the HR to the live R-based CIT OS curve rather than the legacy OS curve based on the PH approach and results are presented in Section 4.

As the EAG considers that the Company's base case approach to estimating the PFS curve for R-based CIT is inappropriate, the EAG includes the OS to PFS HR using KM data for epcoritamab from EPCORE™ NHL-1 based on the unadjusted, DLBCL population, no prior CAR-T (HR [redacted], 95% CI: [redacted]) using the corrected approach, in its revised base case, presented in Section 4.

2.6 Company comment 6 – Treatment discontinuation for reasons other than progression for R-based CIT and Pola + BR

For the comparisons for R-based CIT and Pola + BR, time to treatment discontinuation (TTD) data were unavailable and so for their base case, the Company assumed that TTD was equal to PFS. The EAG notes that R-based CIT and Pola + BR are fixed duration treatments, but patients may discontinue treatment before the fixed duration for reasons such as disease progression or unacceptable toxicity. The EAG and Committee were concerned that the Company's approach fails to capture patients who discontinue treatment for reasons other than disease progression. As such, the Committee requested scenarios exploring treatment discontinuation for reasons other than disease progression for R-based CIT and Pola + BR.

In the original EAG report and in the EAG critique of the Company's TE response, the EAG highlighted findings by Cazelles *et al*.[16] which suggest that 10% of patients discontinued treatment with R-based CIT due to toxicity. The EAG also noted that this estimate was [redacted] with the discontinuation rate for epcoritamab reported in the EPCORE™ NHL trial of [redacted].

In their response to the DG, the Company explored a scenario where approximately 10% of patients receiving R-based CIT and Pola + BR discontinue treatment for reasons other than disease progression before the end of the fixed duration of treatment and results are presented in Section A.5 of the Company's response to the DG.

2.6.1 EAG comment

The EAG is satisfied with the Company's scenario which implements a 10% reduction in TTD for patients receiving R-based CIT and Pola + BR and includes this scenario in the revised EAG base case, presented in Section 4.

2.7 Company comment 7 – Subsequent treatment distribution included in the revised Company base case

In the DG, the Committee concluded that the Company should use subsequent treatment distributions that better reflect NHS clinical practice. In response, the Company sought additional clinical advice from four UK clinical experts and obtained revised proportions of subsequent treatment usage after third-line treatment (presented in Table 3) and included these in their revised base case. However, the EAG notes throughout this appraisal, patients previously treated with a rituximab-based combination should receive subsequent palliative chemotherapy and not a subsequent rituximab combination. However, the Company has stated previously that they did not consider this was relevant to UK clinical practice and so still include R-based CIT as a subsequent treatment for those patients who had previously been treated with a rituximab-based combination.

As part of their revised base case, the Company removed the quality-adjusted life year (QALY) adjustment for subsequent axi-cel for epcoritamab patients, as per the Committee preference.

Table 3. Revised Company base case assumptions of subsequent treatment usage (Table 5 of the Company's response to the DG)

Treatment arm	Percentage of patients receiving subsequent treatments					
	R-based CIT (includes Pola + BR)[a]	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	Palliative care[b]
Population A - Patients ineligible for, or choose not to receive, intensive therapies						
Epcoritamab	40.6%	0.6%	12.5%	0.0%	0.3%	46.0%
R-based CIT	19.4%	1.9%	15.0%	0.0%	0.0%	64.7%
Pola + BR	23.0%	0.6%	13.8%	0.0%	0.0%	63.6%
Population B - Patients eligible for intensive therapies						
Epcoritamab	32.5%	8.1%	13.8%	1.9%	4.4%	40.4%
Axi-cel	39.3%	0.0%	11.3%	1.3%	5.9%	43.4%

Abbreviations: AlloSCT, allogenic stem cell transplant; autoSCT, autologous stem cell transplant, axi-cel: axicabtagene ciloleucel, CAR-T, chimeric antigen receptor T-cell, CIT: chemoimmunotherapy; DG, draft guidance; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; R, rituximab; SCT, stem cell transplant.

[a] R-based CIT includes oral chemotherapy; [b] Palliative care is assumed to incur no treatment costs.

2.7.1 EAG comment

The EAG considers that the Company's revised subsequent treatment proportions still underestimate CAR-T therapy and still do not reflect the subsequent treatment pathway that would be seen in clinical practice, as outlined in the EAG's critique of the Company's TE response.

The EAG reiterates that its preferred proportion of subsequent CAR-T therapy usage are aligned with EPCORE™ NHL-1, where out of the [redacted], [redacted] of patients received subsequent CAR-T, which is the [redacted] by the EAG's clinical experts for population A.

The EAG maintains its approach to subsequent treatment distributions presented in its critique of the Company's TE response (replicated below in Table 4) are more reflective of clinical practice than the Company's base case assumptions. Additionally, the EAG maintains its view that patients receiving R-based CIT or Pola + BR, should receive subsequent palliative chemotherapy (and not a subsequent rituximab combination as assumed by the Company), as per the EAG's clinical experts' advice. As such, the EAG's approach to subsequent treatments in the model, presented in its critique of the Company's TE response (Section 2.19) are still relevant and is maintained for its base case presented in Section 4.

Table 4. EAG base case assumptions of subsequent treatment usage (Table 23 of the EAG's critique of the Company TE response)

Treatment arm	Percentage of patients receiving subsequent treatments					
	R-based CIT	CAR-T therapy	Radiotherapy	AutoSCT	AlloSCT	No active treatment
Population A - Patients ineligible for, or choose not to receive, intensive therapies						
Epcoritamab	30%	11%	25%	1%	3%	30%
R-based CIT	30%*	8%	30%	0%	2%	30%
Pola + BR	30%	8%	30%	0%	2%	30%
Population B - Patients eligible for intensive therapies						
Epcoritamab	30%	30%	25%	1%	3%	12%
Axi-cel	9%	0%	32%	1%	5%	53%

Abbreviations: AlloSCT, allogenic stem cell transplant; autoSCT, autologous stem cell transplant, axi-cel: axicabtagene ciloleucel, CAR-T, chimeric antigen receptor T-cell, CIT: chemoimmunotherapy; DG, draft guidance; EAG, External Assessment Group; Pola + BR, Polatuzumab vedotin with rituximab and bendamustine; R, rituximab; SCT, stem cell transplant; TE, technical engagement.

* Additional chemotherapy following treatment with R-based CIT would be palliative and not R-based.

2.8 Company comment 9 – Reduced follow-up intensity for people who had a complete remission while taking epcoritamab included in the revised Company base case

During ACM1, the clinical experts advised the Committee that they would reduce the follow up intensity for people having epcoritamab while in complete remission (Section 3.19 of the DG). As such, the Committee concluded that it is appropriate to have reduced follow-up intensity for people who had a complete remission while taking epcoritamab.

In their response to the DG, the Company provided updated PFS off-treatment resource use estimates (Table 6 of the Company's response to the DG) based on additional interviews with five UK clinical experts and this is included in their revised base case. Reduced PFS off-treatment resource use estimates are applied from [redacted], based on the Company's original approach in the CS. The Company's timepoint is based on median PFS from the [redacted] data cut for DLBCL patients in EPCORE™ NHL-1 and it is assumed that this timepoint reflects the when the majority of PFS patients will have complete response.

2.8.1 EAG comment

Compared with the Company's original PFS off-treatment resource use estimates, which are used from [redacted] onwards until the LTR assumption begins (whereby no follow-up costs are assumed thereafter), the Company's revised estimates reduce the usage of blood, liver, immunoglobin and calcium phosphate tests, but increase the usage of specialist nurse and haematologist time (Table 6 of the Company's response to the DG). The EAG considers that the deviations from the Company's original resource assumptions have not been justified and in particular notes that the Company's clinical expert advice in the CS and restated in the Company's TE response highlighted that patients are unlikely to require resource use beyond injection service, blood tests, interpretation of blood tests by nurse or pharmacist, and occasional consultant lead contacts after this stage following this timepoint.

Due to a paucity of time, the EAG was unable to validate the Company's new assumptions with its clinical experts, but notes that its clinical experts originally advised that they would not reduce follow up for patients while they are on treatment with epcoritamab. Nonetheless, given the Committee considered that follow-up will reduce for those patients who achieve complete remission on epcoritamab, the EAG considers that it is useful include the Company's original PFS off-treatment resource use estimates in a scenario. However, the timepoint to the apply the scenario (i.e. the timepoint where epcoritamab patients can be considered in complete remission) is still uncertain. The Company maintains the use of using median PFS from the [redacted] data cut for DLBCL patients in EPCORE™ NHL-1 and the EAG still does not understand how median PFS from the trial should dictate resource use for patients on epcoritamab treatment in the model. Thus, as an exploratory analysis, the EAG has run two scenarios where the timepoint for which the reduced follow-up intensity for people who had a complete remission while taking epcoritamab is assumed to be one and two years, presented in Section 4.

2.9 Company comments 10 and 11 – Extrapolations of PFS, OS and TTD

For the revised base case, the Company has maintained its preferred MAIC and selection of extrapolations for PFS, OS and TTD as presented in their response to technical engagement (summarised in Table 5). However, the Company provided scenarios exploring a piecewise approach to extrapolations to address the Committee's concerns that more flexible modelling approaches should be explored to better fit the data from EPCORE TM NHL-1 and the comparator trials. The

Company's piecewise approach implements the KM data for epcoritamab, R-based CIT and axi-cel for the first 24 months and then the Company's preferred extrapolation thereafter. For Pola + BR, KM data are implemented for first 12 months (based on Northend *et al*.)[4] and then the Company's preferred extrapolation thereafter. Results of the Company's scenario analyses are presented in A.5 of the Company's response to the DG.

Table 5. MAIC and extrapolations maintained for the Company revised base case

MAIC/ outcome	Population A				Population B	
	Epcoritamab	R-based CIT	Epcoritamab	Pola + BR	Epcoritamab	Axi-cel
MAIC	Base case analysis A: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 7 variables adjusted to SCHOLAR-1 using Neelapu *et al.*)		Base case analysis A.1: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 6 variables adjusted to Sehn *et al.*)		Base case analysis B: Eligible for intensive therapy (DLBCL, no prior CAR-T, CAR-T eligible, 7 variables adjusted to ZUMA-1)	
PFS	Generalised gamma	OS HR derived from the 7/10 adjusted MAIC of epcoritamab vs R-based CIT ([redacted]), applied to the PFS epcoritamab curve to generate the R-based CIT PFS curve.	Generalised gamma	Gamma	Gompertz	Gompertz
OS	Lognormal	Lognormal	Generalised gamma	Loglogistic	Gompertz	Gompertz
TTD	Exponential	TTD = PFS	Exponential	TTD = PFS	Exponential	N/A

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

2.9.1 EAG comment

As the Company has maintained its base case approach for the source of the MAICs and extrapolations of PFS, OS and TTD for comparisons with R-based CIT, Pola + BR and axi-cel, the EAG considers that the critique and the EAG's preferred MAICs and extrapolations presented in Sections 2.13, 2.14 and 2.15 of the EAG's critique of the Company's TE response still holds. A critique of the Company's preference for partially adjusted MAICs is discussed in Section 2.1.

The EAG has several issues with the Company's scenarios that explored piecewise models based on use of KM data and these are summarised below.

- According to the NICE DSU technical support document (TSD) 21, in a piecewise model, the KM data is used to represent the initial section of the survival curve and then an extrapolation is adjoined to a predetermined point of the KM curve.[9]
- he selection of the "cut point" should be appropriately justified and different scenarios provided to demonstrate the sensitivity of the extrapolation to the chosen cut point;
- The EAG notes the use of KM data from Northend *et al*., in the Company's piecewise model scenario and reiterates its view that use of data from Northend *et al*. over Sehn *et al*. may introduce additional bias given outcomes from trial-based and RWE sources are likely to differ and RWE for epcoritamab when available may similarly differ to outcomes obtained from EPCORE™ NHL-1 (see Section 2.10).[4-7] As such, the EAG considers the piecewise model should use KM data from Sehn *et al*., which also has longer follow-up.

The EAG acknowledges that the direct use of the KM data from the MAIC analyses does mitigate many of the EAG's issues around capturing the points at which KM curves crossed or overlapped based on the MAIC analyses. However, the EAG is unable to predict what the impact on the cost-effectiveness results would be if the Company provided piecewise models that were implemented correctly as per DSU TSD 21.[9] Furthermore, the assumptions around the estimation of long-term survival are intertwined with whether the Committee accepts the LTR assumption of the 36 months for epcoritamab.

However, the EAG considers that is important to provide Committee with its preferred approach with data and analyses available, especially given the Company has now supplied the EAG's preferred MAICs for Pola + BR and axi-cel in the model, as well as reintroduced the LTR assumption (albeit at 36 months after treatment initiation for all treatments). As such, the EAG has made some

revisions to its base case assumptions and these are outlined in Table 6, Table 7 and Table 8, for R-based CIT, Pola + BR and axi-cel, respectively. Additionally, plots of the EAG's preferred PFS and OS curves are presented in Appendix 7. As outlined in the below tables, there is still uncertainty around the long-term extrapolations, especially considering the clinical plausibility of convergence of survival curves for the comparators and epcoritamab. However, the EAG considers that the Company has supplied all the analyses that are plausible to provide. In their response to the DG, the Company explained that they explored the appropriateness of mixture-cure models and cubic spline models but considered that there is not sufficiently robust data for each approach. The EAG agrees with the Company that there is insufficient evidence to justify more complex methods.

Nonetheless, as mentioned previously, the EAG considers that the piecewise models have not been appropriately implemented and if the Committee considers that the LTR assumption does not apply to epcoritamab, then robust application of the piecewise models, in line with guidance is DSU TSD 21 would need to be explored.[9]

Table 6. Population A – epcoritamab vs R-based CIT

MAIC/ Outcome	Epcoritamab	R-based CIT
MAIC	The EAG's preferred MAIC from TE is still the Company's scenario analysis A: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 9 variables adjusted to SCHOLAR-1 using Neelapu *et al.*)	
PFS	As per the EAG's TE response, the preferred extrapolation is generalised gamma curves as this had the best statistical fit and is in line with the Company's clinical experts' expectations that a range of "*20–30% of patients to be progression-free at five years*" with epcoritamab (Section 2.13.2.3 of the EAG's critique of the Company's TE response. However, as the Company has supplied the functionality to use KM data directly as part of a piecewise model, the EAG has updated its base case to use the adjusted KM data for epcoritamab up to 24 months and the generalised gamma curve thereafter.	As per Section 2.5, the EAG prefers the use of the OS to PFS HR using KM data for epcoritamab from EPCORE™ NHL-1 based on the unadjusted, DLBCL population, no prior CAR-T (HR [redacted], 95% CI: [redacted]) applied to the OS curve for R-based CIT to estimate the PFS curve for R-based CIT.
OS	At TE, the EAG preferred the exponential extrapolation to model OS for epcoritamab but were concerned that the parametric survival models explored by the Company might not be flexible enough to accommodate the underlying change in the hazard of the KM OS curve. Thus, for its updated base case, the EAG prefers to use	At TE, the EAG preferred the generalised gamma extrapolation to model OS for R-based CIT but were concerned that the parametric survival models explored by the Company might not be flexible enough to accommodate the underlying change in the hazard of the KM OS curve. Thus, for its

	the adjusted KM data for epcoritamab up to 24 months and the exponential curve thereafter. At TE, in the EAG-preferred analysis, [redacted], after which the EAG took the maximum between the two curves, implying that the epcoritamab curve converged to the R-based CIT OS curve. However, now the Company has implemented the LTR assumption after 36 months, [redacted]. Given the uncertainty around the LTR assumption for epcoritamab, a scenario is run which excludes the LTR assumption and for this scenario, the EAG assumes that after 12 years survival converges between treatment arms, as per the approach taken at TE.	updated base case, the EAG prefers to use the unadjusted KM data for R-based CIT up to 24 months and the generalised gamma curve thereafter.
TTD	At TE, the EAG preferred the lognormal extrapolation to model TTD for epcoritamab but were concerned that the parametric survival models explored by the Company did not fit the observed TTD data well. Thus, for its updated base case, the EAG prefers to use the KM data for epcoritamab up to 24 months and the lognormal curve thereafter.	As discussed in Section 2.6, the EAG prefers to assume TTD = PFS, adjusted for 10% of patients discontinuing treatment for reasons other than disease progression.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; R-based CIT, rituximab-based chemoimmunotherapy; TE, technical engagement; TTD, time to treatment discontinuation.

Table 7. Population A – epcoritamab vs Pola + BR

MAIC/ Outcome	Epcoritamab	Pola + BR
MAIC	At TE, the Company did not implement the fully adjusted MAIC based on Sehn *et al*., in the model, but has now provided this functionality as part of their response to the DG.[5-7] As such, the Company's scenario analysis A.1: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 10 variables adjusted to Sehn *et al*.) has been included in the EAG base case.	
PFS	Based on the KM plot for the fully adjusted MAIC, presented in Figure 25 of the EAG's critique of the Company's response to TE, the KM curves for adjusted epcoritamab and unadjusted Pola + BR [redacted]. As such, the Company's standard parametric extrapolations do not capture the crossing curves.	At TE, the EAG preferred the generalised gamma extrapolation to model PFS for Pola + BR. However, to capture the crossing KM curves observed in the MAIC, for its updated base case, the EAG prefers to use the unadjusted KM data (Sehn *et al.*) for Pola + BR up to 24 months and the generalised gamma curve thereafter.[5-7]

	However, the Company's piecewise approach, which uses KM up to 24 months and extrapolation thereafter for both treatment arms captures the crossing curves. As such, for its updated base case, the EAG prefers to use the adjusted KM data for epcoritamab up to 24 months and the lognormal curve (extrapolation with the best statistical fit) thereafter.	
OS	Based on the KM plot for the fully adjusted MAIC, presented in Figure 6 in the EAG's critique of the Company's TE response, [redacted]. However, when implementing the EAG's preferred lognormal extrapolation (best statistical fit) for both epcoritamab and Pola + BR, [redacted]. As such, the EAG considers the using the adjusted KM data for epcoritamab up to 24 months and then assume that OS is equal to Pola + BR after 24 months [redacted].	At TE, the EAG considered that OS for Pola + BR was likely underestimated from 24 months onwards. The EAG preferred the lognormal distribution to model OS for Pola + BR. However, based on the MAIC, [redacted], the EAG prefers to use unadjusted KM data for Pola + BR up to 24 months (Sehn *et al.*) and then the lognormal distribution thereafter.[5-7]
TTD	At TE, the EAG preferred the lognormal extrapolation to model TTD for epcoritamab but were concerned that the parametric survival models explored by the Company did not fit the observed TTD data well. Thus, for its updated base case, the EAG prefers to use the KM data for epcoritamab up to 24 months and the lognormal curve thereafter.	As discussed in Section 2.6, the EAG prefers to assume TTD = PFS, adjusted for 10% of patients discontinuing treatment for reasons other than disease progression.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DG, draft guidance; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; TE, technical engagement; TTD, time to treatment discontinuation.

Table 8. Population B – epcoritamab vs axi-cel

MAIC/ Outcome	Epcoritamab	Axi-cel
MAIC	At TE, the Company did not implement the MAIC fully adjusted to ZUMA-1 now provided this functionality as part of their response to the DG. As such, the Company's scenario analysis B.1: Eligible for intensive therapy (LBCL, no prior CAR-T, CAR-T eligible, 11 variables adjusted to ZUMA-1) has been included in the EAG base case.	
PFS	At TE, the EAG preferred the lognormal extrapolation to model PFS for epcoritamab. However, [redacted] presented in Figure 31 of the EAG's critique of the Company's TE response, for its updated base case, the EAG	At TE, the EAG preferred the generalised gamma extrapolation to model PFS for axi-cel. However, [redacted] presented in Figure 31 of the EAG's critique of the Company's TE response, for its updated

	prefers to use the adjusted KM data for epcoritamab up to 24 months and the lognormal curve thereafter. The EAG notes that for the scenario where the LTR assumption is removed for epcoritamab, [redacted] and this was also noted in the EAG's critique of the Company's TE response. As such, the EAG has explored two scenarios (presented in Section 4), one where the epcoritamab PFS curve is capped to the axi-cel PFS curve and another where the PFS curves are allowed to cross.	base case, the EAG prefers to use the unadjusted KM data for axi-cel up to 24 months and the generalised gamma curve thereafter.
OS	At TE, the EAG preferred the lognormal extrapolation to model OS for epcoritamab. However, [redacted], presented in Figure 10 of the EAG's critique of the Company's TE response, for its updated base case, the EAG prefers to use the adjusted KM data for epcoritamab up to 24 months and the lognormal curve thereafter.	At TE, the EAG preferred the Gompertz extrapolation to model OS for epcoritamab. However, [redacted], presented in Figure 20 of the EAG's critique of the Company's TE response, for its updated base case, the EAG prefers to use the unadjusted KM data for axi-cel up to 24 months and the Gompertz curve thereafter.
TTD	The Company's piecewise approach to TTD (KM data up to 24 months and extrapolation thereafter) does not address the EAG's concerns that TTD is underestimated for epcoritamab. In the EAG's critique of the Company's TE response, the EAG did not consider the difference between PFS and TTD ([redacted]) to be clinically plausible as the treatment duration is until disease progression or unacceptable toxicity and the Company and clinical experts considered that epcoritamab is well tolerated and few patients discontinue due to AEs or toxicity. As such, the EAG has updated its base case with the scenario presented at TE exploring a HR of 1.2 applied to the epcoritamab PFS curve to estimate TTD and a scenario which uses KM data for epcoritamab up to 24 months and the lognormal curve thereafter.	N/A

Abbreviations: AEs, adverse events; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DG, draft guidance; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; N/A, not applicable; OS, overall survival; PFS, progression-free survival; TE, technical engagement; TTD, time to treatment discontinuation.

2.10 Additional Company comment – Pola + BR is not a relevant comparator and that Sehn *et al.* may overestimate Pola + BR survival

In the summary section at the beginning of its response to DG, the Company reiterates its opinion that Pola + BR is a less relevant comparator for this appraisal compared to R-based CIT and axi-cel (this comment was also made by a clinical expert that submitted a DG response), despite it being agreed by Committee at ACM1 that it is a relevant comparator (Section 3.23). The Company also reiterates limitations of Sehn *et al.* as a source of efficacy data for Pola + BR and makes comparisons to UK real-world data obtained from Northend *et al.*, which has already been discussed in the EAG's TE critique (Section 2.9).[4-7]

Overall, the Company argues that Sehn *et al.* overestimates Pola + BR efficacy given that outcomes are better in this trial compared to the UK real-world evidence source, and that MAICs using Sehn *et al.* may, therefore, bias against epcoritamab. The Company's clinical expert feedback suggests that the efficacy of Pola + BR in clinical practice would likely fall somewhere between estimates in Sehn *et al.* and Northend *et al.*, and that estimates from MAICs using both should be considered in the decision-making; however, later in the DG response document the Company suggests that Northend *et al.* (with adjustment for 11 variables) is the most realistic estimate of the comparative efficacy anticipated by the clinical experts consulted, with the MAIC using Sehn *et al.* adjusted for all available variables concluded to be least representative (comment 1 of the Company's DG response).

2.10.1 EAG comment

The EAG notes that the Committee confirmed its preference was for Pola + BR to be included as a comparator following ACM1 (Section 3.23 of DG). Regarding the limitations of Sehn *et al.* highlighted by the Company, the EAG notes that these points have already been critiqued by the EAG in section 2.9 of its TE critique, including a comparison of OS and PFS curves obtained from the Company's preferred MAICs using Sehn *et al.* (scenario analysis A.1) and Northend *et al.* (scenario analysis A.5) as sources for Pola + BR (adjusted for 6/10 and 11/16 variables, respectively).[4-6]

As noted in its critique of the Company's TE response, the EAG acknowledges that [redacted] benefits of epcoritamab were obtained from the MAIC using Northend *et al.*, while results [redacted] Pola + BR obtained when Sehn *et al.* is used (albeit a non-significant difference). However, the EAG's arguments outlined at TE have not changed and it considers the analyses using Northend *et al.* to be associated with more potential for bias than those using Sehn *et al.* given it is not uncommon

for trial-based outcomes to be better than those observed in real-world evidence (for example, because of inclusion criteria for trials leading to a healthier population being included; as noted in the EAG's TE critique, this was observed for Sehn *et al.* vs Northend *et al.* as there were large differences in some prognostic factors such as ECOG score and IPI, with worse prognosis in Northend *et al.*). While Sehn *et al.* may report higher survival compared to Northend *et al.* for Pola + BR, it is equally possible that survival for patients using epcoritamab could be lower if assessed using real-world data. Therefore, the EAG considers that in terms of estimating the relative effect of epcoritamab vs Pola + BR, Sehn *et al.* is the most appropriate option of the two given it involves trial-based data similar to EPCORE™ NHL-1.

2.11 Additional points raised by stakeholders

The EAG reviewed other comments received from stakeholders related to the DG and, for comments relating to issues that are not already addressed in the sections above, discusses those which it is able to provide a comment on in Table 9 below.

Table 9. EAG response to selected stakeholder comments

Comment summary	EAG response
Gilead Sciences Ltd. (Company for axi-cel)	
Request EAG to reconsider the appropriateness of separate analyses for people who cannot have or choose not to have ASCT or CAR-T (population A) and those who can have these treatments (population B). If appropriate, NICE-recommended criteria should be used rather than clinical trial eligibility criteria. For example patients with ECOG 2 may be considered candidates for CAR-T in the UK.	The EAG considers the division into two analysis populations to be reasonable and notes that the definition used to indicate eligibility for CAR-T appears to include those with ECOG 2, as those with ECOG 2 were not excluded from the "eligible for intensive treatments" population before matching to ZUMA-1 was performed.
The Company is not considering the full evidence base vs axi-cel as real-world evidence has not been considered.	The EAG acknowledges that only ZUMA-1 has been considered as part of the MAICs vs axi-cel, but highlights that limitations would arise were trial-based data from EPCORE™ NHL-1 to be compared with real-world evidence for axi-cel in a MAIC, as outlined by the EAG in Section 2.10.1 for Pola + BR.
Royal College Physicians – ACPRCR	
Glofitamab has been recommended in the same indication, which has an identical response rate and similar adverse event profile based on phase 2 study data (The EAG notes that a similar comment was also made by a clinical expert that submitted a DG response).	Given glofitamab was not included as a comparator in this appraisal, evidence assessing robust comparisons between epcoritamab and glofitamab, for example MAICs allowing adjustment for population differences, is not available. Therefore, the EAG cannot comment on the comparability of these two treatments.

It is clinically implausible based on our experts' experience that epcoritamab will not have an advantage over R-based CIT in this setting.	The EAG notes that the results of the MAIC vs R-based CIT (Company- and EAG-preferred) are not inconsistent with this in terms of clinical outcomes but that cost-effectiveness, and uncertainty associated with this, is also assessed as part of the decision-making process.
It is important to consider the very heavily pretreated nature of patients in the GEN-01 study, including 40% with prior CAR-T treatment. None of the comparator studies will have had such a poor risk, heavily pretreated group. Furthermore, experts note that GEN-01 was conducted in the COVID-19 era which had a negative impact on all studies done at this time. (The EAG notes that a similar comment was also made by a clinical expert that submitted a DG response).	The EAG notes that its own clinical experts also highlighted that EPCORE™ NHL-1 may be slightly worse prognostically in terms of what would be expected in clinical practice; however, for the MAICs, the EAG considers that the group with prior CAR-T was excluded to better align with the comparator studies and matching for prognostic factors should reduce other differences to a certain extent. The EAG acknowledges that any impact of COVID-19 on trial outcomes would not be possible to adjust for between trials.

Abbreviations: ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DG, draft guidance; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy.

3 Company updated results following draft guidance

3.1 Company's revised base case results

Results of the Company's revised base case results are presented in Table 10, Table 11 and Table 12 for the comparisons with rituximab-based chemoimmunotherapy (R-based CIT), polatuzumab vedotin with rituximab and bendamustine (Pola + BR) and axicabtagene ciloleucel (axi-cel), respectively.

Probabilistic sensitivity analysis (PSA) scatterplots and cost-effectiveness acceptability curves (CEACs) for the Company's revised base case results can be found in Section A.3 of the Company's response to the draft guidance (DG). Additionally, the probabilistic and determinist results of the Company's scenario analysis can be found in Section A.5 of the Company's response to the DG. For the revised base case, the Company considers that the 1.2 severity modifier applies for the comparison with R-based CIT and Pola + BR but does not apply for the comparison with axi-cel. As such, base case results for R-based CIT and Pola + BR are presented with and without the 1.2 severity modifier applied. The EAG's assessment of the appropriateness of the 1.2 severity modifier for R-based CIT and Pola + BR is presented in Section 4.4.

Table 10. Company's base case – epcoritamab vs R-based CIT

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
R-based CIT	38,926	[redacted]	0.884	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,230	20,191
Probabilistic results									
R-based CIT	39,369	[redacted]	0.885	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,277	20,912

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 11. Company's base case – epcoritamab vs Pola + BR

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
Pola + BR	109,955	[redacted]	1.729	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,446	6,205
Probabilistic results									
Pola + BR	109,612	[redacted]	1.796	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,230	9,894

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 12. Company's base case – epcoritamab vs axi-cel

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Deterministic results							
Axi-cel	416,171	[redacted]	5.855	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Axi-cel	415,038	[redacted]	5.773	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

4 EAG preferred assumptions following draft guidance

4.1 Model corrections

At technical engagement (TE), the External Assessment Group (EAG) highlighted that the implementation of the Company's correction to the on- and off-treatment progression-free survival (PFS) costs in the polatuzumab vedotin with rituximab and bendamustine (Pola + BR) arm of the model was incorrect as the estimate inputted in the model for this correction is based on Pola + BR patients being on treatment for 6 cycles in the model, when patients receive a fixed duration of 4 cycles of treatment in the model. In the model supplied with the Company's draft guidance (DG) response, the error is still present and therefore, the EAG corrected the company's approach to reflect a treatment duration of 4 cycles with Pola + BR and notes that this correction only impacts the company's base case for the comparison with Pola + BR.

Corrected results for the comparison with Pola + BR are presented in Table 13.

Table 13. Corrected Company's base case – epcoritamab vs Pola + BR

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
Pola + BR	108,141	[redacted]	1.73	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,225	7,688
Probabilistic results									
Pola + BR	108,091	[redacted]	1.79	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,780	10,650

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

4.2 Exploratory and sensitivity analyses undertaken by the EAG

As discussed throughout Section 2, the EAG highlighted a number of scenarios to be explored and these are outlined below. The EAG highlights that scenarios 4 onwards include the EAG's preferred assumptions to treatment effectiveness (scenario 3).

1. Overall survival (OS) to PFS hazard ratio (HR) based on Kaplan-Meier (KM) data for the epcoritamab population adjusted to SCHOLAR-1 using Neelapu *et al.*, with 7/10 variables

matched (HR [redacted], 95% CI: [redacted]) applied to the live OS curve for R-based CIT, to estimate a PFS curve for R-based CIT.[3]

2. OS to PFS HR using KM data for epcoritamab from EPCORE™ NHL-1 based on the unadjusted, diffuse large B-cell lymphoma (DLBCL) population, no prior chimeric antigen receptor T-cell (CAR-T) (HR [redacted], 95% CI: [redacted]) applied to the live OS curve for R-based CIT, to estimate a PFS curve for R-based CIT.
3. Implementation of the EAG-preferred matching-adjusted indirect comparisons (MAICs) along with preferred survival curves and additional assumptions, outlined below in Table 14 for the comparisons with rituximab-based chemoimmunotherapy (R-based CIT), Pola + BR and axicabtagene ciloleucel (axi-cel). This scenario also includes assumptions from scenario 2.
4. Scenario 3 + no long-term treatment remission (LTR) assumption applied to epcoritamab, LTR assumption applied from 36 months for comparators. With this scenario, OS for epcoritamab is capped to the OS for R-based CIT. For the scenario with axi-cel, PFS for epcoritamab is capped to PFS for axi-cel.
    a. The EAG ran a separate scenario for axi-cel where the PFS curve for epcoritamab was allowed to cross the PFS curve for axi-cel.
5. Scenario 3 + EAG's preferred subsequent treatment distributions from TE and removal of subsequent rituximab for patients who have had R-based CIT and Pola + BR.
6. Scenario 3 + Timepoint for which the reduced follow-up intensity for people who had a complete remission while taking epcoritamab is assumed to be:
    a. One year.
    b. Two years.
7. Scenario 6 + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab.

Table 14. EAG preferred treatment effectiveness approach

MAIC/ Outcome	Population A				Population B	
	Epcoritamab	R-based CIT	Epcoritamab	Pola + BR	Epcoritamab	Axi-cel
MAIC	Company scenario analysis A: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 9 variables adjusted to SCHOLAR-1)[3]		Company scenario analysis A.1: Ineligible for, or choose not to receive, intensive therapy (DLBCL, no prior CAR-T, 10 variables adjusted to Sehn *et al.*)[5-7]		Company scenario analysis B.1: Eligible for intensive therapy (LBCL, no prior CAR-T, CAR-T eligible, 11 variables adjusted to ZUMA-1)[17]	
PFS	Adjusted KM data for epcoritamab up to 24 months and the generalised gamma curve thereafter.	OS to PFS HR using KM data for epcoritamab from EPCORE™ NHL-1 based on the unadjusted, DLBCL population, no prior CAR-T (HR [redacted], 95% CI: [redacted]) applied to the OS curve for R-based CIT to estimate the PFS curve for R-based CIT.	Adjusted KM data for epcoritamab up to 24 months and the lognormal curve (extrapolation with the best statistical fit) thereafter.	Unadjusted KM data (Sehn *et al.*) for Pola + BR up to 24 months and the generalised gamma curve thereafter.	Adjusted KM data for epcoritamab up to 24 months and the lognormal curve thereafter.	Unadjusted KM data for axi-cel up to 24 months and the generalised gamma curve thereafter.
OS	Adjusted KM data for epcoritamab up to 24 months and the exponential curve thereafter.	Unadjusted KM data for R-based CIT up to 24 months and the generalised gamma curve thereafter.	Adjusted KM data for epcoritamab up to 24 months and then assume that OS is equal to Pola + BR after 24 months to capture the convergence of the curves seen in the KM data.	Unadjusted KM data for Pola + BR up to 24 months (Sehn *et al.*) and then the lognormal distribution thereafter.	Adjusted KM data for epcoritamab up to 24 months and the lognormal curve thereafter.	Unadjusted KM data for axi-cel up to 24 months and the Gompertz curve thereafter.
TTD	KM data for epcoritamab up to 24 months and the	TTD = PFS, adjusted for 10% of patients discontinuing treatment for reasons other than disease progression.	KM data for epcoritamab up to 24 months and the	TTD = PFS, adjusted for 10% of patients discontinuing treatment for reasons	HR of 1.2 applied to the epcoritamab PFS curve to estimate TTD	N/A

	lognormal curve thereafter.		lognormal curve thereafter.	other than disease progression.		

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; N/A, not applicable; OS, overall survival; PFS, progression-free survival; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time to treatment discontinuation.

Due to time constraints, the EAG was unable to produce probabilistic results for the EAG scenarios, but notes that for the comparisons with R-based CIT and axi-cel, deterministic and probabilistic results are similar. However, as noted in the EAG's critique of the Company's TE response, the probabilistic results for Pola + BR tend to be higher than the deterministic results. Probabilistic results are presented for each of the EAG's preferred base case results for the comparisons with R-based CIT, Pola + BR and axi-cel and scenarios around the EAG base case, presented in Section 4.3.

Table 15. Deterministic results of the EAG's exploratory analyses – R-based CIT

	Results per patient	Epcoritamab	R-based CIT	Incremental value	Incremental value with severity modifier (1.2)
0	Company's base case				
	Total costs (£)	[redacted]	38,926	[redacted]	-
	QALYs	[redacted]	0.88	[redacted]	[redacted]
	ICER (£/QALY)	-	-	24,230	20,191
1	OS to PFS HR based KM data for the epcoritamab population adjusted to SCHOLAR-1 using Neelapu *et al.*, with 7/10 variables matched (HR [redacted], 95% CI: [redacted]) applied to the live OS curve for R-based CIT, to estimate a PFS curve for R-based CIT.				
	Total costs (£)	[redacted]	44,220	[redacted]	-
	QALYs	[redacted]	0.86	[redacted]	[redacted]
	ICER (£/QALY)	-	-	22,805	19,004
2	OS to PFS HR using KM data for epcoritamab from EPCORE™ NHL-1 based on the unadjusted, DLBCL population, no prior CAR-T (HR [redacted], 95% CI: [redacted]) applied to the live OS curve for R-based CIT, to estimate a PFS curve for R-based CIT.				
	Total costs (£)	[redacted]	42,771	[redacted]	-
	QALYs	[redacted]	0.87	[redacted]	[redacted]
	ICER (£/QALY)	-	-	23,231	19,359
3	EAG preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 (including LTR assumption of 36 months for all treatments)				
	Total costs (£)	[redacted]	52,118	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	29,764	24,803
4	Scenario 3 + no LTR assumption applied to epcoritamab and OS for epcoritamab is capped to the OS for R-based CIT.				
	Total costs (£)	[redacted]	52,118	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	71,608	59,673
5	Scenario 3 + EAG's preferred subsequent treatment distributions from technical engagement (TE) and removal of subsequent rituximab for patients who have had R-based CIT.				

	Total costs (£)	[redacted]	82,203	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	32,166	26,805
6a	Scenario 3 + reduced follow-up intensity for people who had a complete remission while taking epcoritamab after one year				
	Total costs (£)	[redacted]	52,118	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	31,456	26,213
6b	Scenario 3 + reduced follow-up intensity for people who had a complete remission while taking epcoritamab after two years				
	Total costs (£)	[redacted]	52,118	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	33,221	27,684
7a	Scenario 6a + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab				
	Total costs (£)	[redacted]	52,017	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	31,409	26,175
7b	Scenario 6b + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab				
	Total costs (£)	[redacted]	52,017	[redacted]	-
	QALYs	[redacted]	1.26	[redacted]	[redacted]
	ICER (£/QALY)	-	-	33,221	27,684

Abbreviations: CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy.

Table 16. Deterministic results of the EAG's exploratory analyses – Pola + BR

	Results per patient	Epcoritamab	Pola + BR	Incremental value	Incremental value with severity modifier (1.2)
0	Corrected Company's corrected base case				
	Total costs (£)	[redacted]	108,141	[redacted]	-
	QALYs	[redacted]	1.73	[redacted]	[redacted]
	ICER (£/QALY)	-	-	9,225	7,688
3	EAG preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 (including LTR assumption of 36 months for all treatments)				
	Total costs (£)	[redacted]	103,189	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	-0.08
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR

4	Scenario 3 + no LTR assumption applied to epcoritamab				
	Total costs (£)	[redacted]	103,189	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR
5	Scenario 3 + EAG's preferred subsequent treatment distributions from technical engagement (TE) and removal of subsequent rituximab for patients who have had Pola + BR.				
	Total costs (£)	[redacted]	135,515	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR
6a	Scenario 3 + reduced follow-up intensity for people who had a complete remission while taking epcoritamab after one year				
	Total costs (£)	[redacted]	103,189	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR
6b	Scenario 3 + reduced follow-up intensity for people who had a complete remission while taking epcoritamab after one year				
	Total costs (£)	[redacted]	103,189	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR
7a	Scenario 6a + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab				
	Total costs (£)	[redacted]	102,816	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR
7b	Scenario 6b + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab				
	Total costs (£)	[redacted]	102,816	[redacted]	-
	QALYs	[redacted]	2.32	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominated by Pola + BR	Dominated by Pola + BR

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year.

Table 17. Deterministic results of the EAG's exploratory analyses – axi-cel

	Results per patient	Epcoritamab	Axi-cel	Incremental value	Incremental value with severity modifier (1.2)
0	Company's base case				
	Total costs (£)	[redacted]	416,171	[redacted]	-
	QALYs	[redacted]	5.86	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
3	EAG preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 (including LTR assumption of 36 months for all treatments)				
	Total costs (£)	[redacted]	403,947	[redacted]	-
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	1,387	N/A
4	Scenario 3 + no LTR assumption applied to epcoritamab and PFS for epcoritamab is capped to PFS for axi-cel.				
	Total costs (£)	[redacted]	403,947	[redacted]	-
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	22,632	N/A
4a	Scenario 3 + no LTR assumption applied to epcoritamab and no cap on PFS for epcoritamab				
	Total costs (£)	[redacted]	403,947	[redacted]	-
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	Dominant	N/A
5	Scenario 3 + EAG's preferred subsequent treatment distributions from technical engagement (TE)				
	Total costs (£)	[redacted]	408,882	[redacted]	N/A
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	45,166	N/A
6a	Scenario 3 + reduced follow-up intensity for people who had a complete remission while taking epcoritamab after one year				
	Total costs (£)	[redacted]	403,947	[redacted]	N/A
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	6,394	N/A
6a	Scenario 3 + reduced follow-up intensity for people who had a complete remission while taking epcoritamab after two years				
	Total costs (£)	[redacted]	403,947	[redacted]	N/A
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	12,528	N/A
7a	Scenario 6a + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab				
	Total costs (£)	[redacted]	403,470	[redacted]	N/A
	QALYs	[redacted]	5.67	[redacted]	N/A

	ICER (£/QALY)	-	-	6,453	N/A
7b	Scenario 6b + Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab				
	Total costs (£)	[redacted]	403,470	[redacted]	N/A
	QALYs	[redacted]	5.67	[redacted]	N/A
	ICER (£/QALY)	-	-	12,749	N/A

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; N/A, not applicable; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.

4.3 EAG preferred base case

Sections 4.3.1, 4.3.2 and 4.3.3 present the results of the EAG's preferred base case for R-based CIT, Pola + BR and axi-cel, respectively.

The assumptions that form the EAG's preferred base case are listed below.

- EAG scenario 3 - implementation of the EAG-preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 for the comparisons with R-based CIT, Pola + BR and axi-cel;
- EAG's preferred subsequent treatment distributions from TE and removal of subsequent rituximab for patients who have had R-based CIT and Pola + BR;
- Timepoint for which the reduced follow-up intensity for people who had a complete remission while taking epcoritamab is assumed to be one year;
- Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab.

The EAG ran a scenario around its base case for each comparator where the LTR assumption is removed for epcoritamab. For this scenario, OS for epcoritamab is capped to the OS for R-based CIT. For the scenario with axi-cel, PFS for epcoritamab is capped to PFS for axi-cel and a second scenario is explored where the PFS curve for epcoritamab was allowed to cross the PFS curve for axi-cel.

Additionally, at the request of NICE, scenarios around the EAG base case exploring the lower and upper range of the chemotherapy administration costs supplied by the Cancer Drugs Fund lead have also been provided.

4.3.1 Population A – R-based CIT

Table 18 presents the EAG's preferred assumptions (deterministic) for epcoritamab vs R-based CIT and Table 19 presents the detailed deterministic and probabilistic EAG base case results.

Table 18. EAG's preferred model assumptions (deterministic) – epcoritamab vs R-based CIT (population A)

Preferred assumption	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative incremental QALYs – 1.2 severity modifier	Cumulative ICER (£/QALY)	Cumulative ICER (£/QALY) – 1.2 severity modifier
Company base case post ACM1	[redacted]	[redacted]	[redacted]	24,230	20,191
EAG scenario 3 – EAG preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 (including LTR assumption of 36 months for all treatments)	[redacted]	[redacted]	[redacted]	29,764	24,803
EAG's preferred subsequent treatment distributions from TE and removal of subsequent rituximab for patients who have had R-based CIT.	[redacted]	[redacted]	[redacted]	32,166	26,805
Timepoint for which the reduced follow-up intensity for people who had a complete remission while taking epcoritamab is assumed to be one year.	[redacted]	[redacted]	[redacted]	33,858	28,215
Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab.	[redacted]	[redacted]	[redacted]	33,811	28,176
EAG preferred base case	[redacted]	[redacted]	[redacted]	**33,811**	**28,176**

Abbreviations: ACM1, appraisal Committee meeting 1; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TE, technical engagement

Table 19. EAG's preferred base case – epcoritamab vs R-based CIT

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									

R-based CIT	82,102	[redacted]	1.26	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,811	28,176
Probabilistic results									
R-based CIT	82,214	[redacted]	1.27	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,039	32,532

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 20 presents a scenario around the EAG base case where the LTR assumption is removed for epcoritamab. For this scenario, OS for epcoritamab is capped to the OS for R-based CIT. Table 21 and Table 22 present scenarios exploring the lower and upper range of chemotherapy administration costs.

Table 20. Scenario excluding the LTR assumption for epcoritamab, OS for epcoritamab is capped to the OS for R-based CIT

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
R-based CIT	82,102	[redacted]	1.26	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82,233	68,528
Probabilistic results									
R-based CIT	82,719	[redacted]	1.28	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82,961	69,134

Abbreviations: ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LYG, life years gained; OS, overall survival; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 21. Scenario using the lower range of chemotherapy administration costs

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
R-based CIT	81,053	[redacted]	1.26	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,395	26,996

Probabilistic results									
R-based CIT	81,405	[redacted]	1.27	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,013	31,677

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

Table 22. Scenario using the upper range of chemotherapy administration costs

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
R-based CIT	84,830	[redacted]	1.26	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,853	31,544
Probabilistic results									
R-based CIT	85,201	[redacted]	1.27	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,870	36,559

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; R-based CIT, rituximab-based chemoimmunotherapy.

4.3.2 Population A – Pola + BR

Table 23 presents the EAG's preferred assumptions (deterministic) for epcoritamab vs Pola + BR and Table 24 presents the detailed deterministic and probabilistic EAG base case results.

Table 23. EAG's preferred model assumptions (deterministic) – epcoritamab vs Pola + BR (population A)

Preferred assumption	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative incremental QALYs – 1.2 severity modifier	Cumulative ICER (£/QALY)	Cumulative ICER (£/QALY) – 1.2 severity modifier
Corrected Company base case post ACM1	[redacted]	[redacted]	[redacted]	**9,225**	**7,688**
EAG scenario 3 – EAG preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 (including LTR assumption of 36 months for all treatments)	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR

EAG's preferred subsequent treatment distributions from TE and removal of subsequent rituximab for patients who have had Pola + BR.	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
Timepoint for which the reduced follow-up intensity for people who had a complete remission while taking epcoritamab is assumed to be one year.	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab.	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
EAG preferred base case	[redacted]	[redacted]	[redacted]	**Dominated by Pola + BR**	**Dominated by Pola + BR**

Abbreviations: ACM1, appraisal Committee meeting 1; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life year; R-based CIT, rituximab-based chemoimmunotherapy; TE, technical engagement.

Table 24. EAG's preferred base case – epcoritamab vs Pola + BR

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
Pola + BR	135,142	[redacted]	2.32	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
Probabilistic results									
Pola + BR	143,961	[redacted]	1.75	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,206,536	27,672,113

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 25 presents a scenario around the EAG base case where the LTR assumption is removed for epcoritamab. Table 26 and Table 27 present scenarios exploring the lower and upper range of chemotherapy administration costs.

Table 25. Scenario excluding the LTR assumption for epcoritamab

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
Pola + BR	135,142	[redacted]	2.32	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
Probabilistic results									
Pola + BR	144,345	[redacted]	1.76	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR

Abbreviations: ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 26. Scenario using the lower range of chemotherapy administration costs

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
Pola + BR	126,744	[redacted]	2.32	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
Probabilistic results									
Pola + BR	135,711	[redacted]	1.76	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,907,400	4,922,833

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

Table 27. Scenario using the upper range of chemotherapy administration costs

Treatment	Total			Incremental				ICER (£/QALY)	ICER (£/QALY) – 1.2 severity modifier
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs with severity modifier		
Deterministic results									
Pola + BR	156,976	[redacted]	2.32	-	-	-	-	-	-

Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by Pola + BR	Dominated by Pola + BR
Probabilistic results									
Pola + BR	166,284	[redacted]	1.74	-	-	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,614,420	3,845,350

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; QALYs, quality-adjusted life years.

4.3.3 Population B – axi-cel

Table 28 presents the EAG's preferred assumptions (deterministic) for epcoritamab vs axi-cel and Table 29 presents the detailed deterministic and probabilistic EAG base case results.

Table 28. EAG's preferred model assumptions (deterministic) – epcoritamab vs axi-cel (population B)

Preferred assumption	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case post ACM1	[redacted]	[redacted]	**Dominant**
EAG scenario 3 – EAG preferred MAICs along with preferred survival curves and additional assumptions, outlined in Table 14 (including LTR assumption of 36 months for all treatments).	[redacted]	[redacted]	1,387
EAG's preferred subsequent treatment distributions from TE.	[redacted]	[redacted]	45,166
Timepoint for which the reduced follow-up intensity for people who had a complete remission while taking epcoritamab is assumed to be one year.	[redacted]	[redacted]	50,173
Company's original assumptions for reduced follow-up intensity for people who had a complete remission while taking epcoritamab.	[redacted]	[redacted]	50,232
EAG preferred base case	[redacted]	[redacted]	**50,232**

Abbreviations: ACM1, appraisal Committee meeting 1; axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; MAIC, matching-adjusted indirect comparison; QALY, quality-adjusted life year; TE, technical engagement.

Table 29. EAG's preferred base case – epcoritamab vs axi-cel

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Deterministic results							
Axi-cel	408,405	[redacted]	5.67	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,232
Probabilistic results							
Axi-cel	407,811	[redacted]	5.64	-	-	-	-

Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,100

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 30 presents a scenario around the EAG base case where the LTR assumption is removed for epcoritamab. For this scenario, PFS for epcoritamab is capped to PFS for axi-cel. The EAG ran an alternative scenario where no cap is applied to PFS for epcoritamab (i.e. PFS curves for epcoritamab and axi-cel are allowed to cross) and results are presented in Table 31. Table 32 and Table 33 present scenarios exploring the lower and upper range of chemotherapy administration costs.

Table 30. Scenario excluding the LTR assumption for epcoritamab, PFS for epcoritamab capped to PFS for axi-cel

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Deterministic results							
Axi-cel	408,405	[redacted]	5.67	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,406
Probabilistic results							
Axi-cel	407,716	[redacted]	5.58	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	93,026

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LYG, life years gained; PFS, progression-free survival; QALYs, quality-adjusted life years.

Table 31. Scenario excluding the LTR assumption for epcoritamab, no cap on PFS for epcoritamab

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Deterministic results							
Axi-cel	408,405	[redacted]	5.67	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,248
Probabilistic results							
Axi-cel	407,342	[redacted]	5.60	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,103

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LYG, life years gained; PFS, progression-free survival; QALYs, quality-adjusted life years.

Table 32. Scenario using the lower range of chemotherapy administration costs

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Deterministic results							
Axi-cel	408,335	[redacted]	5.67	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,639

Probabilistic results							
Axi-cel	408,192	[redacted]	5.63	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,435

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LYG, life years gained; QALYs, quality-adjusted life years.

Table 33. Scenario using the upper range of chemotherapy administration costs

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Deterministic results							
Axi-cel	408,588	[redacted]	5.67	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77,231
Probabilistic results							
Axi-cel	407,277	[redacted]	5.60	-	-	-	-
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	80,392

Abbreviations: axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LYG, life years gained; QALYs, quality-adjusted life years.

4.4 Severity modifier

Estimated total QALYs for the comparators in population A and B for the Company's revised base case and the EAG's preferred base case are presented in Table 35. A summary of the Company-preferred and EAG-preferred baseline characteristics included in the severity modifier calculations can be found in Table 25 and Table 32 of the EAG's critique of the Company's TE response. As the EAG now has its preferred MAIC for the comparison with Pola + BR, the baseline characteristics used for the QALY shortfall analysis are presented in Table 34. The results of the EAG's QALY shortfall analysis, using the Schneider *et al*. calculator are presented in Table 35.[18]

Table 34. Summary of preferred assumptions for general population QALY shortfall estimates – Pola + BR

Factor	Company estimates	EAG estimates
Sex distribution - % female	[redacted]	[redacted]
Baseline mean age - years	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life-year; Pola + BR, polatuzumab vedotin with bendamustine and rituximab.

Table 35. Total QALYs for comparators in the Company revised base case and EAG preferred base case and associated severity modifier

Treatment	Estimated total QALYs (based on probabilistic analysis)			
	Company revised base case	Severity modifier	EAG preferred base case	Severity modifier
Population A				

R-based CIT	0.89	1.2	1.27	1.2
Pola + BR	1.80	1	1.75	1
Population B				
Axi-cel	5.77	1	5.58	1

Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, External Assessment Group; QALY, quality-adjusted life-year; Pola + BR, polatuzumab vedotin with bendamustine and rituximab; R-based CIT, rituximab-based chemoimmunotherapy.

The EAG notes that the Company has assumed that the 1.2 severity modifier applies for their revised base case results for Pola + BR. At TE, the Company removed the LTR assumption for all treatments and this resulted in the severity modifier applying for Pola + BR. However, with the reintroduction of the severity modifier for all treatments, the total QALYs for Pola + BR no longer meets the threshold for the 1.2 severity modifier, both in the Company and EAG base case. Based on the Company revised base case for Pola + BR as the proportional QALY shortfall is 84.48% and absolute shortfall is [redacted], resulting in a severity modifier of 1. The threshold for the 1.2 modifier is a proportional QALY shortfall of 85% to 95% and absolute shortfall of 12 to 18. Even when using the Company's preferred baseline characteristics for the comparison with Pola + BR and the EAG's estimate of total QALYs, the severity modifier is still 1.

5 Conclusions

Issues with the clinical evidence

- Limitations of the matching-adjusted indirect comparisons (MAICs) remain even with full adjustment and the External Assessment Group (EAG) considers them to be associated with considerable uncertainty given the apparent limited overlap between EPCORE™ NHL-1 and comparator studies;
- Unresolvable limitations of the MAICs when using the selected comparator studies were highlighted at technical engagement (TE) and remain, including limitations specific to SCHOLAR-1, Sehn *et al.* and ZUMA-1 (Sections 2.3, 2.9 and 2.10 of the EAG's TE critique, respectively).[2, 3, 5-7, 17] These are mentioned in Sections 3.7, 3.8 and 3.9 of the draft guidance (DG), respectively;
- While the EAG agrees that analyses using Crump *et al.* would be less robust (Section 2.2 above),[2] use of the Neelapu *et al.* is still associated with the limitations highlighted by the EAG previously,[3] including it being unclear whether it was specific to a diffuse large B-cell lymphoma (DLBCL) population (and not being able to adjust for this appropriately if not) and the need to have a preference for an analysis adjusted for 9/10 variables given fully adjusted results were considered implausible;
- The EAG acknowledges that it would not be appropriate to limit the EPCORE™ NHL-1 population to those ineligible for intensive treatments/chimeric antigen receptor T-cell (CAR-T) in MAICs vs rituximab-based chemoimmunotherapy (R-based CIT) and polatuzumab vedotin with bendamustine and rituximab (Pola + BR; Section 2.3 above) but notes that the analysed population is not specifically in line with that defined as population A in the company submission (ineligible for intensive treatments), which may be a minor issue, particularly if it is agreed that treatment options going forward are less likely to depend on eligibility for intensive treatments (and more on time to relapse);
- The EAG and Company preferences with regards to level of adjustment still differ for all comparisons. As discussed in Section 2.1, the EAG maintains its preference for fully adjusted (or 9/10 variables for R-based CIT) MAICs;
- Regarding the MAIC for the comparison vs axicabtagene ciloleucel (axi-cel), the EAG's preference remains for the large B-cell lymphoma (LBCL) analysis (rather than DLBCL which is the Company's preferred analysis) to be used with full adjustment, given ZUMA-1 is not

limited to DLBCL and this can be adjusted for in the LBCL analysis (see Section 2.7.2 of the EAG's TE critique).

Issues with the economic analysis

- Based on the Company's revised base case analysis for epcoritamab vs Pola + BR, the 1.2 severity modifier does not apply and so results with a severity modifier of 1 should be considered by the Committee;
- The Company did not update its base case to include the Committee's preference for the partially adjusted (9 out of 10 variables adjusted to SCHOLAR-1 using Neelapu *et al*.) MAIC for R-based CIT. Instead they maintained the partially adjusted (7 out of 10 variables adjusted to SCHOLAR-1 using Neelapu *et al*.) for the base case analysis.[3]
- The Company provided piecewise models to address the Committee's request for more flexible approaches to model progression-free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD). However, the EAG considers that the Company's piecewise models are not implemented correctly as per guidance in the National Institute for Health and Care Excellence (NICE) Decision Support Unit technical support document 21.[9] The EAG acknowledges that the direct use of the Kaplan-Meier (KM) data from the MAIC analyses does mitigate many of the EAG's issues around capturing the points at which KM curves crossed or overlapped based on the MAIC analyses. However, the EAG is unable to predict what the impact on the cost-effectiveness results would be if the Company provided appropriate piecewise models.
- Inclusion of the long-term treatment remission (LTR) assumption for epcoritamab after 36 months is a key driver in the model and is associated with substantial uncertainty. The Company explained that it assumed LTR begins 36 months after treatment initiation to be consistent with the Committee preferences for the appraisal of glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments (TA927).[8] However, it is important to consider that glofitamab is a fixed duration treatment, which is given for a maximum of 12 cycles or until disease progression or unmanageable toxicity, with each cycle lasting 21 days.[14] Conversely, epcoritamab is given until disease progression or unacceptable toxicity; i.e. it is not provided for a fixed duration.[15] As such, for glofitamab and comparators (which included R-based CIT, Pola + BR and axi-cel and which are also provided for a fixed duration), including the LTR assumption after treatment

initiation could be considered appropriate, as patients are all off treatment by 36 months. The Company's current approach assumes that epcoritamab patients enter LTR and are discharged from any follow-up while still on treatment (although still incurring the costs of treatment), which may be considered clinically implausible.

6 References

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7 Appendix

7.1 EAG preferred progression-free survival and overall survival curves – epcoritamab vs R-based CIT

7.1.1 Long-term treatment remission assumption of 36 months included for all treatments

Figure 5. EAG's preferred progression-free survival curves for epcoritamab and R-based CIT

Figure 6. EAG's preferred overall survival curves for epcoritamab and R-based CIT

7.1.2 Long-term treatment remission assumption of 36 months excluded for epcoritamab

Figure 7. EAG's preferred progression-free survival curves for epcoritamab and R-based CIT

Figure 8. EAG's preferred overall survival curves for epcoritamab and R-based CIT

7.2 EAG preferred progression-free survival and overall survival curves – epcoritamab vs Pola + BR

7.2.1 Long-term treatment remission assumption of 36 months included for all treatments

Figure 9. EAG's preferred progression-free survival curves for epcoritamab and Pola + BR

Figure 10. EAG's preferred overall survival curves for epcoritamab and Pola + BR

7.2.2 Long-term treatment remission assumption of 36 months excluded for epcoritamab

Figure 11. EAG's preferred progression-free survival curves for epcoritamab and Pola + BR

Figure 12. EAG's preferred overall survival curves for epcoritamab and Pola + BR

7.3 EAG preferred progression-free survival and overall survival curves – epcoritamab vs axi-cel

7.3.1 Long-term treatment remission assumption of 36 months included for all treatments

Figure 13. EAG's preferred progression-free survival curves for epcoritamab and axi-cel

Figure 14. EAG's preferred overall survival curves for epcoritamab and axi-cel

7.3.2 *Long-term treatment remission assumption of 36 months excluded for epcoritamab*

Figure 15. EAG's preferred progression-free survival curves for epcoritamab and axi-cel - without cap

Figure 16. EAG's preferred progression-free survival curves for epcoritamab and axi-cel - with cap

Epcoritamab for treating relapsed or refractory large B-cell lymphoma after 2 or more systemic treatments [ID4045]

EAG response to Company draft guidance comments - addendum

December 2023

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1 Time to treatment discontinuation – Company base case

Figure 1. Company's preferred TTD curves for epcoritamab for the comparison with R-based CIT

Mean TTD = [redacted].

Figure 2. Company's preferred TTD curves for epcoritamab for the comparison with Pola + BR

Mean TTD = [redacted]

Figure 3. Company's preferred TTD curves for epcoritamab for the comparison with axi-cel

[redacted]

Mean TTD = [redacted]

2 Time to treatment discontinuation – EAG preferred base case

Figure 4. EAG's preferred TTD curves for epcoritamab for the comparison with R-based CIT

Mean TTD = [redacted]

Figure 5. EAG's preferred TTD curves for epcoritamab for the comparison with Pola + BR

Mean TTD – [redacted]

Figure 6. EAG's preferred TTD curves for epcoritamab for the comparison with axi-cel

[redacted]

Mean TTD – [redacted] (includes assumption of a hazard ratio of 1.2 applied to the epcoritamab PFS curve).