Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from AbbVie**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Lymphoma Action

3. **Comments on the Draft Guidance from experts:**
   a. Mr Andrew Brown, patient expert, nominated by nominated by Lymphoma Action
   b. Professor Kim Linton, clinical expert, nominated by nominated by AbbVie

4. **Comments on the Draft Guidance received through the NICE website**

5. a. **External Assessment Group critique of company comments on the Draft Guidance**
   b. Addendum
   c. Exploratory scenario analysis

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. 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**.**

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

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

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

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.	Not applicable

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
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.
Overview of Response to Committee Requests	AbbVie is naturally disappointed by the draft recommendation from NICE not to recommend epcoritamab to treat relapsed or refractory follicular lymphoma in adults after 3 or more lines of systemic treatment, given the high unmet need and urgent need for patient access. Nevertheless, AbbVie welcomes the opportunity to respond to the draft guidance document (DGD) to address the key areas identified by the committee. In response to the draft guidance, AbbVie have provided detailed comments to each of the following topics summarised in Section 3.16 of the draft guidance:

Committee Requests	DGD Section	Response
3L+ cost-effectiveness outcomes	3.3	As requested, an economic evaluation in the 3L+ population has been presented, however the 4L+ analysis remains the base-case. As noted in the DGD "*the committee understood that the company could choose to restrict the population in its submission.*" For context, there is an ongoing NICE appraisal [ID6586] of epcoritamab in combination with rituximab and lenalidomide in the 2L+ population.
EPCORE NHL-1 Dose Optimisation Cohort	3.4	At the committee's request, data from the latest data cut-off of the dose optimisation cohort have been provided. No COVID associated deaths were recorded in this post peak pandemic cohort and the clinical results are similar to the results from the COVID-adjusted dose expansion cohort described in the main company submission. Furthermore, this longer-term follow-up data demonstrates the sustained benefit of epcoritamab.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	Alternative options for accounting for COVID-19 deaths	3.6	AbbVie have explored alternative options for accounting for COVID-19 deaths as requested by the Committee, and concludes that full censoring of patients with COVID resembles the current clinical setting most accurately – a conclusion that is supported by the post-pandemic Dose Optimisation Cohort data.
	Comparator source data	3.5 and 3.7	AbbVie has explored alternative comparator data for both the 3L+ and 4L+ populations and attempted to use these to validate model outcomes. HMRN represents the only available UK relevant source of comparator data. Scenario analysis accounting for different approaches to modelling HMRN survival have been presented to aid decision making.
	Exploration of MAIC variables	3.9	At the Committee's request, AbbVie have provided additional MAIC analyses with further exploration of prognostic factors where feasible. The analyses robustly demonstrate that epcoritamab has improved efficacy compared with current standard of care.
	Simulated treatment comparison (STC)	3.5 and 3.7	AbbVie has considered a simulated treatment comparison (STC) to validate the MAIC as requested by the committee but given time limitations, other requested analyses were prioritised. The decision to conduct a MAIC over an STC considered various factors, including precedent in prior appraisals, the degree of overlap between population characteristics, the number of observed events, and variables requiring adjustment.
	Censoring of CAR-T therapy	3.11	At the request of the Committee, the impact of subsequent CAR-T therapy on patient survival was investigated, demonstrating that censoring at receipt of a subsequent CAR-T therapy or exclusion at baseline of CAR-T treated patients had minimal impact on OS and PFS.
1. Summary of updates to the base-case model	Throughout this draft guidance response, AbbVie have provided an updated base case, aligning with many of the Committee's preferred assumptions as outlined below. Further details of modelling assumptions and scenarios are detailed in Appendix 1 and 2:		

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Table 1: Updated base case

Item	Original submission (Base case)	Updated base case (to align with the Committee's preferred assumptions)
Utility analyses	Treatment-specific, CR-derived progression-free health state utility values.	No treatment specific health state utility values.
Application of hazard ratios	Hazard ratios derived from the MAIC were applied to the baseline epcoritamab survival data to generate outcomes for current 4L+ care.	Hazard ratios derived from the MAIC are now applied to the reweighted epcoritamab survival data, as per the Committee's request.
Resource use	Once-monthly haematologist consultations for epcoritamab.	Haematological consultations to take place weekly for the first month, before reducing to monthly.
Adverse events	Due to limited reporting, adverse event rates for R-CHOP were used to generate AE costs for the entire comparator basket.	Implemented the EAG approach to weighting adverse events, but continued to exclude cytokine-release syndrome (CRS) as per the Committee's preferred approach.

2

AbbVie's base-case remains in the 4L+ FL population. We have now provided exploratory analyses demonstrating cost-effectiveness in the 3L+ population.

Section 3.3 of the Draft Guidance details the Company's decision to submit evidence for epcoritamab in a population after 3 or more lines of systemic treatment (fourth line or later), acknowledging that this is the population with the greatest clinical unmet need and for whom there are limited treatment options. Based on input from the EAG's clinical experts, "*the committee concluded that it would like to see cost-effectiveness modelling for the full marketing authorisation population (to include people having third-line treatment). It noted that a full justification, including a full breakdown of available evidence, and clear definition of the fourth line or later population would be needed should this modelling still not be possible*."

AbbVie have thus performed an economic evaluation exploring the use of epcoritamab in patients with 3L+ relapsed refractory (R/R) follicular lymphoma (FL), comparing efficacy outcomes with those from 3L+ FL patients recorded in the Haematological Malignancy Research Network (HMRN) database (n = 96). As detailed further in Appendix 2, this analysis uses the log-normal extrapolation for overall survival (OS), time to treatment discontinuation (TTD), and progression-free survival (PFS), and assumes proportional hazards to model outcomes for the current 3L+ care arm (COVID-modified hazard ratios: HR = 0.238 for OS and HR = 0.448 for PFS), while retaining the Committee's other

preferred assumptions. HMRN TTD is extrapolated independently using the log-logistic model. The outputs of this analysis are presented in Table 2.

Table 2: Scenario analysis: Epcoritamab in a 3L+ R/R FL population (COVID-modified)

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
3L+ patient population	Epcoritamab	[redacted]	12.628	6.217	[redacted]	9.757	4.362	[redacted]
	Current 3L+ Care	[redacted]	2.871	1.855				

Analysis performed using epcoritamab PAS price and using committee preferred assumptions (retaining AbbVie's preference for a MAIC to derive comparator outcomes, with HR's applied to the MAIC-adjusted epcoritamab survival, and fully COVID-modified outcomes for epcoritamab and HMRN)
Costs and QALYs discounted; LYs undiscounted
No severity modifier applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

A summary of additional exploratory scenarios is provided in Appendix 1. Together, these demonstrate the robustness of the cost-effectiveness case in the 3L+ and 4L+ populations, albeit with the 4L+ population representing a more significant unmet need. Note that there is an ongoing NICE appraisal for the 2L+ FL population (ID6586), which will also cover the 3L population.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

3	**Extended follow-up from the post-peak pandemic Dose Optimisation cohort validates the choice of extrapolations and approach to adjusting for COVID-related mortality in the base-case model.** In Section 3.4 of the Draft Guidance, the Committee stated that "*Longer follow-up data was recently made available for the Dose Optimisation cohort. So, it concluded that it would like to see this data."* As a reminder, data collected from the Dose Expansion cohort of EPCORE NHL-1 were impacted by the COVID-19 pandemic and, consequently, excess patient mortality was observed (as detailed in Section 2.6 of the Company Submission). In contrast, the majority of recruitment for the Dose Optimisation cohort occurred following the height of the COVID-19 pandemic. This means these data are vitally important in being able to accurately reflect the current clinical landscape and outcomes for epcoritamab use without the confounding influence of the pandemic. Updated 4L+ FL efficacy data from the December 2024 data cut of the Dose Optimisation cohort have been presented below. Patients were followed-up for a median of [redacted] months at the point of analysis. Deaths were observed in [redacted]% (n = [redacted]) of patients in the 4L+ cohort. At 18-months, [redacted]% of patients remained alive and [redacted] further mortality event occurred by [redacted] months (Figure 1). No deaths related to COVID-19 were reported in the extended follow-up from the Dose Optimisation cohort. Additionally, no Grade 3-4 COVID-19 TEAEs were noted. Similar outcomes were reported in 3L+ FL. In total, [redacted]% (n = [redacted]) experienced a progression or mortality event with a median PFS reached at [redacted] months (95% CI: [redacted], [redacted]; Figure 2). These outcomes align with those from the COVID-modified Dose Expansion cohort. The estimated percentage of patients remaining progression-free at 18 months was not available due to the lack of follow-up at this timepoint. Full details of the efficacy and safety of epcoritamab are available for 3L+ (n = 86) and 4L+ (n=41) in Appendix 3. Efficacy outcomes from the extended follow-up from the Dose Optimisation cohort closely align with the COVID-modified outcomes seen in the Dose Expansion cohort. Dose Optimisation OS outcomes at 18 months were better than those in the COVID-modified Dose Expansion cohort at 18 months ([redacted]% vs. [redacted]% respectively).

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Figure 1: Kaplan–Meier Plot of overall survival. Dose Optimisation 4L+ FL cohort

Data cut 9 December 2024. Arm A: Epcoritamab Priming 0.16mg, Intermediate 0.8mg, Second intermediate 3mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

Figure 2: Kaplan–Meier Plot of progression-free survival. Dose Optimisation 4L+ FL cohort

Data cut 9 December 2024, assessed by investigator. Arm A: Epcoritamab Priming 0.16mg, Intermediate 0.8mg, Second intermediate 3mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

These data strongly support the Company's base case approach and validates the appropriateness of fully modifying for deaths due to COVID-19 in the trial.

To aid the Committee in their decision-making and conclusions around the use of COVID-modified data, AbbVie have provided a comparison of the OS Kaplan–Meier curve from the latest December 2024 Dose Optimisation data cut with the extrapolated COVID-modified OS curve from the Dose Expansion cohort presented in the Company base case (Figure 3).

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Figure 3: Company modelled base case (4L+) compared with the Kaplan–Meier data from the latest Dose Optimisation data cut (December 2024) – Overall survival

Data cut for Dose Optimisation KM Curve: 9 December 2024, 4L+ median follow-up: [redacted] months
Extrapolation curve refers to the COVID-modified curve from the expansion cohort presented in the Company Submission (April 2025)

As illustrated in Figure 3, the OS data from the Dose Optimisation December 2024 data cut demonstrates more favourable outcomes compared with the extrapolated COVID-modified curve derived from the Dose Expansion cohort of EPCORE NHL-1 used in the Company's base case. This reinforces AbbVie's position that the data underpinning the initial base case for epcoritamab is appropriate for decision-making and is conservative compared with Dose Optimisation outcomes. By censoring COVID-19 deaths, outcomes from the Dose Expansion cohort are most similar to outcomes from the Dose Optimisation cohort. As such COVID-19 censoring serves as a middle ground that is reflective of current practice, without the confounding nature of the COVID-19 pandemic.

Similarly, it was suggested by the EAG and Committee that they would prefer to see outcomes for epcoritamab estimated by applying the inverse of the HR derived from the MAIC to the underlying HMRN extrapolations. This is shown in Figure 4, whereby once again, epcoritamab survival is below the observed data from the Dose Optimisation cohort of the clinical trial. A scenario exploring these outcomes is presented in Appendix 1.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Figure 4: Company modelled 4L+ Epcoritamab using inverse hazard ratios compared with the Kaplan Meier curves from the latest Dose Optimisation data cut (December 2024) – Overall survival

Data cut for Dose Optimisation KM Curve: 9 December 2024, median follow-up: [redacted] months
Extrapolation curve refers to the EAG's preferred HMRN extrapolation (log-normal), with the inverse HR applied to derive epcoritamab outcomes

In summary, the outcomes from the latest data cut of the Dose Optimisation cohort provide reassurance that the Company's modelled extrapolations for epcoritamab are not optimistic, but rather conservative. Thus COVID-modified data from the Dose Expansion Cohort is a middle-ground and is suitable for decision making.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

4

Analyses exploring alternative options accounting for COVID-19 deaths demonstrates that full censoring of patients with COVID resembles the current clinical setting most accurately – a conclusion that is supported by the post-pandemic Dose Optimisation Cohort data.

All analyses have been conducted for both the 3L+ and 4L+ populations. The discussion in this section focuses on 4L+ FL, while the 3L+ analyses are presented in Appendix 1. A summary of the data described in this section is presented below:

	Period of follow-up	Follow-up (Median)	OS at 18 Months	COVID-related mortality?	Grade 3-4 COVID-related TEAEs
Dose Expansion	[redacted]	[redacted] months	[redacted]%*	Yes	[redacted]%
Dose Optimisation	[redacted]	[redacted] months	[redacted]%	No	0%

OS, overall survival; TEAE, treatment emergent adverse event
*COVID modified outcomes

In the submission, AbbVie presented outcomes from the Dose Expansion cohort that recruited patients during the COVID-19 pandemic. In their Draft Guidance "*The committee agreed that in principle the impact of COVID-19 should be accounted for in the EPCORE NHL-1 clinical evidence,*" though "*it would like to see more complex methods for accounting for COVID-19 deaths, instead of only censoring them, such as using causal inference*."

There are no perfect approaches for handling the uncertainty in outcomes caused by the confounding nature of COVID-19 and the particularly infectious Omicron wave. As such, emphasis must be placed on any available data following the height of the pandemic. At the first committee meeting, clinical experts highlighted that the Dose Optimisation Cohort, from which the marketing authorisation dosage is derived, largely took place following the pandemic and is crucial for decision-making on COVID-19-related mortality:

- **Updated outcomes from the post-pandemic Dose Optimisation cohort show improved epcoritamab survival throughout follow-up, compared with the company base-case approach.** Figure 5 demonstrates that the COVID-modified Dose Expansion curve reflects a middle-ground between the outcomes observed following the pandemic (i.e. in the Dose Optimisation cohort) and those seen during the pandemic (i.e. in the COVID-unmodified data). Clinical opinion has confirmed that Dose Optimisation follow-up is sufficiently long to be used as validation for the COVID-modified extrapolations used in the Dose Expansion Cohort. These results prove that the COVID-modified approach taken in the company base-case is pragmatic and reflective of expected current outcomes in the UK.
- **A scenario accounting for the impact of the Omicron wave on COVID-modified Dose Expansion results shows a minimal impact on the ICER.** An alternative scenario considers the Omicron wave: a period during the height of the pandemic when a highly infectious variant surfaced when many COVID restrictions were being lifted. The Dose Expansion cohort was particularly exposed to the Omicron variant as recruitment had largely completed before the start of the Omicron wave; today, patients do not have

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	the same risk of mortality with COVID-19 than they had during the Omicron wave. In this scenario, patients with a post-pandemic COVID-19 related death (N=[redacted]) from the Dose Expansion cohort contribute as a mortality event in analyses. Conversely, patients who died during the Omicron wave had been censored (N=[redacted]). This scenario reflects a second middle ground between the Dose Optimisation outcomes and the COVID-unmodified approach. The outcomes presented in Table 3 and Table 4 provide the committee with an alternate scenario for decision-making and one that is more reflective of expected current outcomes than the COVID-unmodified approach. • **Finally and notwithstanding the limitations of causal inference methods, Inverse Probability of Censoring Weighting (IPCW) was performed in line with TSD 16 and is presented in Figure 6 and Appendix 4.** In the Draft Guidance, the Committee requested that "*it would like to see more complex methods for accounting for COVID-19 deaths, instead of only censoring them, such as using causal inference*." An IPCW approach handles censored data by assigning each patient a weight equal to the inverse of their probability of remaining uncensored, so the data is reweighted to account for bias associated with potential informative censoring. In summary, when considering the IPCW-adjusted survival data, both the OS and PFS data for epcoritamab closely follow the survival estimated under the COVID-modified approach presented in the Company base case. Causal inference approaches rely on a high number of events to allow for stable estimation of weights and to sufficiently capture differences in characteristics across treatment groups. Due to the low number of COVID-related mortality events (N=[redacted]), interpreting outcomes from approaches such as IPCW is challenging. As such, the Company base-case COVID-modified Dose Expansion extrapolations are preferred.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Figure 5: Comparison of overall survival Kaplan–Meier curves between the 4L+ Dose Optimisation cohort and the 4L+ expansion cohort (COVID-modified and COVID-unmodified) of EPCORE NHL-1

Data cut for Dose Optimisation KM Curve: 9 December 2024, median follow-up: [redacted] months
Data cut for expansion COVID-modified KM Curve: [redacted], median follow-up = [redacted] months
Data cut for expansion COVID-unmodified KM Curve: [redacted], median follow-up = [redacted] months
These are the unadjusted outcome data for epcoritamab prior to being matched to HMRN

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Figure 6: Comparison of overall survival Kaplan–Meier curves between the 4L+ Dose Optimisation cohort and the IPCW analysis

Data cut for Dose Optimisation KM Curve: 9 December 2024, median follow-up: [redacted] months

To aid in committee decision making, AbbVie have conducted an Omicron-modified analysis. This approach only captures COVID-related mortality following the Omicron wave of the pandemic. The outcomes of this scenario are presented alongside the COVID-censoring analysis in Table 3.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Table 3: Unadjusted and matched MAIC-adjusted OS and PFS of EPCORE NHL-1 COVID-modified, COVID-unmodified, and Omicron-modified MAICs vs current 4L+ care

	COVID-modified		COVID-unmodified		Omicron-modified	
MAIC-unadjusted						
Outcome	HR [95% CI]	p-value	HR [95% CI]	p-value	HR [95% CI]	p-value
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAIC-adjusted						
Outcome	HR [95% CI]	p-value	HR [95% CI]	p-value	HR [95% CI]	p-value
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; OS, overall survival

AbbVie has extended these scenario analyses to explore the impact of these assumptions on the outputs of the economic evaluation. The outputs of this analysis are presented in Table 4.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Table 4: Scenario analysis: Alternative methods to modifying for COVID-19 deaths in 4L+

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Base case (COVID-modified)	Epcoritamab	[redacted]	9.275	5.999	[redacted]	7.292	4.457	[redacted]
	Current 4L+ Care	[redacted]	1.983	1.542	-	-	-	-
COVID-unmodified	Epcoritamab	[redacted]	7.144	4.833	[redacted]	5.113	3.268	[redacted]
	Current 4L+ Care	[redacted]	2.031	1.565	-	-	-	-
Omicron-modified	Epcoritamab	[redacted]	9.090	5.899	[redacted]	7.099	4.352	[redacted]
	Current 4L+ Care	[redacted]	1.991	1.547	-	-	-	-

Analysis performed using epcoritamab PAS price and using committee preferred assumptions (but retaining Company's preference for MAIC to derive comparator outcomes and fully COVID-modified outcomes for epcoritamab)
Costs and QALYs discounted; LYs undiscounted
Severity modifier of ×1.2 applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

As detailed previously, the UK is no longer experiencing a high number of COVID-19 related deaths relative to the peak of the COVID-19 pandemic in which the EPCORE NHL-1 trial was conducted. Additionally, it is not expected that this will change in the future. Of the [redacted] deaths attributed to COVID-19, [redacted] had occurred in patients in a complete response at the time of their death. Such patients with a CR would typically have significantly extended OS compared with patients who achieve a partial response or no response. Data from the Dose Optimisation cohort further supports these outcomes. The Company base-case reflects these realities by fully adjusting for COVID-19 related deaths; an approach that aligns with ID5082, wherein the Committee asked the Company to present a survival analysis censoring for deaths related to COVID-19.

In summary, we have explored multiple options in response to this issue in the Draft Guidance. Preliminary data from the Dose Optimisation cohort (Table 4), which enrolled the majority of patients following the Omicron wave of the COVID-19 pandemic, show no COVID-19 related deaths and no Grade 3-4 COVID-19 TEAEs. Further, complex causal inference analyses (e.g. IPCW) conducted in response to the draft guidance have demonstrated that outcomes are very similar to the fully COVID-modified approach. Therefore, the COVID-modified analysis used in the Company base-case represents an appropriate middle-ground between outcomes seen following the pandemic (i.e. updated Dose Optimisation outcomes) and during the pandemic (i.e. the COVID-unmodified approach; Figure 5). A second middle-ground scenario, between the Dose Optimisation data and the Dose Expansion COVID-unmodified outcomes has also been presented.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

5	**Outcomes from large international datasets are not generalisable to the UK and so are not appropriate for an indirect treatment comparison (ITC). The HMRN dataset remains the only relevant source of comparator data in 3L+ and 4L+ FL and has been explored upon the request of the committee.** The committee has correctly observed that outcomes in large international datasets appear to be improved compared with the UK HMRN dataset. Upon reassessing the published evidence (see Appendix 5), there appear to be demonstrable differences in patient profile, treatment pathway, and study conduct that lead to variation in survival outcomes when compared with the HMRN dataset. The committee noted that "*there were potential inconsistencies between alternative sources of comparator data and the HMRN dataset that required further exploration.*" We agree that these exist and upon reassessing published evidence, we have described the key inconsistencies that could partly explain differences in survival outcomes between HMRN and published literature: • **Large international datasets are more oriented towards academic centres where patients can receive the best possible care for their FL.** Such centres offer patients access to top specialists at renowned medical schools. Additionally, academic centres are better-resourced, are involved in research and clinical trials, and are consistent in implementing rigorous protocols and best practices set by academic bodies. In large countries like the US, only the fittest patients are able to travel the distances required to access such care. The HMRN dataset consists of a mix between academic centres in the north of England and general hospitals and is more reflective of the balance seen across the UK. • **Routine access to novel therapies with alternative mechanisms of action, such as CAR-T and bispecific antibodies, would likely improve outcomes in international datasets compared with HMRN.** The NCCN Guidelines only recommend R-Chemo and/ or R^2 in 1L and 2L and not in 3L+ FL. By 3L+ FL, only novel treatments are recommended due to the severity of the disease. The NCCN Guidelines recommend either bispecific antibodies (epcoritamab or mosunetuzumab) or CAR-T therapy (axicabtagene ciloleucel, lisocabtagene maraleucel, or tisagenlecleucel). Other recommended treatments include EZH2 inhibitors, BTK inhibitors, and loncastuximab tesirine-lpyl with rituximab.[1] Conversely in the UK, no such treatment options are routinely available at 3L+ FL and patients receive a variation of R-Chemo that they had previously not received. This can be seen in the treatment pattern data for 3L+ FL and 4L+ FL in the HMRN dataset, making outcomes from HMRN more generalisable to the UK compared with published international data. • **The average patient profile in many large international datasets is fitter and younger than the typical 3L+ or 4L+ FL patient in the UK.** Such datasets have largely been funded by the pharmaceutical industry to serve as historical controls for single-arm trials of CAR-T therapies. For example, the SCHOLAR-5[2], ReCORD-FL[3], and US Flatiron[4] datasets have all been used for these purposes. CAR-T eligible patients are typically

more likely to tolerate aggressive treatments and have favourable disease characteristics for long-term survival. CAR-T eligible cohorts are not reflective of all patients with 3L+ and 4L+ FL in the UK. For example, patients may present with higher ECOG scores, disease stage, and may simply be older than patients in SCHOLAR-5, ReCORD-FL, or public US Flatiron data. While there are some CAR-T-eligible and fitter patients in the UK, such patients are not reflective of the entire 3L+ and 4L+ FL populations with most patients presenting with more aggressive disease. Accordingly, the patient characteristics observed in HMRN are more generalisable to the UK than alternate published data sources.

A full and detailed explanation for excluding all potentially relevant 3L+ and 4L+ publications is provided in Appendix 5.

Clinical opinion sought on this issue has suggested that a combination of all of the above as well as additional and unknown confounding variables could explain the inconsistencies in survival outcomes between UK clinical practice and data from other countries. Given the fundamental differences between UK practice and large international datasets for 3L+ and 4L+ FL, we did not consider it appropriate to match Dose Expansion data with data in the public domain. Any outcomes from matching would not be generalisable and would not reflect the reality of being treated for 3L+ or 4L+ FL in the UK. Therefore, the HMRN dataset was found to be the only relevant source of comparator data for this appraisal.

There are however challenges with the HMRN dataset that need to be considered in the interpretation of outcomes and decision-making. A large time window had been considered to ensure the maximum amount of data available from UK practice for decision-making. The Committee correctly note that "*the intention of fourth line treatment may have changed over time as different treatments became available*." Indeed, clinical opinion has noted that while treatment options and outcomes remain the same, practices and the intention of treatment have changed. These are issues that other publicly available retrospective data sources also present with. This has since been explored further within the HMRN dataset:

- **Verifying clinical opinion from the Committee meeting, the introduction of R^2 and OB have not meaningfully changed outcomes in 3L+ and 4L+ FL.** In 3L+ FL in HMRN, the median OS with R^2 and OB was just over a year ([redacted] months and [redacted] months respectively)[5]. Similar data for 4L+ FL show that, since the routine commissioning of R^2 and OB, survival outcomes have not changed in practice (Figure 7). In summary, these results support the inclusion of patients across the HMRN time horizon in order to collect data for the largest possible sample size without materially impacting results.
- **Inclusion of patients recruited early in the HMRN dataset (as early as pre-2010) is appropriate as survival outcomes have not changed since their inclusion.** All patients in the HMRN dataset were relapsed or refractory and were available to receive R-based therapies. In 3L+ FL, patients recruited before 2010 (n=[redacted]) had a median OS of [redacted] months. In 4L+ FL, the median OS was not reached for these patients (n=[redacted]). These

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	anomalous outcomes are likely a function of the small sample size pre-2010. As such, excluding patients who were recruited earliest in the HMRN dataset would likely improve cost-effectiveness results for epcoritamab. • **Despite the small sample size for 4L+ FL in HMRN (n=36 patients), outcomes are consistent with clinical opinion, including one expert within the HMRN network, and have been validated by corresponding 3L+ FL data.** In a larger sample size of [redacted] patients with relapsed or refractory 3L+ FL, survival outcomes were [redacted] months. There is extensive literature to demonstrate deteriorating outcomes following each line of therapy. As such, it is unsurprising that the median OS in 4L+ FL is [redacted] months. Further details on the outcomes of patients with 3L+ FL in HMRN can be found in the HMRN report in the reference pack. • **Whilst acknowledging the longer median follow-up of HMRN relative to EPCORE-NHL 1, a MAIC between both data sources is considered suitable and reliable and aligns with previous NICE precedence.** Retrospective studies, by design, have longer follow-up than recently initiated trials. In HMRN, due to the high number of mortality events within the first couple of years, follow-up calculations are based on a very small number of patients (as all data are censored at the time of death). For example, by the median follow-up of the Dose Expansion cohort ([redacted] months), approximately [redacted]% of patients in HMRN had died. At Year 4 in HMRN, follow-up calculations are based on [redacted] patients who survived and were not lost to follow-up. Despite this inherent uncertainty with differing follow-up, a MAIC between both data sources is suitable and reliable.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	Figure 7: HMRN 4L+: OS/ PFS for patients initiating 4L+ treatment ≥2020 vs. <2020 (inc. Kaplan-Meier curves)  Note: Of the [redacted] patients who were followed-up after 2020, none had a COVID-19 related death in the HMRN dataset. As such, mortality events cannot be censored for the confounding nature of the pandemic.
6	**AbbVie have explored alternative variables within the MAIC in multiple scenarios. Analyses show that the current base-case is robust while maintaining the effective sample size (ESS).** The committee correctly draws attention to uncertainty in the MAIC, particularly noting the challenges comparing real-world data with outcomes from a single-arm trial, such as EPCORE NHL-1. Below, we have sought to provide clarity on the justification for the base-case MAIC by comparing outcomes with scenarios requested by the committee in the Draft Guidance. • **Further exploration of refractory disease in the MAIC yields improved outcomes for epcoritamab compared with the base-case approach.** In their Draft Guidance, the Committee requested "*a full exploration of prognostic factors, especially for people with refractory disease*". During the Clarification Questions stage, AbbVie presented a scenario (CQ A24) accounting for alternate definitions for refractory disease. We have since conducted a further scenario in response to Draft Guidance to account for all available refractory variables. Analyses show that OS and PFS outcomes for epcoritamab improve compared with the base-case MAIC. These improvements come at the expense of a smaller ESS, down from

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	N=40 to N=31 and N=26 for each respective scenario. AbbVie prefer the Company base-case at submission; such an approach represents a pragmatic balance between adjusting for prognostic variables and accounting for the ESS. Further details on the scenarios that had been explored are presented in Appendix 6. • **Improvements in MAIC outcomes for epcoritamab are not unexpected as patients are adjusted to be less refractory and fitter than in the unadjusted data.** Relative to the unadjusted data, the adjusted epcoritamab characteristics are younger (69.1% aged ≥ 60 to [redacted]%) less refractory (76.5% to [redacted]% and 74.1% to [redacted]%), and had fewer prior lines of therapy ≥4 (49.4% to [redacted]%). By match-adjusting to a relatively healthier population, OS and PFS outcomes would expect to improve compared with unadjusted data. This observation is also reflected in the scenarios that we have explored at Clarification Questions in response to Draft Guidance. • **The base-case ESS in the MAIC is consistent with other relevant appraisals in lymphomas that used HMRN for informing comparative outcomes.** The base-case ESS presented in this appraisal (N=40) is similar to that in TA1001, where after adjusting for 5 variables that had been captured in HMRN, the ESS was approximately N=40.[6] Separately, a recent review of MAICs conducted in oncology appraisals found that after adjusting, there was on average a ~45% reduction in the starting sample size. A similar reduction had been observed in the Company base-case MAIC for this appraisal. We have presented "*a full exploration of prognostic factors, especially for people with refractory disease*" in response to Draft Guidance and at Clarification Questions. In 3L+ and 4L+ FL, OS and PFS improves for epcoritamab when considering refractory variables; however this comes at the expense of a lower ESS compared with the base-case. The base-case approach yields pragmatic outcomes while maintaining a more robust ESS compared with the explored scenarios. Nevertheless, if these scenarios were used directly within the model, we would expect them to result in more favourable ICERs for epcoritamab than with the base-case MAIC. Whilst we acknowledge the challenges of comparing trial-based cohorts with real-world cohorts, the HMRN data have been effectively utilised in this way in various prior NICE appraisals,[6] and we have sought to explore uncertainty around the conduct of the indirect comparisons as thoroughly as possible and the alignment of populations before estimating relative effects.
7	**AbbVie has considered a simulated treatment comparison (STC) to validate the MAIC as requested by the committee. However, given time limitations, other requested analyses were prioritised. The decision to conduct a MAIC over an STC considered various factors, including precedent in prior appraisals, the degree of overlap between population characteristics, the number of observed events, and variables requiring adjustment.** Section 3.7 of the Draft Guidance states that '*The Committee concluded that the Company's technical approach to the indirect treatment comparison was appropriate. But it noted that a simulated treatment comparison may be possible, and it would like to see this analysis to validate the matching adjusted indirect treatment comparison.*'

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	We acknowledge the Committee's request to further explore the feasibility of a STC and appreciate the opportunity to consider this approach. Considering the volume of additional analyses and requests highlighted in the Draft Guidance, we have aimed to strike a balance between providing as much additional information as feasible with the desire to, considering the time constraints, prioritise analyses that are most pressing to the overall submission. In response, we have carefully reviewed the methodological suitability of an STC within the context of the trial characteristics and outcomes. The decision to prioritise a MAIC over an STC has been taken considering various factors, including precedent in prior NICE TAs, the degree of overlap between population characteristics (STC is generally considered more useful where covariate overlap is poor), the number of observed events, the number of variables requiring adjustment and the preservation of effective sample size. MAIC approaches are generally considered more appropriate than STCs when there is high covariate overlap between two populations. This has been demonstrated in the base-case MAIC for this appraisal. After adjusting for 10 covariates, the ESS was effectively half of the overall 4L+ FL population (N=40). In 3L+ FL, the ESS was even greater (N=79; ~60% of trial population). Prior appraisals that used a MAIC to compare with HMRN showed much lower covariate overlap. For example in TA1001, a similar ESS was achieved (approximately N=40; ~50% trial population) after only adjusting for 5 covariates to match HMRN data.[6] Additionally and as discussed in the Company Submission, STC analyses rely on the number of events (not the number of patients) to determine the degrees of freedom; the lower the number of events, the lower the number of predictors that can be included in the model. Methodological guidance indicates that time-to-event regression models should include at least around 10 events per covariate to ensure stable and unbiased estimates.[7] Given that there were only 25 OS and 37 PFS events in the 4L+ COVID-modified Dose Expansion dataset, this would permit adjustment for only 2-3 covariates, which is insufficient to capture key prognostic and effect-modifying variables. Substantially more events would need to be captured to provide any certainty in STC outcomes. Including additional covariates when there are so few events would risk model overfitting and unreliable treatment effect estimates. As such, a decision was made to prioritise additional MAIC analyses, which have stronger precedent in the disease area and are better suited to the available data. These additional MAIC scenarios are detailed in Response 6.
8	**CAR-T therapy is not routinely available for FL in the UK and so cannot be costed in the model. Separate analyses removing and censoring patients who had subsequent CAR-T therapy showed the impact to be minimal, and so the Company base-case extrapolations for epcoritamab are suitable for decision-making.** The question of subsequent CAR-T therapy use is a relevant consideration. The EAG and Committee have hypothesised that because a small number of patients in the trial received subsequent CAR-T therapy that this may be associated with some undue influence on extending long-term survival outcomes of patients treated with epcoritamab. The impact of CAR-T therapy on outcomes has been explored in multiple ways: • **Removing patients who received subsequent CAR-T, as requested in the Draft Guidance, has a minimal impact on overall survival outcomes in 3L+ and 4L+ FL.** OS outcomes after removing patients who

received subsequent CAR-T were very similar to the ITT population for 3L+ and 4L+ FL. The respective hazard ratios (HRs) were [redacted] (95% CI: [redacted], [redacted]) and [redacted] (95% CI: [redacted], [redacted]). However, such an approach for accounting for subsequent CAR-T may introduce bias into the analysis of OS with epcoritamab. Additionally, it would mean that important data are excluded from PFS estimates leading to improved PFS outcomes for epcoritamab compared with the ITT population.

- **An alternate analysis, censoring patients at initiation of their subsequent CAR-T, also confirmed the impact to be minimal.** This approach would retain pre-progression outcomes while still accounting for the impact of subsequent CAR-T. When compared with the 3L+ and 4L+ ITT analyses, the HRs were [redacted] (95% CI: [redacted], [redacted]) and [redacted] (95% CI: [redacted], [redacted]) respectively. This indicates almost identical OS data after censoring for subsequent CAR-T. As such, and given the minor impact of subsequent CAR-T on outcomes, the company base-case was maintained for modelling. Further details are provided in Appendix 7. The 3L+ and 4L+ FL ITT OS curves with both subsequent CAR-T scenarios are presented in Figure 8 and
-
-

- Figure 9.
- **In the base-case MAIC, the Dose Expansion cohort had already been matched to HMRN data and UK practice using the variable "prior CAR-T."** The adjusted epcoritamab sample included 0% for prior CAR-T (presented as Table 28 in the CS). We would like to clarify that these patients had not been "*censored in the matching adjusted indirect comparison*" as had been described in the Draft Guidance. The EAG correctly note that patients "*were not censored in the unadjusted trial data that was used to model outcomes for treatment at fourth line or later in the company model.*" The updated base-case model curves for epcoritamab now adjust for the variables in the MAIC, including for patients with "prior CAR-T."

The various censoring approaches are presented below and in Appendix 7. It can be concluded that the inclusion of a small number of patients who received subsequent CAR-T therapy has very little impact on the OS estimate for patients

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

	treated with epcoritamab, and as such, the Committee should have confidence that this is not a meaningful area of uncertainty. **Figure 8: 4L+ OS KM data with subsequent CAR-T censored and removed at baseline** 

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Figure 9: 3L+ OS KM data with subsequent CAR-T censored and removed at baseline

References

1. Network NCC. Follicular Lymphoma. 2024. Available from: https://www.nccn.org/patients/guidelines/content/PDF/nhl-follicular-patient.pdf.
2. Ghione P, Palomba ML, Ghesquieres H, et al. Treatment patterns and outcomes in relapsed/refractory follicular lymphoma: results from the international SCHOLAR-5 study. Haematologica. 2023;108(3):822.
3. Salles G, Schuster SJ, Fischer L, et al. A retrospective cohort study of treatment outcomes of adult patients with relapsed or refractory follicular lymphoma (ReCORD-FL). Hemasphere. 2022;6(7):e745.
4. Hao Y, Hsu W-C, Parzynski CS, et al. Effectiveness of tisagenlecleucel versus real-world standard of care in relapsed/refractory follicular lymphoma. Journal of Comparative Effectiveness Research. 2023;12(7):e220173.
5. Haematological Malignancy Research Network. Clinical Management and Outcome in Follicular Lymphoma to understand survival outcomes, clinical characteristics, and management of patients with relapsed/refractory Follicular Lymphoma (FL) receiving at least their fourth-line standard of care [Data on File]. 2025.
6. National Institute for Health and Care Excellence. Zanubrutinib for treating marginal zone lymphoma after anti-CD20-based treatment (TA1001). 2024.
7. van Domburg R, Hoeks S, Kardys I, et al. Tools and techniques—statistics: how many variables are allowed in the logistic and Cox regression models. EuroIntervention. 2014;9(12):1472-3.
8. Phillippo D A. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
9. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolations with patient level data. 2011.
10. Wild D, Walker M, Pettengell R, et al. Pcn62 Utility Elicitation in Patients with Follicular Lymphoma. Value in Health. 2006;9(6).
11. Casulo C, Larson MC, Lunde JJ, et al. Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study. The Lancet Haematology. 2022;9(4):e289-e300.
12. Coiffier B, Osmanov EA, Hong X, et al. Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naive or rituximab-sensitive, follicular lymphoma: a randomised phase 3 trial. The Lancet Oncology. 2011;12(8):773-84.
13. Wästerlid T, Dietrich CE, Oksanen A, et al. Treatment sequencing and impact of number of treatment lines on survival in follicular lymphoma: A national population-based study. eJHaem. 2024;5(3):516-26.
14. Salles G, Schuster SJ, Dreyling M, et al. Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma. Blood advances. 2022;6(22):5835-43.
15. Johnson PC, Bailey A, Ma Q, et al. Quality of Life Evaluation in Patients with Follicular Cell Lymphoma: A Real-World Study in Europe and the United States. Advances in therapy. 2024;41(8):3342-61.
16. Johnson PC, Abramson JS, LaCasce AS, et al. Longitudinal Patient-Reported Outcomes in Older Adults With Aggressive Lymphomas Receiving Chemoimmunotherapy. Journal of the National Comprehensive Cancer Network. 2025;23(3).
17. Vitolo Uea. EPCORITAMAB MONOTHERAPY DEMONSTRATES DEEP AND DURABLE RESPONSES AT 3-YEAR FOLLOW-UP IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA. 2025. Available from: https://library.ehaweb.org/eha/2025/eha2025-congress/4160287/.
18. National Institute for Health and Care Excellence. Lenalidomide with rituximab for previously treated follicular lymphoma (TA627). 2020. Available from: https://www.nice.org.uk/guidance/ta627.

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [redacted]' in turquoise, and all information submitted as '[redacted]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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 comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on Friday 14 November 2025. Please submit via NICE Docs.

Appendix Contents

Appendix 1: Cost-effectiveness model scenarios

Curve choices

Table 1 below presents the various curves selected to run both base case and scenario analyses described in these appendices and the primary draft guidance response document. In base case analyses where the MAIC is used to derive HMRN outcomes, hazard ratios are applied to the MAIC-reweighted epcoritamab survival, with the exception of TTD, where both epcoritamab and HMRN data are extrapolated directly. For inverse hazard ratio scenarios, curves are fit to the HMRN data with the inverse hazard ratio applied to derive epcoritamab outcomes (again with the exception of TTD, which is independently modelled for both arms).

Table 1: Curve selections for 3L+ and 4L+ base case and scenario analyses

	3L+ COVID adjusted	3L+ non-COVID adjusted	3L+ Omicron adjusted	4L+ COVID adjusted	4L+ non-COVID adjusted	4L+ Omicron adjusted
Reweighted Epcor OS	Log-normal	Log-logistic	Log-normal	Log-normal	Log-normal	Log-normal
HMRN OS	Log-normal	Log-normal	Log-normal	Log-normal	Log-normal	Log-normal
Reweighted Epcor PFS	Log-normal	Log-normal	Log-normal	Log-normal	Log-normal	Log-normal
HMRN PFS	Weibull	Weibull	Weibull	Log-normal	Log-normal	Log-normal
Reweighted Epcor TTD	Log-normal	Log-normal	Log-normal	Log-normal	Log-normal	Log-normal
HMRN TTD	Log-logistic	Gen-gamma	Gompertz	Exponential	Exponential	Exponential

PFS, progression free survival; OS, overall survival; TTD, time to discontinuation

4L+

Scenario analysis: Inverse hazard ratios (HR) applied to HMRN data

In their Draft Guidance, the Committee expressed a preference "*to see hazard ratios from the indirect comparison applied to comparator survival curves to generate the survival curves for epcoritamab*." To explore the impact of using the 4L+ HMRN data to inform outcomes for the epcoritamab arm, AbbVie has performed an analysis

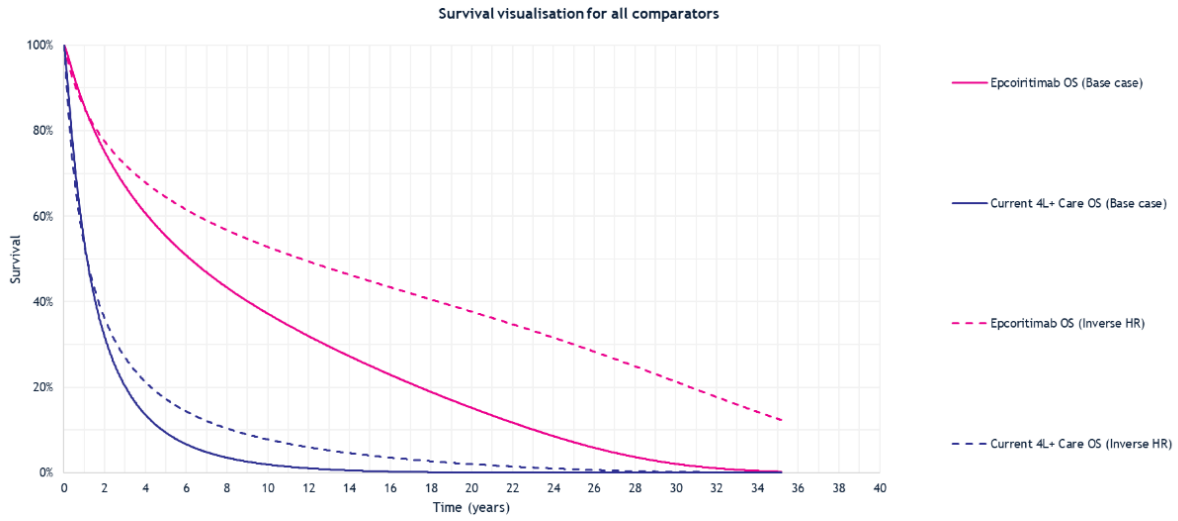
whereby the inverse hazard ratios from the matching adjusted indirect comparison (MAIC) are applied to the extrapolated HMRN curve to inform survival outcomes for patients treated with epcoritamab.

This scenario analysis applies the most appropriate extrapolations for HMRN based on goodness-of-fit statistics, plausibility of long-term extrapolations and alignment with clinical opinion. These curve choices are also aligned with the EAG preferences for extrapolating data from HMRN, as described in the Draft Guidance Section 3.9:

- PFS – Log-normal
- OS – Log-normal
- TTD – Exponential

The inverse of the hazard ratio is then applied to the comparator arm to derive outcomes for epcoritamab. The OS outputs of this analysis are presented in Figure 1, demonstrating a greater relative difference in OS outcomes between epcoritamab and current 4L+ care than observed in the base case analyses where the MAIC is used to derive HMRN outcomes. Of note is that both approaches yield survival outcomes for epcoritamab that are poorer than outcomes from the Dose Optimisation Cohort (as is presented in response to Topic 3 above (Figure 4), where it is clearly shown that Dose Optimisation Cohort survival sits above the modelled extrapolation from the company analyses of the Dose Expansion Cohort). Nevertheless, AbbVie prefers to use the standard approach of using the MAIC to derive HMRN outcomes as it aligns with what the Committee has accepted in previous NICE appraisals.

Figure 1: Comparison of OS outcomes for epcoritamab and current 4L+ care, where inverse hazard ratios applied to 4L+ HMRN data are used to derive OS and PFS for epcoritamab



The outputs of this cost-effectiveness analysis are provided in Table 2 and demonstrate that under this scenario, the ICER is [redacted], which compares with an ICER of [redacted] in the base case analysis.

Table 2: Scenario analysis: Inverse HR applied to 4L+ HMRN data

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Inverse HR applied to HMRN	Epcoritamab	[redacted]	15.079	7.063	[redacted]	12.082	5.292	[redacted]
	Current 4L+ Care	[redacted]	2.997	1.771	-	-	-	-

Analysis performed using epcoritamab PAS price and using Committee preferred assumptions (but applying inverse HR to derive outcomes for epcoritamab using proportional hazards assumption)
Costs and QALYs discounted; LYs undiscounted
No severity modifier applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

3L+

Scenario analysis: Inverse hazard ratios (HR) applied to HMRN data

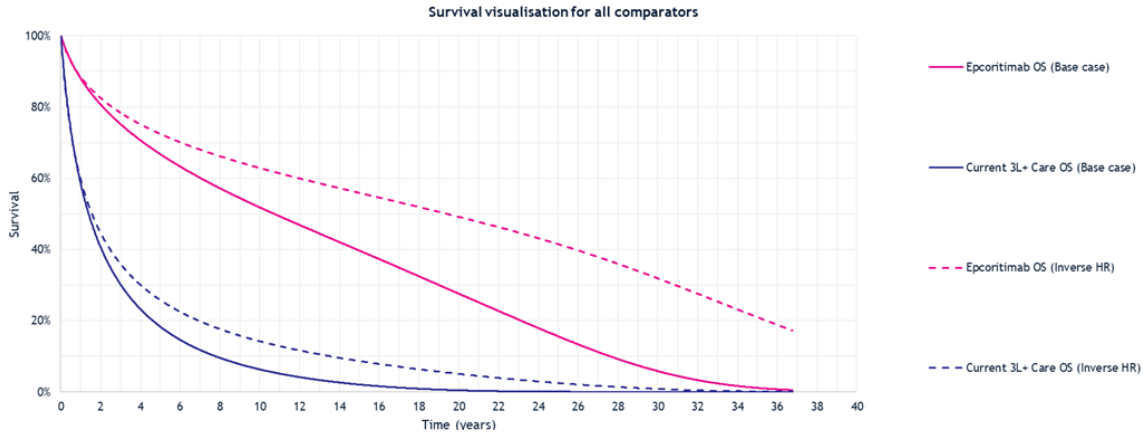
Similar to the 4L+ scenario presented above and at the Committee's preference, AbbVie have explored the impact of using the 3L+ HMRN data to inform outcomes for the epcoritamab arm by applying the inverse hazard ratios to the extrapolated HMRN curve to inform survival outcomes for patients treated with epcoritamab.

Like the 4L+ analysis above, this scenario analysis applies the most appropriate extrapolations based on goodness-of-fit statistics, plausibility of long-term extrapolations and alignment with clinical opinion. The Weibull model for PFS had the lowest AIC/BIC and good visual fit to the KM. For OS, the generalized gamma had the lowest AIC and the log-normal had the lowest BIC. The generalized gamma produced extrapolations that were not clinically plausible based on conversations with clinicians while the log-normal produced an extrapolation more in line with expectations. Similarly, although the gompertz distribution had the lowest AIC/BIC, it produced an extrapolation which has a tail that might be considered too optimistic for HMRN TTD. The log-logistic has the second lowest AIC/BIC and appears more clinically plausible.

- PFS – Weibull
- OS – Log-normal
- TTD – Log-logistic

The inverse of the hazard ratio is then applied to the comparator arm to derive outcomes for epcoritamab. The OS outputs of this analysis are presented in Figure 2:

Figure 2: Comparison of OS outcomes for epcoritamab and current 3L+ care, where inverse hazard ratios applied to 3L+ HMRN data are used to derive OS and PFS for epcoritamab



The outputs of this cost-effectiveness analysis are provided in Table 3 and demonstrate that under this scenario, the ICER is [redacted], which compares with an

ICER of [redacted] based on the standard approach of applying the MAIC HR to the epcoritamab.

Table 3: Scenario analysis: Inverse HR applied to 3L+ HMRN data

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Inverse HR applied to HMRN	Epcoritamab	[redacted]	18.814	8.217	[redacted]	14.410	5.603	[redacted]
	Current 3L+ Care	[redacted]	4.403	2.614	-	-	-	-

Analysis performed using epcoritamab PAS price and using Committee preferred assumptions (but applying inverse HR to derive outcomes for epcoritamab using proportional hazards assumption)
Costs and QALYs discounted; LYs undiscounted
No severity modifier applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

Scenario analysis: COVID-19

Section 2.2.13 of the Company Submission presents COVID-modified analysis for the 4L+ population; scenarios with COVID-unmodified analysis and Omicron-modified analysis are presented in Section 4 of the DGD consultation response. This section presents the same scenarios for the 3L+ population. In all scenarios, hazard ratios from the MAICs are applied to the epcoritamab reweighted data. Note that one other method for modelling COVID-19 deaths, IPCW, is provided in Appendix 4 for both 4L+ and 3L+ FL. For clarity, Table 4 below displays the impact of the COVID-19 pandemic in the respective populations.

Table 4: COVID deaths reported in EPCORE NHL-1 and HMRN

	Dose Expansion Cohort	HMRN
4L+	• [redacted] COVID-19 deaths overall • [redacted] COVID-19 deaths during Omicron wave	• No COVID deaths, so no adjustments necessary
3L+	• [redacted] COVID-19 deaths overall • [redacted] COVID-19 deaths during Omicron wave	• [redacted] COVID-19 deaths in follow-up between 2007-2023

The COVID-modified scenario uses the log-normal extrapolation for overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (TTD)

and assumes proportional hazards to model outcomes for the current 3L+ care arm (COVID-modified hazard ratios: HR = [redacted] for OS and HR = [redacted] for PFS). Similarly, the Omicron-modified scenario uses log-normal for OS, PFS and for TTD (omicron-modified hazard ratios: HR = [redacted] for OS and HR = [redacted] for PFS). There were few COVID-19 deaths in the 3L+ FL HMRN cohort (N=[redacted]). A 3L+ FL MAIC would not create a like-for-like comparison between datasets if COVID is not accounted for. This is because epcoritamab data are only available from 2020 onwards, whereas the HMRN dataset includes patients over a wider timeframe (i.e. 2007-2023 – the time from first 3L+ treatment to latest follow-up). Therefore, the impact of COVID-19 mortality would be reduced in HMRN compared with EPCORE NHL-1 as there are a large proportion of patients in HMRN that were not followed-up over the COVID pandemic. An approach to restrict the HMRN population to patients initiating 3L+ treatment after 2020 would yield a small sample size that makes any comparison uninformative. Additionally, the "*committee agreed that in principle the impact of COVID-19 should be accounted for*" and the post-pandemic Dose Optimisation data supports an approach to account for COVID-19 mortality. Nonetheless, a COVID-unmodified scenario has been explored. The COVID-unmodified scenario uses log-logistic for OS, log-normal for PFS and log-normal for TTD and also assumes proportional hazards to model outcomes for the current 3L+ care arm (COVID-unmodified hazard ratios: HR = [redacted] for OS and HR = [redacted] for PFS). The outcomes of all these scenario analyses are presented in Table 5.

Table 5: Scenario analysis: Alternative methods to modifying for COVID-19 deaths in 3L+

		Total			Incremental			
		Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER (£/QALY)**
COVID-modified	**Epcoritamab**	[redacted]	12.628	6.217	[redacted]	9.757	4.362	[redacted]
	Current 3L+ Care	[redacted]	2.871	1.855	-	-	-	-
Omicron-modified	**Epcoritamab**	[redacted]	11.230	5.635	[redacted]	8.515	3.844	[redacted]
	Current 3L+ Care	[redacted]	2.714	1.791	-	-	-	-
	Epcoritamab	[redacted]	6.410	4.414	[redacted]	4.144	2.557	[redacted]

COVID-unmodified	**Current 3L+ Care**	[redacted]	2.266	1.857	-	-	-	-

Analysis performed using epcoritamab PAS price and using Committee preferred assumptions (but retaining company's preference for MAIC to derive comparator outcomes and fully COVID-modified outcomes for epcoritamab)
Costs and QALYs discounted; LYs undiscounted
Severity modifier of ×1.2 applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

Appendix 2: Summary of 3L+ cost-effectiveness modelling

Survival analysis

As described in the base case for 4L+, the proportion of patients in the PFS, PD, and Death health states at each cycle in the model is determined by PFS and OS curves using data from the dose expansion part of EPCORE NHL-1. As this exploratory analysis compares the outcomes for epcoritamab with current 3L+ care over a lifetime horizon, longer than the follow-up duration available from EPCORE NHL-1 and HMRN, the MAIC-reweighted survival curves required extrapolation. These analyses consider COVID-modified outcomes from EPCORE NHL-1, aligned with the 4L+ modelling base case.

Extrapolation of survival outcomes

To extrapolate survival outcomes over the lifetime horizon, standard parametric curves (exponential, gamma, generalized gamma, gompertz, log-normal, log-logistic, and Weibull) were fitted to the MAIC-reweighted epcoritamab PFS, OS, and TTD curves as per NICE TSD14.[9]

Curve selection was performed according to the same criteria as described in Section 3.3.2.2 of the Company Submission, namely consideration of Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), comparison of visual fit, assessment of the underlying hazard profile observed from smoothed hazard plots, plausibility of long-term suggestions, and alignment with landmark survival estimates obtained during consultation with UK clinical experts.

Overall survival

Parametric distributions were applied to the observed OS data from EPCORE NHL-1 using the methodology described previously. As observed in Figure 1, all distributions fit well to the observed KM curve and remained within the 95% confidence interval.

Figure 1: Long-term OS estimates of standard parametric distributions fit to epcoritamab data re-weighted to HMRN characteristics

Cut-off date: [redacted], Median follow-up = [redacted],
OS, overall survival

Based on the AIC and BIC values (Table 1), the exponential distribution provided the best statistical fit to the observed data. However, all curves demonstrated acceptable and comparable fit.

Table 1: AIC and BIC values of standard parametric distributions fit to re-weighted epcoritamab and HMRN OS data

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

Cut-off date: [redacted], Median follow-up = [redacted] months
AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

The long-term OS predictions varied across distributions. The Log normal model generated the most optimistic survival estimates, while the Generalized gamma producing the most pessimistic outcomes.

Table 2: Landmark estimates of long-term survival for re-weighted epcoritamab OS data from EPCORE NHL-1 (3L+)

Distribution	Median (months)	24 months	48 months	60 months	120 months
Observed Epcoritamab data re-weighted to HMRN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cut-off date: [redacted], Median follow-up = [redacted] months
CI, confidence interval; NR, not reached; OS, overall survival

Additional clinical validation exercises were undertaken with four UK clinical experts in order to elicit estimates of long-term survival for patients treated at 3L+. These were performed following guidance from TSD26, the result of which are provided in Table 3.

Table 3: Clinician estimates of long-term OS for patients treated with epcoritamab and Current Care (3L+)

Epcoritamab	Lower plausible limit	Most likely value	Upper plausible limit
5 years	53%	61%	67%
10 years	30%	42%	51%
Current Care	**Lower plausible limit**	**Most likely value**	**Upper plausible limit**
5 years	13%	**25%**	36%
10 years	2%	**13%**	25%

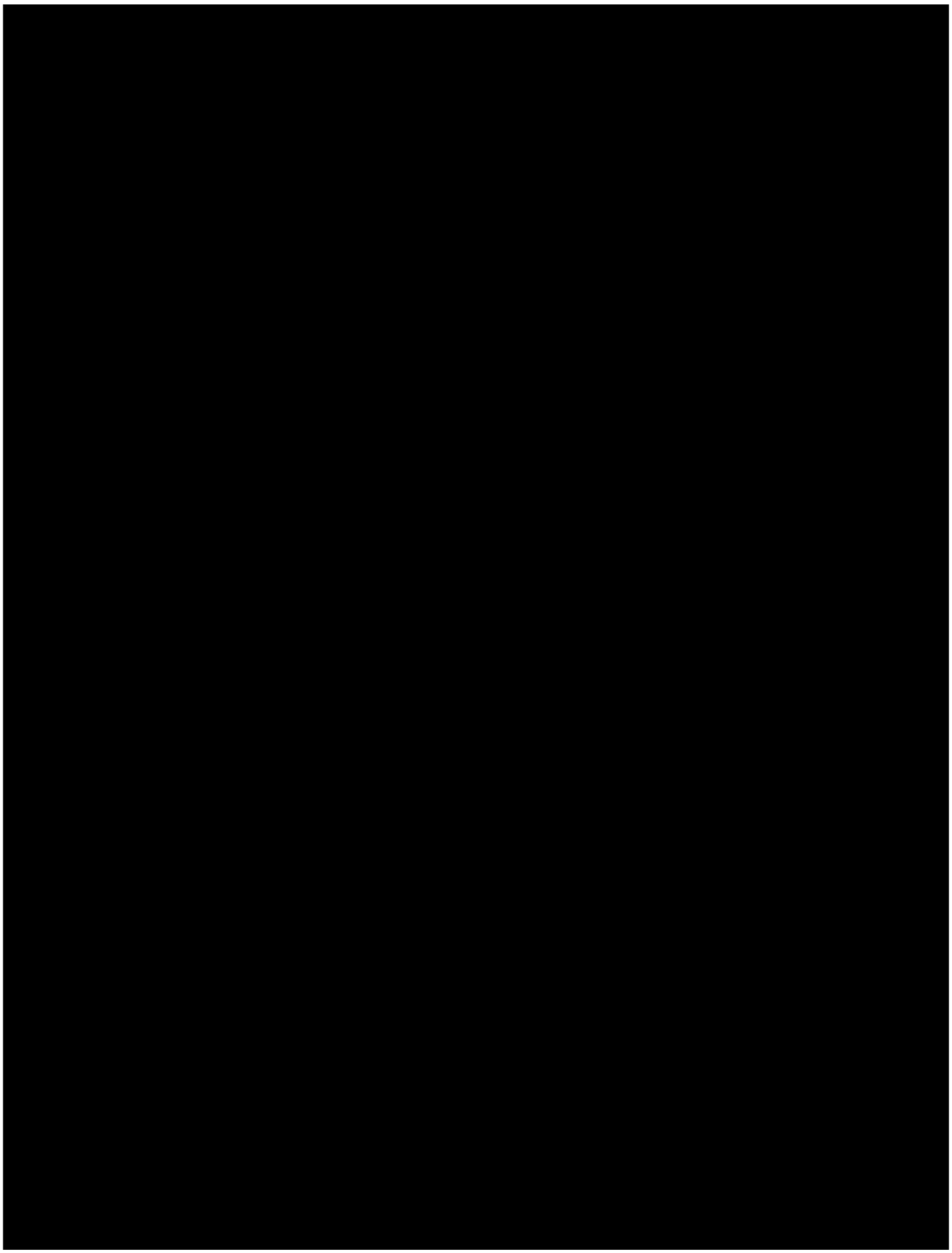
Estimates based on individual interviews with UK clinical experts
OS, overall survival

Among the models, the log-normal distribution provided a reasonable fit to the EPCORE NHL-1 data, and yielded long-term OS extrapolations consistent with clinical estimates, whereas the exponential distribution, which had the lowest AIC and BIC, is overly pessimistic compared with clinician estimates. With regards to the smoothed hazard plots shown in Figure 2, it is observed that the hazard for epcoritamab OS is neither constant nor monotonic (which was also supported by

Draft guidance comments form, Appendix 2 [ID6338]

clinicians given the expectation of strong survival outcomes for those with CR), excluding the selection of the exponential and Weibull models.

Figure 2: Hazard plot of all distributions fit to re-weighted epcoritamab OS data



Cut-off date: [redacted], Median follow-up = [redacted] months,
OS, overall survival

Considering all (visual, statistical and clinical) data available, the log-normal distribution is considered the most appropriate for extrapolating OS in the base case analysis as it provides a reasonable fit to the observed Kaplan-Meier data and produces clinically plausible long-term outcomes.

Progression-free survival

Parametric distributions were applied to the MAIC-reweighted PFS data from EPCORE NHL-1 using the methodology described previously. As observed in Figure 3, the gompertz and generalized gamma distributions followed the observed data most closely, with both remaining within the 95% confidence interval for the entire observed period. While the gompertz distribution predicted a plateauing PFS, the log-normal and generalised gamma distributions offer more clinically plausible projections.

Figure 3: Long-term PFS estimates of standard parametric distributions fit to epcoritamab data re-weighted to HMRN characteristic

Cut-off date: [redacted], Median follow-up = [redacted] months,
PFS, progression-free survival

Based on AIC and BIC values (Table 4), the gompertz and Generalized gamma distributions provided the best statistical fit. The next lowest AIC/BIC was for the log-normal.

Table 4: AIC and BIC values of standard parametric distributions fit to re-weighted epcoritamab and HMRN PFS data

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

Cut-off date: [redacted], Median follow-up = [redacted] months,
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

The survival estimates generated from the gompertz distribution have a minimal decline over time; thus, these estimates may be less clinically plausible. The generalized gamma distribution provides a comparable survival estimate at 24 months and tends to produce more optimistic . The log-normal and log-logistic curves provide very similar survival estimates and were broadly aligned with clinician feedback (Table

Table 5).

Table 5: Landmark estimates of long-term survival for re-weighted epcoritamab PFS data from EPCORE NHL-1

Distribution	Median (months)	24 months (%)	48 months (%)	60 months (%)	120 months (%)
Observed Epcoritamab data re-weighted to HMRN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cut-off date: [redacted], Median follow-up = [redacted] months
CI, confidence interval; NR, not reached; PFS, progression free survival

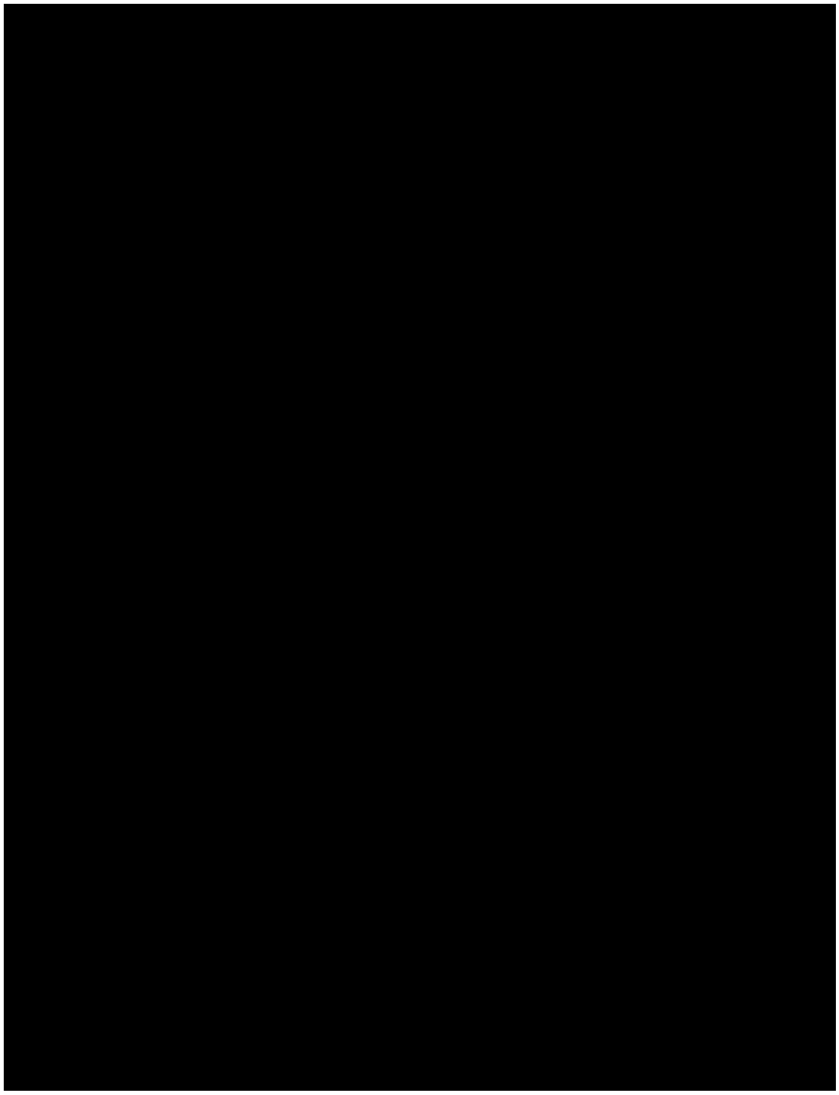
Table 6: Clinician estimates of long-term PFS for patients treated with epcoritamab and Current Care (3L+)

Epcoritamab	Lower plausible limit	Most likely value	Upper plausible limit
5 years	39%	49%	57%
10 years	27%	33%	43%
Current Care	**Lower plausible limit**	**Most likely value**	**Upper plausible limit**
5 years	9%	**19%**	28%
10 years	1%	**7%**	14%

Estimates based on individual interviews with UK clinical experts
PFS, progression free survival

With regards to the smoothed hazard plots shown below in Figure 4, hazards are the highest at the beginning of the trial period, which is consistent with the biological rationale that the treatment effect may not be observed immediately at the start of the trial. Relating to the extrapolations, gompertz and log logistic distributions follow the observed smoothed hazard the best when compared with the rest of the distributions.

Figure 4: Smoothed hazard plot of epcoritamab PFS data



Cut-off date: [redacted], Median follow-up = [redacted] months,
PFS, progression free survival

In full consideration of the available evidence, the log-normal distribution is selected as the most appropriate and conservative choice, balancing reasonable statistical fit with clinical plausibility.

Time to treatment discontinuation

As observed in Figure 5, all fitted distributions follow the data well and mostly fell within the 95% confidence interval estimates of survival.

Figure 5: Long-term extrapolation of re-weighted epcoritamab TTD data

Cut-off date: [redacted], Median follow-up = [redacted] months
TTD, time to treatment discontinuation

Based on AIC and BIC values, the log-normal or exponential appeared to be the best fitting distributions (Table 7).

Table 7: AIC and BIC values of standard parametric distributions fit to re-weighted epcoritamab TTD data

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

Cut-off date: [redacted], Median follow-up = [redacted] months
Best-fitting distributions are in green font colour
Values shaded in green denote AIC/BIC values that are ≤ 2 from the best-fitting distribution
AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation

When observing the long-term estimates, the exponential, gamma, and Weibull distributions have comparable, conservative long-term time to treatment discontinuation estimates, whereas long-term estimates produced by the generalized log-normal and log-logistic distributions are the most optimistic. The remaining

distributions predict a long-term TTD that falls between the most conservative and most optimistic distribution.

Table 8: Landmark estimates of long-term survival for re-weighted epcoritamab TTD data from EPCORE NHL-1

Distribution	Median (months)	24 months (%)	48 months (%)	60 months (%)	120 months (%)
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cut-off date: [redacted], Median follow-up = [redacted] months
CI, confidence interval; NR, not reached; TTD, time to treatment discontinuation

Based on the best statistical fit and the reasonable extrapolations and landmark estimates, the log normal distribution is recommended to model re-weighted epcoritamab TTD data.

Assessing the proportional hazards assumption

The proportional hazards assumption (PHA) was assessed using the same criteria as described in Section 3.3.2.1 of the Company Submission.

The results of all tests described in Table 9 indicate that the PHA is likely to hold for both OS and PFS; therefore, in line with the guidance within TSD14, applying constant HRs is suitable in all cases for long-term extrapolations.[9]

Scenario	Outcome	Log-cumulative hazard plots	Schoenfeld residuals plot‡	Grambsch - Therneau test†	PHA violated ?	HR applied	p-value
Epcoritamab vs Current 3L+ Care	OS	Parallel	Time-independent	[redacted]	No	[redacted]	[redacted]
	PFS	Parallel	Time-independent	[redacted]	No	[redacted]	[redacted]

Table 9: Assessing the PHA for epcoritamab compared with HMRN (3L+)

† p value > 0.05, no evidence to reject PHA
‡ if the covariate is time-independent, no evidence to reject PHA
HMRN, Haematological Malignancy Research Network; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PHA, proportional hazards assumption

Figure 6: Assessing the PHA for epcoritamab compared with HMRN (3L+)

OS, overall survival; PFS, progression free survival

Based on the results in Table 10 and Figure 6, PFS and OS outcomes for current 3L+ care are derived by applying the MAIC-adjusted hazard ratios (HRs) to the adjusted epcoritamab data, ensuring comparability between treatment arms in an EPCORE NHL-1 trial population.

Selection of variables for MAIC adjustment in 3L+ population

In line with the 4L+ analysis presented in the Company Submission, variables selected for adjustment in the unanchored matching-adjusted indirect comparison (MAIC) were identified after careful consideration with UK clinical experts, balancing the need to align populations between evidence sources, reporting limitations and the desire to preserve effective sample size.

A summary of the considerations for selecting the variables is presented in Table 10.

Table 10: Selection of prognostic variables and treatment effect modifiers

Characteristic	Level	Recommended by clinical experts?	Prognostic variable or effect modifier in EPCORE NHL-1?		Available at 3L+ for HMRN?	Reason for Inclusion/Exclusion?
		Y/N	PFS at 36 months?	OS at 36 months?		
Age	< 65 ≥ 65 ≥ 60	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted] **FLIPI component** Adjusted in TA627
ECOG PS	0 1 2	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted], **Data only available at diagnosis in HMRN so unable to accurately adjust for this. Adjusting towards a value from diagnosis would bias in favour of epcoritamab**
FLIPI	0-1 2 ≥3 Unknown	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted]**Data only available at diagnosis in HMRN so unable to accurately adjust for this. Adjusting towards a value from diagnosis would bias in favour of epcoritamab**
Stage	1-2 3-4	-	[redacted]	[redacted]	[redacted]	Not recommended explicitly by clinicians due to being superseded by the importance of FLIPI [redacted] **FLIPI component** Adjusted in TA627 [redacted]
Sex	F M Y	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians
Prior ASCT	N Y	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted]
Prior CAR T therapy	N Y	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians
Prior Lines	2 3 >3 ≥4	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted]Adjusted in TA627 (prior lines of therapy [1 vs. 2 vs. >2])
Progression within	N Y	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians Adjusted for in TA627

24 months of first line CIT						
Refractory to both anti-CD20 and alkylator therapy	N	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted]
	Y					
Refractory to most recent anti-lymphoma therapy	N	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted]
	Y					
Prior R^2	N	Y	[redacted]	[redacted]	[redacted]	Recommended by clinicians [redacted] (P<0.25)Adjusted for prior rituximab-based treatment in TA627
	Y					

Variables highlighted in green were used for matching within the MAIC
As ECOG performance status and FLIPI were only available at diagnosis, these were not selected as matching covariates, in line with the rationale provided in TA1001.[6]
ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor therapy; CIT, chemoimmunotherapy; ECOG, eastern cooperative oncology group; FLIPI, follicular lymphoma international prognostic index; HMRN, Haematological malignancy research network; OS, overall survival; PFS, progression free survival; R^2 , lenalidomide + rituximab

Before adjustment, fewer EPCORE patients were of disease stage III-IV, but more of them were pre-treated with R^2, more were on higher number of prior therapy, and more were refractory than patients in HMRN. After match-adjusting the EPCORE population to current 3L+ care, the effective sample size decreased to ESS=79 compared with unadjusted N=128 (Table 11). Alternative matching approaches used to capture different refractory outcomes were explored in scenario analyses presented in the Draft Guidance Response.

Table 11: Baseline characteristics for Epcoritamab vs current 3L+ care

	Unadjusted Epcoritamab FL, no additional inclusion/exclusion criteria (N=128)	Adjusted Epcoritamab FL, no additional inclusion/exclusion criteria (N_{eff} =79) *	HMRN 3L+ (n=[redacted])
Age ≥ 60	64.8%	[redacted]	[redacted]
Male	61.7%	[redacted]	[redacted]
Disease stage III-IV (At baseline for EPCORE, at diagnosis for HMRN)	85.2%	[redacted]	[redacted]
Prior ASCT	18.8%	[redacted]	[redacted]
Prior CAR T	4.7%	[redacted]	[redacted]
Progression within 24 months after 1st line CIT	42.2%	[redacted]	[redacted]
Refractory to last prior therapy	68.8%	[redacted]	[redacted]
Refractory to any Anti-CD20 and an alkylator	70.3%	[redacted]	[redacted]
Prior lines of therapy ≥ 3	63.3%	[redacted]	[redacted]
Prior treatment with R^2	21.1%	[redacted]	[redacted]

* Match-adjusted for age ≥60,male, disease stage III-IV, prior ASCT, prior CAR T, POD24, refractoriness to last prior therapy, double refractory, prior treatment with R^2, and number of prior lines of therapy.
ASCT, autologous stem cell transplant; CAR T, chimeric antigen receptor (CAR) T-cell therapy; CIT, chemoimmunotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; N_{eff}, effective sample size

As was the case in the analyses conducted at 4L+, adjusted epcoritamab patient characteristics show slight improvements in fitness relative to the unadjusted epcoritamab baseline characteristics, mostly driven by a down-weighting of the number of prior lines, prior treatment with R2 and refractoriness.

Kaplan-Meier curves for the MAIC-unadjusted and -adjusted epcoritamab data and comparator data are presented below for both outcomes (Figure 7).

Figure 7: Unadjusted and adjusted overall survival and progression-free survival for EPCORE Epcoritamab (NHL-1) vs current 3L+ care (HMRN), COVID-adjusted in 3L+ indication

OS*

PFS IRC

	OS HR [95% CI]	p-value		PFS HR [95% CI]	p-value
Unadjusted	[redacted]	[redacted]	Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]	**Adjusted**	[redacted]	[redacted]

*The data used for epcoritamab for OS is still relatively immature (median follow-up [redacted] months). In particular, a large drop in OS is observed after [redacted] months due to a single event (death) in the curve. The number of patients at risk is extremely low at this point resulting in a very small at risk denominator and proportionally larger impact of this death event on the probability of survival at this point. This effect is exacerbated in the adjusted OS curve as a result of the weights applied to individual patient results. This part of the curve (around the 36 month timepoint) is likely not representative of the full anticipated OS benefit, and with more mature data (i.e., longer follow-up) the shape is expected to change towards the tail.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Other inputs

As aligned with the 4L+ model, and the Committee's preferred assumptions around estimation of health state utilities in the 4L+ setting, utility values are calculated based on EQ-5D data collected in EPCORE-NHL-1, which were mapped using UK-specific value sets. Progressed Disease (PD) utility was then adjusted using the decrement described in Wild et al. (2006).

Table 12: Utility values used in the 3L+ model

Utility setting	Value	Reference
EPCORE-NHL-1 health state utilities (adjusted PD using Wild et al. (2006) PD decrement)[10]		
Utility: Progression-free	[redacted]	EPCORE-NHL-1 trial; and Wild et al. (2006)
Utility: Progressed	[redacted]	

PD, progressed disease

Healthcare resource use inputs are aligned with the updated base case for the 4L+ model and includes weekly haematologist-led consultations in the first month of treatment with epcoritamab, followed by monthly consultation thereafter.

Aligned with the approach taken in the 4L+ analyses, incidence of Grade 3 and 4 adverse events occurring at a rate >5% of patients in any treatment arm are included within the model.

The same approach is taken to the costing of the Current 3L+ care treatment basket and to the costing of subsequent therapies. In both cases, as with the 4L+ model, a basket approach has been taken with proportions derived from HMRN.

Table 13: Current 3L+ treatment mix

Market shares of Current 3L+ care					
Current 3L+ Care and subsequent treatment mix	**Other immuno-chemotherapies (Bendamustine + obinutuzumab)**	**R-Chemo (R-Benda)**	**Chemotherapy (Chlorambucil)**	**R^2**	**Reference**
	[redacted]	[redacted]	[redacted]	[redacted]	HMRN

Appendix 3: EPCORE NHL-1 Dose Optimisation cohort, 9 December 2024 Data cut

1. Dose Optimisation 4L+ Cohort, 9 December 2024 Data cut

To provide extra context to aid decision making and to provide an insight into the efficacy of epcoritamab outside of the Omicron wave of the COVID-19 pandemic, AbbVie presented clinical data pertaining to the 8th January 2024 data cut-off of the Dose Optimisation Part of the EPCORE NHL-1 trial in Section 2.14 of the Company Submission. Since the Company Submission, a further data cut (9th December 2024, [redacted] months median follow-up) for the Dose Optimisation cohort has become available, the results of which are presented in this appendix for completeness. To reiterate, no deaths due to COVID-19 have been observed in the Dose Optimisation part of EPCORE NHL-1, and therefore, this data has not been modified.

The baseline characteristics of the Dose Optimisation 4L+ cohort can be found in the Company Submission, Section 2.14.2.

The results from the 9 December 2024 data cut were consistent with the 8th January 2024 data cut for the Dose Optimisation 4L+ cohort (Company submission, Section 2.14.4), demonstrating the sustained clinical benefits of epcoritamab in OS and PFS whilst observed TEAEs remained low.

1.1 Clinical effectiveness

Progression-free survival

Progression or mortality events were observed in approximately half ([redacted]%; [redacted] patients) of patients, with a median follow-up time of [redacted] months (Table 1, Figure 1). Of the evaluated patients at 12 months, [redacted]% remained progression-free and alive.

Table 1: Progression free survival, Dose Optimisation 4L+ FL Cohort

	Optimisation Part, Arm A 4L+ (N= 41)
Number of Events	[redacted]
Number Censored	[redacted]
Reason for censoring	
Clinical Cutoff	[redacted]
PFS (months)	
Median follow-up (95%CI)[a]	[redacted]
Median (95% CI)[b]	[redacted]
Estimated percentage of patients remaining progression-free (95% CI)[b]	
6-month	[redacted]
12-month	[redacted]
18-month	[redacted]

Data cut 9 December 2024, assessed by investigator. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval, NR, not reached

Figure 1: Kaplan-Meier plot of progression-free survival, Dose Optimisation 4L+ FL Cohort

Data cut 9 December 2024, assessed by investigator. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

Overall survival

Overall survival from the latest data cut is presented in Figure 2 and Table 2. Overall survival rates remained high in the 4L+ FL cohort with only [redacted] deaths ([redacted]%) observed as of the 9 December 2024 data cut, with a mean follow-up of [redacted] months. At 6- and

18-months, [redacted] events occurred, with [redacted]% and [redacted]% of patients remaining alive, respectively. [redacted] before the end of follow-up. Taken collectively, the data from the Optimisation Part of the EPCORE NHL-1 trial demonstrate the improved efficacy and safety of epcoritamab following the COVID-19 pandemic.

As discussed in Section 2.6.2.1 of the Company Submission, the majority of recruitment in the Dose Optimisation Part of EPCORE NHL-1 took place outside of the Omicron wave of the COVID-19 pandemic. As of the 9 December 2024 data cut, no COVID-19 associated deaths were recorded for the Dose Optimisation 4L+ cohort, further supporting how epcoritamab is expected to perform in a current clinical setting.

Table 2: Overall Survival, Dose Optimisation 4L+ Cohort

	Optimisation Part, Arm A
	4L+ **(N= 41)**
Number of Events	[redacted]
Number Censored	[redacted]
OS (months)	
Median follow-up (95%CI)[a]	[redacted]
Median (95% CI)[b]	[redacted]
Estimated percentage of patients remaining alive (95% CI)[b]	
6-month	[redacted]
12-month	[redacted]
18-month	[redacted]

Data cut 9 December 2024, assessed by investigator. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval, NR, not reached

Figure 2: Kaplan-Meier plot of Overall Survival, Dose Optimisation 4L+ FL cohort

Data cut 9 December 2024. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

1.2 Safety

Rates of TEAEs leading to treatment discontinuation remained low in the Dose Optimisation 4L+ cohort. This was reported in [redacted] patients ([redacted]%; [redacted] pneumonia pseudomonal, [redacted] myelodysplastic syndrome, [redacted] pneumonitis). A summary of Grade 3 and 4 TEAEs is presented in Table 3, of which the most frequent TEAEs were blood and lymphatic disorders ([redacted]%; [redacted] patients) and investigations ([redacted]%; [redacted] patients). No Grade 3-4 COVID-19 TEAEs were noted. TEAEs reported in the 9 December 2024 data cut were reported at similar or lower rates than those reported in Dose expansion Part of the trial, as presented in Section 2.13.3 of the Company Submission.

Table 3: Summary of serious Grade 3 and 4 TEAEs, Dose Optimisation 4L+ Cohort

	Optimisation Part, Arm A
	4L+ (N= 41)
Serious Grade 3 - 4 TEAEs	
Infections and infestations	[redacted]
Gastrointestinal disorder	[redacted]
Metabolism and nutrition disorders	[redacted]
Investigations	[redacted]
Immune system disorders	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Blood and lymphatic	[redacted]
Nervous system disorders	[redacted]
Eye disorders	[redacted]
Neoplasm benign, malignant and unspecified	[redacted]

Data cut 09 December 2024
Percentages calculated based on number of subjects in Safety Analysis Set.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ lass and only once per preferred terms.
TEAE, treatment emergent adverse events

2. Dose Optimisation 3L+ Cohort, 9 December 2024 Data cut

To further support the data presented in the Company Submission, data for the 3L+ FL cohort from the Dose Optimisation 9 December 2024 data cut are presented within this section. Baseline characteristics for the Dose Optimisation 3L+ cohort can be found in Appendix M.4, which accompanied the Company Submission.

2.1 Clinical effectiveness

Progression-free survival

Progression or a mortality event was observed in less than half of patients ([redacted]%; [redacted] patients), with a median follow-up of [redacted] months (Table 4, Figure 3). Of the evaluated patients, [redacted]% and [redacted]% remained progression-free at 6- months and 18-months, respectively.

Table 4: Progression free survival, Dose Optimisation 3L+ FL Cohort

	Optimisation Part, Arm A
	3L+ (N = 86)
Number of Events	[redacted]
Number Censored	[redacted]
Reason for censoring	
Clinical Cutoff	[redacted]
New anti-lymphoma therapy	[redacted]
Lost to follow-up	[redacted]
Subject withdrew consent	[redacted]
No post-baseline assessments	[redacted]
≥ consecutive missed tumour assessments	[redacted]
PFS (months)	
Median follow-up (95%CI)[a]	[redacted]
Median (95% CI)[b]	[redacted]
Estimated percentage of patients remaining progression-free (95% CI)[b]	
6-month	[redacted]
12-month	[redacted]
18-month	[redacted]

Data cut 9 December 2024, assessed by investigator. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval, NR, not reached

Figure 3: Kaplan-Meier Plot of progression-free survival, Dose Optimisation 3L+ FL

Data cut 9 December 2024. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

Overall survival

Overall survival for the 3L+ cohort from the 9 December 2024 latest data cut are presented in Table 5 and Figure 4. Only [redacted] deaths ([redacted]%) were observed, none of which were associated with COVID-19. A mean follow-up of [redacted] months was reported. At 6- and 18-months, [redacted]% and [redacted]% of patients remained alive, respectively.

Table 5: Overall Survival, Dose Optimisation 3L+ Cohort, December 2024

	Optimisation Part, Arm A
	3L+ (N = 86)
Number of events	[redacted]
Number Censored	[redacted]
OS (months)	
Median follow-up (95%CI)[a]	[redacted]
Median (95% CI)[b]	[redacted]
Estimated percentage of patients remaining alive (95% CI)[b]	
6-month	[redacted]
12-month	[redacted]
18-month	[redacted]

Data cut 9 December 2024, assessed by investigator. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval, NR, not reached

Figure 4: Kaplan-Meier plot of Overall Survival, Dose Optimisation 3L+ FL cohort

Data cut 9 December 2024. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

2.2 Safety

TEAEs leading to treatment discontinuation were reported in [redacted] patients. Reported TEAEs remained low; a summary of Grade 3 and 4 TEAEs is presented in Table 6, of which the most frequent TEAEs were blood and lymphatic disorders ([redacted]%; [redacted] patients, primarily neutropenia [redacted]%; [redacted] patients), investigations ([redacted]%; [redacted] patients) and infections and infestations ([redacted]%; [redacted] patients). No Grade 3-4 COVID-19 TEAEs were noted.

Table 6: Summary of serious Grade 3 and 4 TEAEs, Dose Optimisation 3L+ Cohort

	Optimisation Part, Arm A
	3L+ (N = 86)
Serious Grade 3 - 4 TEAEs	
Infections and infestations	[redacted]
Gastrointestinal disorder	[redacted]
Metabolism and nutrition disorders	[redacted]
Investigations	[redacted]
Immune system disorders	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Blood and lymphatic	[redacted]
Nervous system disorders	[redacted]
Eye disorders	[redacted]
Neoplasm benign, malignant and unspecified	[redacted]
Cardiac disorders	[redacted]
Vascular disorders	[redacted]
Reproductive system and breast disorders	[redacted]

Data cut 9 December 2024. Arm A: Priming 0.16 mg, Intermediate 0.8 mg, Second intermediate 3 mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

Appendix 4: Inverse Probability of Censoring Weighting (IPCW)

1. Background

Causal inference methods aim to estimate treatment effects that more closely reflect what would be observed in the absence of confounding or informative censoring. These approaches rely on assumptions about the relationships between variables and require that relevant baseline and time-varying factors are adequately captured in the available data. In particular, their validity depends on the inclusion of all relevant covariates that may influence both the treatment and the outcome, as described in NICE Technical Support Document 16 as ‘no unmeasured confounders.’ In practice, particularly for trials designed before the COVID-19 pandemic, such comprehensive data capture is rarely feasible. Nevertheless, causal inference techniques can be used in an exploratory way to assess the potential impact of external factors such as COVID-19 on treatment outcomes.

As the EPCORE NHL-1 trial was conducted during the COVID-19 pandemic, excess mortality due to COVID-19 might lead to biased estimates of overall survival (OS) and progression-free survival (PFS) from this single-arm trial. AbbVie’s base case submitted an analysis whereby deaths due to COVID-19 were censored to avoid underprediction of the survival benefit in patients treated with epcoritamab.

In response to concerns raised by the EAG and committee, AbbVie have performed an exploratory competing risks analysis termed the Inverse Probability of COVID-19 censoring weighting (IPCW). The IPCW is a recognised technique in survival analysis described in NICE TSD 16 in the context of treatment switching, whereby data for switchers are censored at the point of switch and remaining observations are weighted with the aim of removing any censoring-related selection bias. Taking this approach in the context of COVID-19 death allows us to distinguish between excess COVID-19-related mortality and disease or background-related mortality to aid in the estimation of the ‘unbiased’ treatment effect of epcoritamab. The results of

this analysis were compared with the other censoring scenarios described to determine the effect of IPCW on epcoritamab survival outcomes.

2. Data

3L+ population

This excess mortality related to COVID-19 was clinically adjudicated in a thorough review of each mortality event in the trial, to identify cases where COVID-19 was the cause of death with certainty. Based on the clinical adjudication and review of the [redacted] trial data and site investigator reports, a total of [redacted] patients were identified as death attributed to COVID-19. Of these N=[redacted] patients, N=[redacted] patients had progressed and N=[redacted] were still progression-free at the time of attributed COVID-19 death. Furthermore, N=[redacted] patient did not progress; however, the progression-free survival was censored as this patient received a new anti-cancer therapy. As a result, the data was adjusted for COVID-19 through the censoring of patients whose cause of death was attributed to COVID-19.

4L+ population

For the 4L+ population, the excess mortality related to COVID-19 was also clinically adjudicated in a thorough review of each mortality event in the trial, to identify cases where COVID-19 was the cause of death with certainty. Based on the clinical adjudication and review of the [redacted] trial data and site investigator reports, a total of [redacted] patients were identified as death attributed to COVID-19. Of these N=[redacted] patients, N=[redacted] were still progression-free at the time of attributed COVID-19 death and N=[redacted] patient had progressed. As a result, the data was adjusted for COVID-19 through the censoring of patients whose cause of death was attributed to COVID-19.

Methods

The NICE Committee recommended exploring causal inference methods in their Draft Guidance. The IPCW method is an established method used to adjust survival in cases of informative censoring, such as treatment crossover, and has been described previously in NICE DSU TSD 16 in the context of adjustment for treatment switching. This analysis was used within a competing risk approach, as patients can either die from COVID-19 or progress/die due to disease or background-mortality-related causes.

IPCW involved censoring observations at the time of COVID mortality and re-weighting observations by the inverse of the probability of COVID-19 mortality being observed. The follow-up survival data was partitioned into weekly intervals with a flag for whether death, progression, or COVID-19 mortality occurred on a particular week. Once progression or mortality due to COVID-19 had occurred, subsequent days continued to have the daily flag for 'COVID-19 mortality' and 'progression' until the end of the observed follow-up period.

Subsequently, the probability of dying due to COVID-19 was estimated for each subject. These probabilities were estimated using a pooled logistic regression using the generalized linear model function in R that predicts the probability of censoring based on observed covariates such as demographic and clinical characteristics. The general form of a logistic regression model is defined below:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

Where p is the probability of COVID-19 related mortality, $\beta_0,\beta_1,\ldots,\beta_n$ are the parameters of the model to be estimated, and $X_1,X_2,\ldots,X_n$ are the observed covariates.

The resulting estimated probabilities were converted to weights by taking their inverse. Stabilised weights were constructed by dividing the weights estimated from the first model (a model where time is the only predictor of COVID-19 mortality) by the weights from the second model (the base-case model with the full set of variables, where more than one variable is a predictor of COVID-19 mortality). Through re-weighting the observations, the IPCW creates a pseudo-population that mimics the distribution of the original population without censoring, thus, reducing the bias caused by informative censoring. In order to generate unbiased estimates of survival for epcoritamab compared with its relative comparators, the weights derived from IPCW were applied to PFS and OS data.

Kaplan–Meier curves were then plotted using the COVID-modified mortality data for both PFS and OS and compared with curves plotted with the COVID-unmodified and

the COVID-modified PFS and OS data. This was conducted to determine how adjusting for COVID-19 censoring through the use of IPCW affected survival outcomes in EPCORE NHL-1.

A summary of the steps taken in this analysis can be found below in Table 1.

Table 1: Analysis steps taken for the IPCW

Analyses steps	Method
Fit a logistic regression model to selected variables	*stats* R package
Selection of model fit	- Statistical model fit (AIC/BIC)[1] - Clinical feedback
Derivation of weights	*geepack* R package
Application of weights to survival data	*flexsurv* R package

AIC, Akaike information criterion; BIC, Bayesian information criterion

Variable selection

Clinicians were consulted to identify variables that are associated with progression and/or death, as well as COVID-19 related mortality. These were considered to be associated with both the outcome and the competing-risk event. The variables that were identified can be found in Table 2 and were subsequently validated as appropriate during clincial expert consultation.

Table 2: Variables that were selected based on clinical feedback for IPCW

Variable name	Description
Baseline characteristics	
Age	Continuous
Sex	Female vs Male
Country	France vs Korea vs Other
BMI	(≤30 kg/m^2 vs. >30 kg/m^2)
Use of corticosteroids at any point beyond cycle 1	Yes or No
Underlying medical conditions	Any respiratory, cardiovascular, metabolic, hepatorenal, neurological, tuberculosis or psychological condition Classified as 0 vs ≥1
Time-varying variables	
COVID-19 infection status	Yes or No
Progression status (only included as a variable for OS)	Yes or No
Other exploratory variables	
Number of prior lines of treatment	2, 3, or 4+

In the model, age was used as a continuous variable to retain information. Countries were grouped as France vs Korea vs Other as the epcoritamab NHL-1 trial took place during the Omicron wave of COVID-19 and these were the two countries that had a higher number of infections during that period of the COVID-19 pandemic. Additionally, as data surrounding underlying medical conditions was sparse, the classification was reduced to having either none versus one or more than one of these conditions to preserve as much of the sample size as possible.

With regards to COVID-19 infection status, two scenarios were explored as the time from COVID-19 infection to COVID-19 mortality observed in the data varied. This was because data on COVID-19 infection start and end dates also varied considerably in the epcoritamab NHL-1 trial and was missing for some patients. In this analysis, patients were assumed to have ended their COVID-19 infection after [redacted] days, as that was the median length of COVID-19 infection in the trial (interquartile range [redacted], [redacted]). Alternatively, the use of the 75th percentile ([redacted] days) was also used to impute a COVID-19 infection end date for patients whom this was missing, assuming that patients were infected with COVID-19 for [redacted] days.

Defining weight estimation

The probability of COVID-19 was estimated from the time of the first COVID-19 infection a patient experienced instead of limiting the estimation from the time patients were COVID-19 positive. This resulted in patients receiving a weight of 1 until the date of their COVID-19 infection. Throughout the duration of their infection and beyond, they were weighted based on the inverse probability of the weights derived from the predictor variables selected, which included COVID-19 infection status. This method ensured that only patients who had COVID-19 were at risk of experiencing COVID-19 mortality and were included in the re-weighting process, whilst including all COVID-19 mortality cases in the prediction of weights. It also does not exclude potential long-COVID-19 cases, accounting for the variability of COVID-19 infection outcomes in the epcoritamab iNHL population.

Crucially, for PFS, the COVID-19 censoring approach utilised previously used the date for the last confirmed progression-free status before COVID-19 mortality occurred to censor patients, not the date of their COVID-19 mortality event. On the other hand, the non-COVID-19 adjusted data marked COVID-19 mortality as an event on the date that it occurred. In the IPCW-adjusted approach for PFS, patients are censored at the time of their COVID-19 mortality, assuming that patients remain progression-free until that time, as estimating the COVID-19 related mortality cannot be conducted if patients are censored for PFS before they got infected with COVID-19.

3. Results – 3L+ population

OS

A generalized linear model with a binomial logit link function was fit to data, where the natural log odds of the probability of experiencing COVID-19 mortality is a linear function of the predictors fit. This was used to predict COVID-19 mortality based on time-varying covariates was carried out on all variables identified in Table 2 based on clinical feedback. Age was significantly associated with an increased odds of COVID-19 mortality, and most factors (Country: France, Country: South Korea, body mass index (BMI), previous medical use, progression, and being COVID-19 positive)

were associated with an increased odds of COVID-19 mortality, except time (Table 3).

Table 3: OS linear logistic regression results

Coefficient	Odds Ratio (95% CI)	P-value
Age (continuous)	[redacted]	[redacted]
Country: France	[redacted]	[redacted]
Country: South Korea	[redacted]	[redacted]
BMI: >30	[redacted]	[redacted]
Corticosteroid use: True	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]
Previous medical condition: N ≥ 1	[redacted]	[redacted]
Time	[redacted]	[redacted]
$I(time^2)^*$	[redacted]	[redacted]
Progressed	[redacted]	[redacted]
COVID-19 positive: True	[redacted]	[redacted]

* Time was transformed into a non-linear variable by squaring it (adding a quadratic term) to capture any non-linear effects of time on the log-odds of COVID-19 mortality
BMI, body mass index
Reference categories: Country: Other, BMI: ≤ 30, Corticosteroid use: False, Sex: Female, Previous medical condition: 0, Progressed: Did not progress, COVID-19 positive: False

PFS

Similarly, for PFS, a generalized linear model with a binomial logit link function was fit to data, where the natural log odds of the probability of experiencing COVID-19 mortality is a linear function of the predictor's fit. This was used to predict COVID-19 mortality based on the time-varying covariates and was carried out on all variables identified in Table 2, based on clinical feedback. Time and having a BMI of higher than 30 were the only variables not associated with an increased risk of COVID-19 mortality. Note that progression was not included as a variable for PFS. As the number of variables fit for predicting the number of events was high, certain results (e.g., Country: France) could have been overfit to the data, resulting in unrealistic coefficient estimates (Table 4).

Table 4: PFS linear logistic regression results

Coefficient	Odds Ratio (95% CI)	P-value
Age (continuous)	[redacted]	[redacted]
Country: France	[redacted]	[redacted]
Country: South Korea	[redacted]	[redacted]
BMI: >30	[redacted]	[redacted]
Corticosteroid use: True	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]
Previous medical condition: N ≥1	[redacted]	[redacted]
Time	[redacted]	[redacted]
$I(time^2)^*$	[redacted]	[redacted]
COVID-19 positive: True	[redacted]	[redacted]

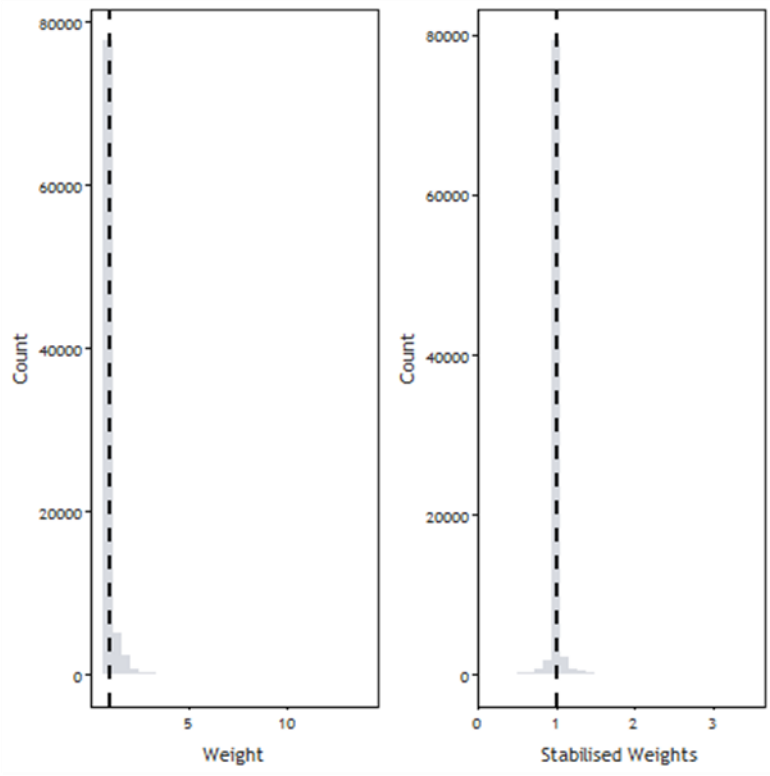
* Time was transformed into a non-linear variable by squaring it (adding a quadratic term) to capture any non-linear effects of time on the log-odds of COVID-19 mortality
BMI, body mass index; CI, confidence interval
Reference categories: Country: Other, BMI: ≤ 30, Corticosteroid use: False, Sex: Female, Previous medical condition: 0, Progressed: Did not progress, COVID-19 positive: False

4. Effect of IPCW-adjusted method on survival outcomes (3L+)

OS

For OS, [redacted] patients were censored due to COVID-19 mortality, and [redacted] other deaths occurred. Weights and stabilised weights did not include extremely large weights, implying that individual observations did not have an unduly effect on the results. As a result, weight trimming was not required (Figure 1).

Figure 1: Distribution of weights and stabilised weights estimated using OS data



The mean weights were 1.41 (range 1.00, 13.92) and the mean stabilised weights were 1.05 (0.22, 3.43). When compared with other censoring scenarios (i.e., non-COVID-19 adjusted data and COVID-19 adjusted data based on simple censoring [naïve censoring]), the non-COVID-19 adjusted method produced the most conservative results of OS as COVID-19 related mortality was not considered.

In the naïve COVID-19 censoring method and IPCW-adjusted methods, patients were censored at the time of COVID-19 mortality, resulting in the KM curve having fewer events. All COVID censoring methods showed comparable results with only minor differences observed at the tail of the curve, caused by slight differences in the number of patients at risk (due to the reweighting within the IPCW approaches) (Figure 2).

Figure 2: Adjusted epcoritamab OS data based on varying censoring methods

The non-COVID-19 censoring method estimated a higher number of events, whereas the simple censoring and IPCW-adjusted stabilised weights produced similar estimates. The non-stabilised IPCW-adjusted method estimated a slightly higher share of events compared with the stabilised weights and the simple censoring method (Table 5).

Table 5: Variation in event estimation based on OS censoring method

	Not censored	Naïve censored	Weights	Stabilised weights
Events, n (%)	[redacted]	[redacted]	33.1 (26)	31.3 (24)
Median OS (95% CI)	[redacted]	[redacted]	NA (NA, NA)	NA (36.7, NA)

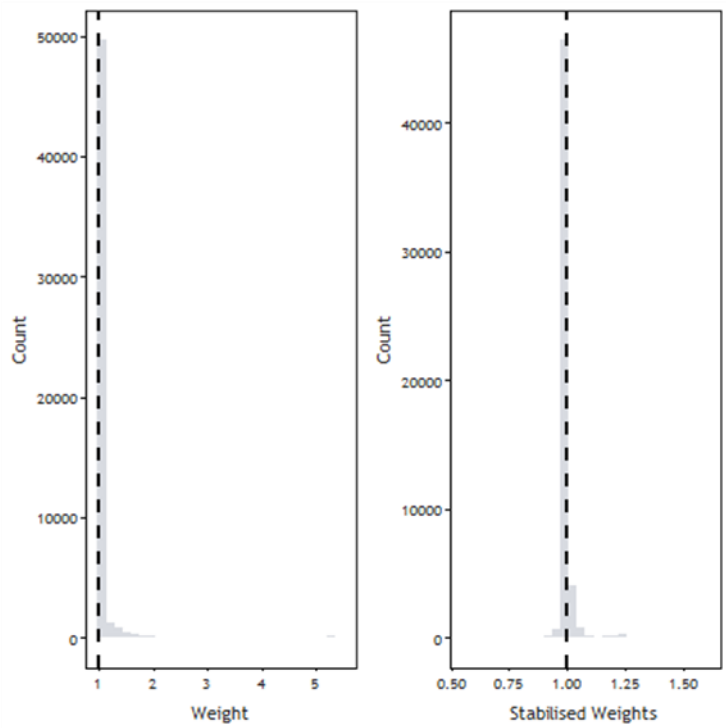
NA, not available; OS, overall survival

PFS

For PFS, [redacted] patients were censored due to COVID-19 mortality, and [redacted] other events occurred. Note that for this analysis, patients were censored at the time of their COVID-19 mortality event. Weights and stabilised weights did not include extremely

large weights, implying that individual observations did not have an unduly effect on the results. As a result, weight trimming was not required (Figure 3).

Figure 3: Distribution of weights and stabilised weights estimated using PFS data



The mean weights were 1.24 (range 1.00, 5.38) and the mean stabilised weights were 1.02 (0.56, 1.59). When compared with other censoring scenarios (i.e., non-COVID-19 adjusted data and COVID-19 adjusted data based on simple censoring [naïve censoring]), the non-COVID-19 adjusted method produced the most conservative results of PFS as COVID-19 related mortality was not considered. In the naïve COVID-19 censoring method and IPCW-adjusted methods, patients were censored at the time of COVID-19 mortality, resulting in the KM curve having fewer events (Figure 4). However, all three methods (COVID-adjusted, non-stabilised IPCW, stabilised IPCW) produce comparable results as shown by the overlap in KM curves in Figure 4.

Figure 4: Adjusted epcoritamab PFS data based on varying censoring methods

Additionally, the non-COVID-19 censoring method estimated a higher number of events, whereas the simple censoring and IPCW-adjusted method produced similar estimates. The weights and stabilised weights estimated varied only marginly. Overall, utilising the weights and stabilised weights estimated by the IPCW-adjusted method also produced similar results, showing that there was little variance in the estimates produced (Table 6).

Table 6: Variation in event estimation based on PFS censoring method

	Not censored	Naïve censored	Weights	Stabilised weights
Events, n (%)	[redacted]	[redacted]	54.5 (43)	52.0 (41)
Median PFS (95% CI)	[redacted]	[redacted]	NA (14.9, NA)	NA (16.9, NA)

NA, not available; PFS, progression-free survival

5. Results – 4L+ population

OS

Similarly, a generalized linear model with a binomial logit link function was fit, predicting COVID-19 mortality based on time-varying covariates for all variables identified in Table 2 based on clinical feedback. Most factors were associated with an increased risk of COVID-19 mortality except for time, being COVID-19 positive, and having a BMI of more than 30. However, the number of variables fit for predicting the number of events (N=[redacted]) was high, certain results (e.g., Country: France, Age, and previous medical conditions) could have been overfit to the data, resulting in unrealistic coefficient estimates (Table 7).

Table 7: OS linear logistic regression results

Coefficient	Odds Ratio (95% CI)	P-value
Age (continuous)	[redacted]	[redacted]
Country: France	[redacted]	[redacted]
Country: South Korea	[redacted]	[redacted]
BMI: >30	[redacted]	[redacted]
Corticosteroid use: True	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]
Previous medical condition: N ≥ 1	[redacted]	[redacted]
Time	[redacted]	[redacted]
I(time^2)*	[redacted]	[redacted]
Progressed	[redacted]	[redacted]
COVID-19 positive: True	[redacted]	[redacted]

* Time was transformed into a non-linear variable by squaring it (adding a quadratic term) to capture any non-linear effects of time on the log-odds of COVID-19 mortality
BMI, body mass index; CI, confidence interval; NA, not available
Reference categories: Country: Other, BMI: ≤ 30, Corticosteroid use: False, Sex: Female, Previous medical condition: 0, Progressed: Did not progress, COVID-19 positive: False

PFS

Similarly, for PFS, a generalized linear model with a binomial logit link function was fit, predicting COVID-19 mortality based on time-varying covariates for all variables identified in Table 2 based on clinical feedback. The same factors listed for OS were also associated with an increased risk of COVID-19 mortality, however, progression was not included as a variable for PFS. As the number of variables fit for predicting the number of events (N=[redacted]) was high, certain results (e.g., Country: France, Corticosteroid use: True, and previous medical condition) could have been overfit to the data, resulting in unrealistic coefficient estimates (Table 8).

Table 8: PFS linear logistic regression results

Coefficient	Odds Ratio (95% CI)	P-value
Age (continuous)	[redacted]	[redacted]
Country: France	[redacted]	[redacted]
Country: South Korea	[redacted]	[redacted]
BMI: >30	[redacted]	[redacted]
Corticosteroid use: True	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]
Previous medical condition: N ≥1	[redacted]	[redacted]
Time	[redacted]	[redacted]
I(time^2)*	[redacted]	[redacted]
COVID-19 positive: True	[redacted]	[redacted]

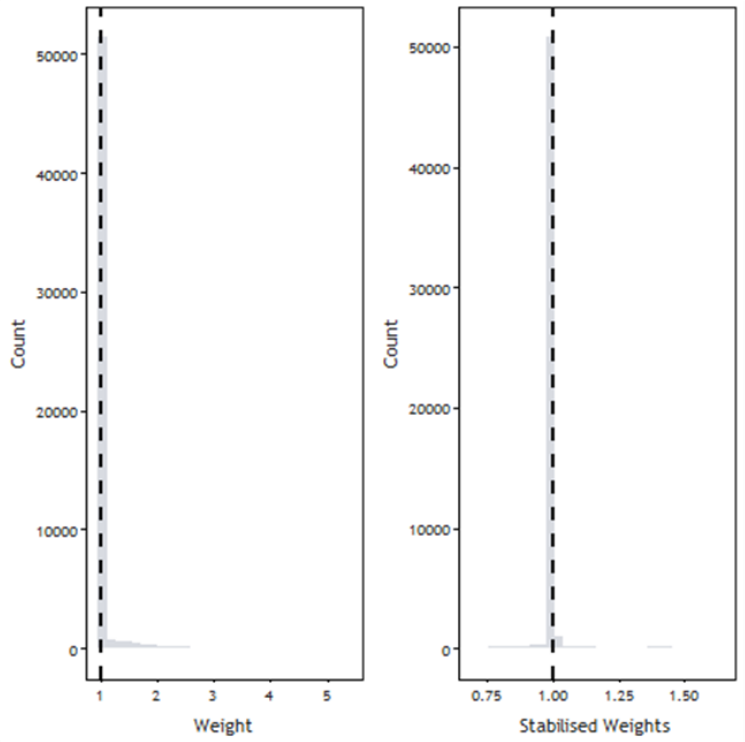
* Time was transformed into a non-linear variable by squaring it (adding a quadratic term) to capture any non-linear effects of time on the log-odds of COVID-19 mortality
BMI, body mass index; CI, confidence interval; NA, not available
Reference categories: Country: Other, BMI: ≤ 30, Corticosteroid use: False, Sex: Female, Previous medical condition: 0, Progressed: Did not progress, COVID-19 positive: False

6. Effect of IPCW-adjusted method on survival outcomes (4L+)

OS

For OS, [redacted] patients were censored due to COVID-19 mortality, and [redacted] other deaths occurred. Weights and stabilised weights did not include extremely large weights, implying that individual observations did not have an unduly effect on the results. As a result, weight trimming was not required (Figure 5).

Figure 5: Distribution of weights and stabilised weights estimated using OS data



The mean weights were 1.14 (range 1.00, 5.35) and the mean stabilised weights were 1.01 (0.71, 1.63). When compared with other censoring scenarios (i.e., non-COVID-19 adjusted data and COVID-19 adjusted data based on simple censoring [naïve censoring]), the non-COVID-19 adjusted method produced the most conservative results of OS as COVID-19 related mortality was not considered.

In the naïve COVID-19 censoring method and IPCW-adjusted methods, patients were censored at the time of COVID-19 mortality, resulting in the KM curve having fewer events (Figure 6). The estimates produced by the stabilised and non-stabilised IPCW weights were comparable to the original COVID-adjusted approach, with only minor differences observed at the tail end of the KM curve due to the different numbers at risk observed between the weighted and non-weighted data (Figure 6).

Figure 6: Adjusted epcoritamab OS data based on varying censoring methods

Additionally, the non-COVID-19 censoring method estimated a higher number of events, whereas the simple censoring and IPCW-adjusted method produced similar estimates. Utilising the weights and stabilised weights estimated by the IPCW-adjusted method also produced similar results, showing that there was little variance in the estimates produced (Table 9).

Table 9: Variation in event estimation based on OS censoring method

	Not censored	Naïve censored	Weights	Stabilised weights
Events, n (%)			26.8 (33)	25.6 (32)
Median OS (95% CI)			NA (34.8, NA)	NA (34.8, NA)

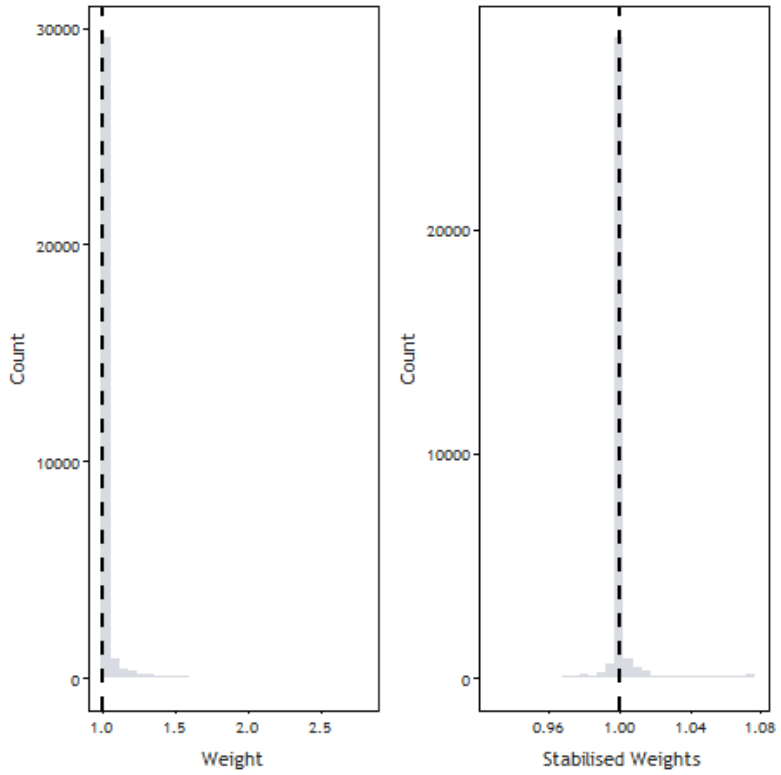
NA, not available; OS, overall survival

PFS

For PFS, patients were censored due to COVID-19 mortality, and other events occurred. Note that for this analysis, patients were censored at the time of their COVID-19 mortality event. Weights and stabilised weights did not include extremely

large weights, implying that individual observations did not have an unduly effect on the results. As a result, weight trimming was not required (Figure 7).

Figure 7: Distribution of weights and stabilised weights estimated using PFS data



The mean weights were 1.11 (range 1.00, 5.64) and the mean stabilised weights were 1.00 (0.93, 1.15). When compared with other censoring scenarios (i.e., non-COVID-19 adjusted data and COVID-19 adjusted data based on simple censoring [naïve censoring]), the non-COVID-19 adjusted method produced the most conservative results of PFS as COVID-19 related mortality was not considered. In the naïve COVID-19 censoring method and IPCW-adjusted methods, patients were censored at the time of COVID-19 mortality, resulting in the KM curve having fewer events (Figure 8).

Figure 8: Adjusted epcoritamab PFS data based on varying censoring methods

Additionally, the non-COVID-19 censoring method estimated a higher number of events, whereas the simple censoring and IPCW-adjusted method produced similar estimates. The weights and stabilised weights estimated varied slightly, however, this may be due to variance in the weights that is not adjusted for. Overall, utilising the weights and stabilised weights estimated by the IPCW-adjusted method also produced similar results, showing that there was little variance in the estimates produced (Table 10).

Table 10: Variation in event estimation based on PFS censoring method

	Not censored	Naïve censored	Weights	Stabilised weights
Events, n (%)	[redacted]	[redacted]	38.8 (48)	37.1 (46)
Median PFS (95% CI)	[redacted]	[redacted]	22.1 (8.5, NA)	22.8 (8.5, NA)

NA, not reached; PFS, progression-free survival

7. Effect of IPCW-adjusted method on survival outcomes (4L+) [Reduced Variable Set]

As described above, an IPCW analysis was conducted for the 4L+ cohort fitted to 9 variables that were determined to be associated with progression and/or death as well as COVID-19 related mortality and were selected based on clinical feedback. These included age, sex, BMI, country, previous medical history, corticosteroid treatment, COVID-19 infection status, progression (OS only), and time (Table 7, Table 8). However, as the number of variables fit for predicting the number of events was high, resulting in potential overfitting, a reduced set of variables was also selected for the 4L+ OS data. As age and previous medical conditions had the largest p-values (0.99) and produced unrealistic coefficient estimates (Table 7, Table 8), they were removed from the variable set, and the IPCW was carried out on 4L+ OS and PFS for the reduced variable set. The results of this analysis are presented below.

OS

The results from the generalized linear model with a binomial logit link fit to the reduced set of variables are presented in Table 11 for OS. Most factors are associated with an increased risk of mortality except time, being male, and having progressed. These variables had furthermore also the highest p-values (≥ 0.59).

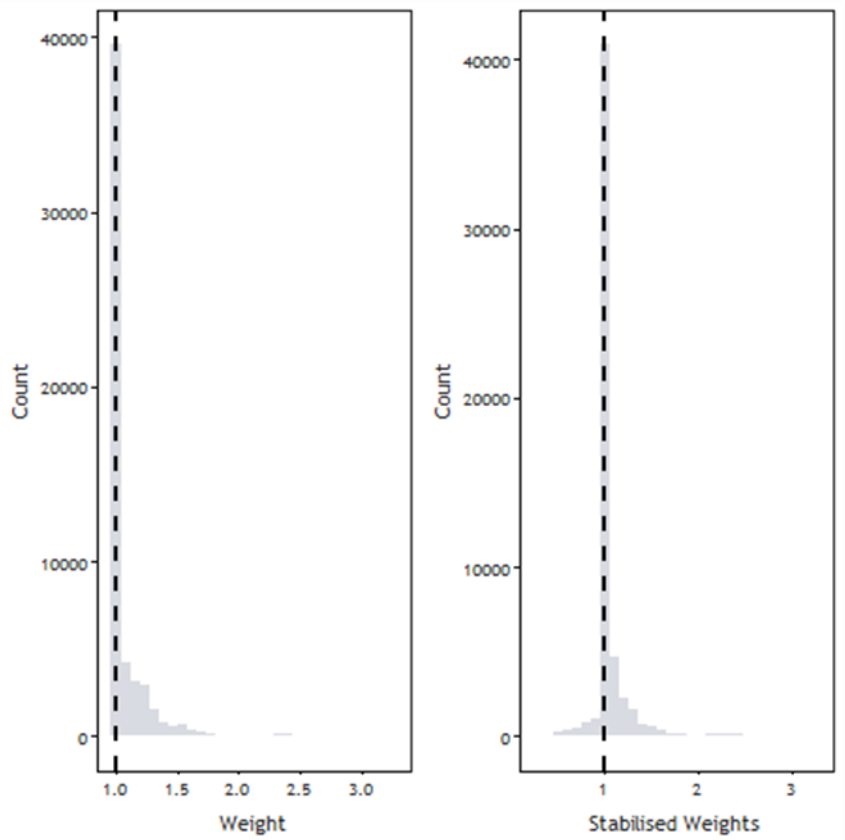
Table 11: OS linear logistic regression reduced variables set results

Coefficient	Odds Ratio (95% CI)	P-value
Country: France	[redacted]	[redacted]
Country: South Korea	[redacted]	[redacted]
BMI: >30	[redacted]	[redacted]
Corticosteroid use: True	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]
Time	[redacted]	[redacted]
I(time^2)*	[redacted]	[redacted]
Progressed	[redacted]	[redacted]
COVID-19 positive: True	[redacted]	[redacted]

* Time was transformed into a non-linear variable by squaring it (adding a quadratic term) to capture any non-linear effects of time on the log-odds of COVID-19 mortality
BMI, body mass index; CI, confidence interval
Reference categories: Country: Other, BMI: ≤ 30, Corticosteroid use: False, Sex: Female, Progressed: Did not progress, COVID-19 positive: False

For OS, [redacted] patients were censored due to COVID-19 mortality, and [redacted] other deaths occurred. This did not change in the reduced variable set analysis. Weights and stabilised weights did not include extremely large weights, implying that individual observations did not have an unduly effect on the results. As a result, weight trimming was not required (Figure 9).

Figure 9: Distribution of weights and stabilised weights estimated using OS data fit to the reduced variable set



The mean weights were 1.28 (range 1.00, 3.24) and the mean stabilised weights were 1.18 (0.31, 3.23). When compared with other censoring scenarios (i.e., non-COVID-19 adjusted data and COVID-19 adjusted data based on simple censoring [naïve censoring]), the non-COVID-19 adjusted method produced the most conservative results of OS as COVID-19 related mortality was not considered.

In the naïve COVID-19 censoring method and IPCW-adjusted methods, patients were censored at the time of COVID-19 mortality, resulting in the KM curve having fewer events (Figure 10). The estimates produced by the stabilised and non-stabilised IPCW weights were comparable with the original COVID-adjusted approach, with only minor differences observed at the tail end of the KM curve due to the different numbers at risk observed between the weighted and non-weighted data (Figure 10).

Figure 10: Adjusted epcoritamab OS data based on varying censoring methods, fit on the reduced variable set

Additionally, the non-COVID-19 censoring method estimated a higher number of events, whereas the simple censoring and IPCW-adjusted method produced similar estimates. Utilising the weights and stabilised weights estimated by the IPCW-adjusted method also produced similar results, showing that there was little variance in the estimates produced (Table 12). These results also did not differ largely from the results produced by the IPCW conducted on the full variable set.

Table 12: Variation in event estimation based on OS censoring method, reduced variable set

	Not censored	Naïve censored	Weights	Stabilised weights
Events, n (%)	[redacted]	[redacted]	25.7 (32)	25.2 (31)
Median OS (95% CI)	[redacted]	[redacted]	NA (34.8, NA)	NA (34.8, NA)

NA, not reached; OS, overall survival

PFS

Similarly, for PFS, a generalized linear model with a binomial logit link was fit, predicting COVID-19 mortality based on time-varying covariates was carried out on the reduced variable set. However, as the age variable produced reasonable results and was shown to significantly influence COVID-19 mortality for PFS, it was included in the reduced variable set. The variable 'previous medical history' was removed, in line with the reduced variable set carried out for OS. The results of the reduced variable set linear logistic regression are shown below (Table 13). Age and the variable Country: France were significantly associated with COVID-19 mortality with a p-value <0.05. The remaining variables were not significantly associated with COVID-19 mortality, as their p-values were > 0.05 and the 95% confidence intervals of the estimated odds ratios did not overlap. However, most of the variables were associated with higher odds of COVID-19 mortality, except for BMI, which was associated with a lower odd of COVID-19 mortality. All of these associations were not statistically significant.

Despite the reduced variable set, certain variables (Country: France and Corticosteroid use: True) still estimated a very large odds ratio which may not be clinically plausible, indicating that potential overfitting issues may have occurred. Moreover, the 95% confidence intervals of each variable were large. This may be because there were only [redacted] COVID-19 mortality events observed for PFS, leading to increased uncertainty in results due to the analysis being run on a small sample size.

Table 13: PFS linear logistic regression results

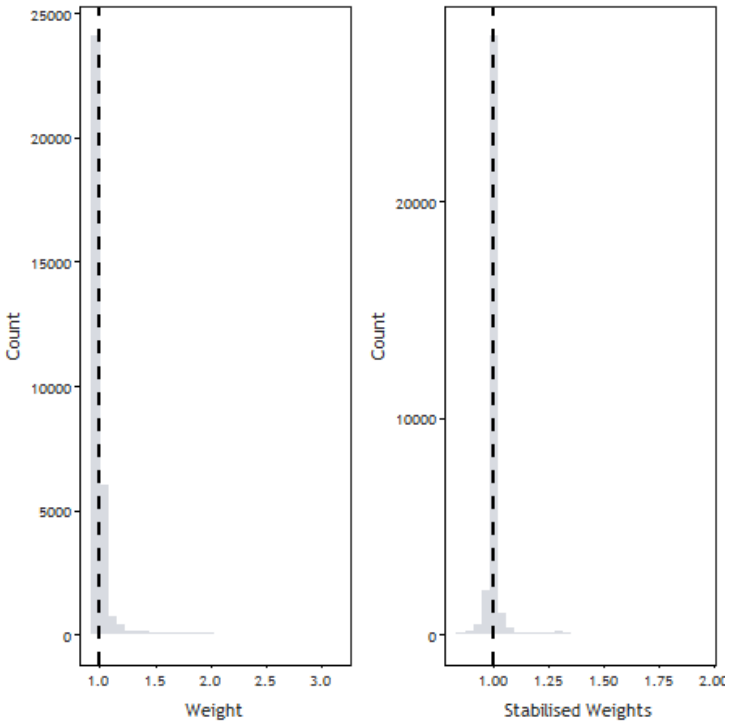
Coefficient	Odds Ratio (95% CI)	P-value
Age (Continuous)	[redacted]	[redacted]
Country: France	[redacted]	[redacted]
Country: South Korea	[redacted]	[redacted]
BMI: >30	[redacted]	[redacted]
Corticosteroid use: True	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]
Time	[redacted]	[redacted]
I(time2)*	[redacted]	[redacted]
COVID-19 positive: True	[redacted]	[redacted]

* Time was transformed into a non-linear variable by squaring it (adding a quadratic term) to capture any non-linear effects of time on the log-odds of COVID-19 mortality
BMI, body mass index; CI, confidence interval
Reference categories: Country: Other, BMI: ≤ 30, Corticosteroid use: False, Sex: Female, Progressed: Did not progress, COVID-19 positive: False

For PFS, [redacted] patients were censored due to COVID-19 mortality, and [redacted] other events occurred. This remained true for the reduced variable set analysis. Note that for this

analysis, patients were censored at the time of their COVID-19 mortality event. Weights and stabilised weights did not include extremely large weights, implying that individual observations did not have an unduly effect on the results. As a result, weight trimming was not required (Figure 11).

Figure 11: Distribution of weights and stabilised weights estimated using PFS data fit to the reduced variables set



The mean weights were 1.13 (range 1.00, 3.62) and the mean stabilised weights were 1.01 (0.74, 1.92). When compared with other censoring scenarios (i.e., non-COVID-19 adjusted data and COVID-19 adjusted data based on simple censoring [naïve censoring]), the non-COVID-19 adjusted method produced the most conservative results of PFS as COVID-19 related mortality was not considered. In the naïve COVID-19 censoring method and IPCW-adjusted methods, patients were censored at the time of COVID-19 mortality, resulting in the KM curve having fewer events (Figure 12).

Figure 12: Adjusted epcoritamab PFS data based on varying censoring methods, fit on the reduced variable set

Additionally, the non-COVID-19 censoring method estimated a higher number of events, whereas the simple censoring and IPCW-adjusted method produced similar estimates. The weights and stabilised weights estimated varied slightly, however, this may be due to variance in the weights that are not adjusted for as shown above. Overall, utilising the weights and stabilised weights estimated by the IPCW-adjusted method also produced similar results, showing that there was little variance in the estimates produced in Table 14. The results produced also did not largely differ when compared with the full set of variables.

Table 14: Variation in event estimation based on PFS censoring method

	Not censored	Naïve censored	Weights	Stabilised weights
Events, n (%)	[redacted]	[redacted]	38.5 (48)	36.9 (46)
Median PFS (95% CI)	[redacted]	[redacted]	22.1 (8.5, NA)	22.8 (8.5, NA)

NA, not reached; PFS, progression-free survival

8. Discussion

In the submission, AbbVie presented outcomes from the Dose Expansion cohort which recruited patients during the COVID-19 pandemic. In their Draft Guidance "*The committee agreed that in principle the impact of COVID-19 should be accounted for in the EPCORE NHL-1 clinical evidence*", though that "*it would like to see more complex methods for accounting for COVID-19 deaths, instead of only censoring them, such as using causal inference*".

There are no perfect approaches for handling the uncertainty in outcomes caused by the confounding nature of COVID-19 and the particularly infectious Omicron wave. As such, emphasis must be placed on any available data following the height of the pandemic, such as outcomes from the Dose Optimisation cohort. Nevertheless, a competing risk approach using IPCW was employed as an alternative explorative method for accounting for COVID-19 deaths. The key strengths of the IPCW analysis were that the model specification was clinically informed, ensuring that variables selected were related to both the outcome and competing risk event. The results remained robust across different model specifications, showing that the survival data was not largely influenced by the inclusion or exclusion of a specific covariate. However, the number of variables fitted was very high when considering the amount of data available (N = [redacted] for the 3L+ population and N = [redacted] for the 4L+ population). A reduction of variables was also explored in order to reduce overfitting present in the data, particularly for the 4L+ population. Due to the low number of COVID-related mortality events (n=[redacted]), interpreting outcomes from approaches such as IPCW is limited.

Notwithstanding the uncertainty of the IPCW approach arising from the assumption that data must be available for all variables of interest and the relatively small sample size, the results show that both the standard censoring and IPCW approaches produce very similar results, further supporting the use of the company approach to censoring COVID deaths. Alternative causal inferences approaches exist, such as competing risk models, however, these are more sensitive to event sparsity and given the small number of COVID-19 mortality events and the limited available data (especially for time-varying variables), these have an increased risk of

overfitting. The IPCW is a recognised method endorsed by the NICE DSU and was performed using clinically informed covariates, ensuring that the weighting reflects real-world risk factors for COVID-19 mortality. These analyses confer that survival data from the Dose Expansion cohort was adversely influenced by the exogenous COVID-19 pandemic. When these IPCW analyses are considered alongside both the COVID-censored analyses presented in the company base case and the data from the Dose Optimisation Cohort, it can be seen clearly that not accounting for COVID-19 deaths underestimates the potential survival offered by epcoritamab. At the first committee meeting, clinical experts highlighted that the Dose Optimisation Cohort, from which the marketing authorisation dosage is derived, largely took place following the pandemic and is crucial for decision-making on COVID-19-related mortality.

Appendix 5: Reassessment of Alternative Data Sources

Section 3.5 of the Draft Guidance states that the committee concluded that "*a full assessment of feasibility for all available comparator data should be explored within scenario analyses and this data should be used to validate model outcomes. It also concluded that a more complete assessment of generalisability should be provided for all analyses*."

For the submission, a systematic literature review (SLR) was undertaken to identify, extract and analyse the relevant clinical evidence for 3L+ and 4L+ therapies in R/R FL. The feasibility assessment showed that of the studies identified during the SLR, none were appropriate to estimate relative effects for patients treated with 3L+ and 4L+ care in England.

We have since reassessed the included publications in both 3L+ and 4L+ FL from the SLR. Outcomes of the reassessment demonstrated that none of the excluded publications are appropriate for informing a comparison with epcoritamab:

- **SCHOLAR-5**[2] was considered not generalisable to the UK, with approximately 40% of patients at 4L+ having been administered experimental treatments that are not available on the NHS (such as PI3Kis, CAR-Ts, and bispecific antibodies). Further, SCHOLAR-5 considered transplant as a line of therapy (LOT), which applied to 20-25% of patients. This is incongruous with how LOT is defined in UK clinical practice and in the EPCORE NHL-1 trial, where transplant is not considered as a LOT. Given the inclusion of experimental treatments and HSCT as a LOT, SCHOLAR-5 was not considered an appropriate comparator data source for 3L+ or 4L+ FL analyses.
- In the **LEO cohort,**[11] patients were exclusively from the United States and only 6% were at 4L+. Of those from the LEO cohort, almost half were from either the Mayo Clinic or MD Anderson Cancer Center sites (46.9%). The remaining patients were from other academic centres (Cornell, Emory, Iowa, Miami, Rochester, and Washington universities). Of the 441 patients enrolled in the LEO cohort, 98 received an experimental treatment option in a clinical

trial. As such, the LEO cohort is not applicable for use in 3L+ or 4L+ FL analyses.

- **Coiffier et al, 2011,[12]** this study investigated a rituximab+bortezomib combination therapy that is not approved or routinely used for the treatment of FL in England.
- **Wasterlid et al, 2024,[13]** this analysis of the Swedish Lymphoma Register reports on 3L+ and 4L+ FL populations. Additionally, the treatment pathway and patient profile are reflective of the UK; for example, many patients in the study received variations of R-Chemo and chemotherapy. However, this study only reports baseline characteristics for 1L FL patients, as such it lacks the granularity required for matching in a MAIC.
- In the **ReCORD-FL** study,[3] PFS was not reported, preventing an assessment of comparative PFS. Furthermore, the patient population investigated within this study was considerably healthier than those expected in UK clinical practice. This is likely because ReCORD-FL was designed to be a historical control for CAR-T eligible patients in the ELARA trial.[14] The ReCORD-FL study excluded patients with ECOG score of >1, which represents a moderate proportion of patients with heavily relapsed/ refractory 4L+ FL. Finally, the study was an international study taking place across several academic research institutes. Taken together, the ReCORD-FL dataset was not considered generalisable to the UK patient population.
- **Johnson et al, 2024,[15]** this study was deemed an inappropriate comparator study as it does not report on the required survival outcomes meaning it lacks the required metrics to enable the ITCs to be performed.
- **Johnson et al, 2025,[16]** this study reports on an 1L FL population, and as such would not have met the 3L+ requirements for this Decision Problem.
- **Hao et al, 2023[4]** was excluded for similar reasons to ReCORD-FL. The inclusion/ exclusion criteria of the CAR-T trial, ELARA, were applied to a small US Flatiron cohort to create a CAR-T eligible population for comparison. This would not be reflective of the UK general population in 3L+ or 4L+ FL and was subsequently excluded.

- **Vitolo et al, 2025,**[17] this abstract was published after the November 2024 cut off for the SLR. However, the publication would not be appropriate to inform a comparison as it is a single-arm study of epcoritamab and would not be reflective of UK practice.

As none of the studies identified during the SLR were appropriate for use in an indirect treatment comparison (ITC) in 3L+ or 4L+ FL, AbbVie engaged with the Haematological Malignancy Research Network (HMRN) to identify the most appropriate data to inform the MAIC. This is a similar approach to what was taken during the NICE submissions for rituximab with lenalidomide (R^2) for 2L+ FL in TA627[18] and recently for zanubrutinib for marginal zone lymphoma (MZL) in TA1001.[6] In these cases, while challenges using the HMRN dataset had been identified, it had been considered appropriate for decision making. A full list of the HMRN variables that had been adjusted for in TA627 and TA1001 is provided in Appendix K of the Company Submission.

Appendix 6: Exploration of Refractory Variables in the MAIC

Section 3.7 of the Draft Guidance lists several concerns the EAG had with the Company MAIC, including with the effective sample size (ESS), differences between trial and real-world populations, the directional impact of the results following matching and the selection of variables for adjustment. We acknowledge the uncertainties inherent in indirect comparisons and note the Committee's and EAG's feedback on the issue. We've aimed to address this by providing a range of alternative approaches with the aim of balancing uncertainty and providing the Committee with as much relevant evidence as possible on which to base their decision.

Exploration of Refractory Variables in the MAIC

Section 3.7 of the Draft Guidance concludes that '*prognostic factors had not been fully explored, especially prognostic factors for people with refractory disease.*' As detailed in the Company Submission Section 2.12.2.2 and Appendix K, and Appendix 2 of this response, selection of variables for adjustment was taken after careful consideration, balancing the need to align populations between evidence sources, reporting limitations and the desire to preserve ESS. Decisions around variable selection were made by triangulating findings from clinical expert consultation, review of prior NICE TAs in FL and MZL, and investigation of the EPCORE NHL-1 patient-level data. Each of these investigations found that refractory status was a meaningful effect modifier and, as such, was considered a key element of variable selection.

All patients within the HMRN cohort were relapsed or refractory, and refractory status was measured in various ways in the EPCORE NHL-1 study. As such, different iterations of the MAIC explored the impact of these different refractory variables. The base case MAIC adjusted for

i. Refractory to most recent anti-lymphoma therapy

ii. Refractory to both anti-CD20 and an alkylator

Exploratory analyses presented by the Company in response to EAG Clarification Question A24 (Sensitivity Analysis 2 – Patient refractoriness to prior therapies) investigated whether varying the definition for refractory status would impact the outputs of the MAIC. Specifically, the 'Refractory to most recent anti-lymphoma therapy' and 'Refractory to both anti-CD20 and an alkylator' variables included in the base case analysis were replaced with the 'Primary refractory' and 'Refractory to any prior anti-CD20 therapy' variables. This analysis yielded improved efficacy outcomes for epcoritamab compared with current 4L+ care, but at the expense of a reduced ESS. Therefore, AbbVie consider that the variables selected and adjusted for in the base case analysis are conservative and robust. The results of this analysis, alongside the base case matching are presented in Table 1 and

Table 2.

Table 1: Base case, Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4L+ care in 4L+ indication (COVID-modified)

OS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]
PFS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; OS, overall survival

Table 2: Baseline characteristics for MAIC sensitivity analysis 2 (CQ A24): Patient refractoriness to prior therapies: Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4L+ care in 4L+ indication (COVID-modified)

	Unadjusted Epcoritamab FL (n = 81)	Adjusted Epcoritamab (n= 31)	HMRN (n = [redacted])
Age ≥ 60	69.1%	[redacted]	[redacted]
Male	65.4%	[redacted]	[redacted]
Disease stage III-IV (At baseline for EPCORE, at diagnosis for HMRN)	85.2%	[redacted]	[redacted]
Prior ASCT	18.5%	[redacted]	[redacted]
Prior CAR-T	7.4%	[redacted]	[redacted]
POD24 after first line CIT	37.0%	[redacted]	[redacted]
Primary refractory	50.6%	[redacted]	[redacted]
Refractory to any prior anti-CD20 therapy	82.7%	[redacted]	[redacted]
Prior lines of therapy ≥4	49.4%	[redacted]	[redacted]
Prior treatment with R2	30.9%	[redacted]	[redacted]

Table 3: MAIC sensitivity analysis 2 (CQ A24): Patient refractoriness to prior therapies: Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4L+ care in 4L+ indication (COVID-modified)

OS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]
PFS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; OS, overall survival

The results of these analyses show that the Company was not biased in its selection of refractory variables to include in its base case, selecting variables that best preserved ESS. In response to the Draft Guidance, an additional analysis has been conducted, whereby matching was performed using all four refractory variables (refractory to most recent anti-lymphoma therapy, refractory to both anti-CD20 and an alkylator, primary refractory and refractory to any prior anti-CD20 therapy). Table 4 and 5 shows the impact on the matching of characteristics when considering the Company base case variable selection updated with the additional refractory variables included. Again, outcomes were improved for epcoritamab relative to the base case MAIC but this scenario analysis is associated with an updated ESS of n=26. Nevertheless, if these data were used directly within the model, we would expect it to result in a lower ICER than with the base case MAIC.

Table 4: MAIC sensitivity analysis 3: All refractory variables: Unadjusted and matched MAIC-adjusted baseline characteristics for EPCORE NHL-1 vs current 4L+ care in 4L+ indication (COVID-modified)

	Unadjusted Epcoritamab FL (n = 81)	Adjusted Epcoritamab FL (n = 26)	HMRN (n = [redacted])
Age >= 60	69.1%	[redacted]	[redacted]
Male	65.4%	[redacted]	[redacted]
Disease stage III-IV (At baseline for EPCORE, at diagnosis for HMRN)	85.2%	[redacted]	[redacted]
Prior ASCT	18.5%	[redacted]	[redacted]
Prior CAR T	7.4%	[redacted]	[redacted]
Progression within 24 months after 1st line CIT	37.0%	[redacted]	[redacted]
Refractory to last prior therapy	76.5%	[redacted]	[redacted]
Primary refractory	50.6%	[redacted]	[redacted]
Refractory to any prior anti-CD20 therapy	82.7%	[redacted]	[redacted]
Refractory to any anti-CD20 and an alkylator	74.1%	[redacted]	[redacted]
Prior lines of therapy >4	49.4%	[redacted]	[redacted]
Prior treatment with R^2	30.9%	[redacted]	[redacted]

Table 5: MAIC sensitivity analysis 3: All refractory variables: Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4+ care in 4L+ indication (COVID-modified)

OS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]
PFS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

As with the scenarios presented above, these analyses show that the associated hazard ratio for OS and PFS is more favourable than the Company base case. On balance, the Company preferred base-case yields outcomes that are generally more conservative than those seen in the scenarios presented at Clarification Questions and in the response to draft guidance, while best preserving the effective sample size. The 'All refractory variables' sensitivity analyses described above was also performed for the 3L+ population, with patients characteristics and outcomes presented in Table 6 & 7.

Table 6: MAIC sensitivity analysis 3: All refractory variables: Unadjusted and matched MAIC-adjusted baseline characteristics for EPCORE NHL-1 vs current 3L+ care in 3L+ indication (COVID-modified)

	Unadjusted Epcoritamab FL (n = 128)	Adjusted Epcoritamab FL (n = 63)	HMRN (n = [redacted])
Age >= 60	64.8%	[redacted]	[redacted]
Male	61.7%	[redacted]	[redacted]
Disease stage III-IV (At baseline for EPCORE, at diagnosis for HMRN)	85.2%	[redacted]	[redacted]
Prior ASCT	18.8%	[redacted]	[redacted]
Prior CAR T	4.7%	[redacted]	[redacted]
Progression within 24 months after 1st line CIT	42.2%	[redacted]	[redacted]
Refractory to last prior therapy	68.8%	[redacted]	[redacted]
Primary refractory	53.9%	[redacted]	[redacted]
Refractory to any prior anti-CD20 therapy	78.9%	[redacted]	[redacted]
Refractory to any anti-CD20 and an alkylator	70.3%	[redacted]	[redacted]
Prior lines of therapy >4	63.3%	[redacted]	[redacted]
Prior treatment with R^2	21.1%	[redacted]	[redacted]

Table 7: MAIC sensitivity analysis 3: All refractory variables: Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 3L+ care in 3L+ indication (COVID-modified)

OS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]
PFS	**HR [95% CI]**	**p-value**
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

This MAIC results in a more favourable adjusted HR for OS and slightly less favourable adjusted HR for PFS when compared with the MAIC using the original set of variables that were selected for the 4L+ base case MAIC presented by the Company, see Appendix 2.

Appendix 7: Assessment of Subsequent CAR-T on Survival

The EAG and Committee have hypothesised that because a small number of patients in the trial received subsequent CAR-T therapy that this may be associated with some undue influence on extending long-term survival outcomes of patients treated with epcoritamab. The EAG recommended that these patients be 'fully removed' from the analysis or that the associated CAR-T costs be included. There are limitations with both proposals by the EAG, in that removing patients is associated with the potential to introduce additional bias. Either they are 'removed' at baseline in which case they are unable to meaningfully contribute to pre-progression survival outcomes, or they are 'removed' on receipt of subsequent therapy, introducing additional uncertainty into the extrapolation of long-term outcomes.

Nevertheless, the important first step would be to understand whether the original hypothesis holds, that those who receive subsequent CAR-T therapy may be benefitting from a treatment which is not available in UK clinical practice, and that this benefit meaningfully contributes to post-progression survival outcomes for epcoritamab in EPCORE NHL-1. Figure 1 shows data from the [redacted] cut of the EPCORE NHL-1 study, where overall survival outcomes for the 4L+ cohort are presented with patients who received subsequent CAR-T therapy censored from the OS analyses at the point in which their subsequent CAR-T therapy was received. As seen in Figure 1 by censoring the patients who received subsequent CAR-T therapy, there is relatively little divergence in the Kaplan–Meiers when considered alongside the overall 4L+ cohort (HR 1.017 (0.634-1.630; log-rank p-value 0.9441). This is to be expected considering only a very small number of patients went on to receive a subsequent CAR-T, meaning they were never meaningfully contributing to the OS for the overall ITT 4L+ cohort.

Figure 1: 4L+ OS KM data with subsequent CAR-T censored

A similar trend is observed when performing the same analysis on the 3L+ cohort, as shown in Figure 2. By censoring the patients who received subsequent CAR-T therapy in the 3L+ cohort, there is relatively little divergence in the Kaplan–Meiers when considered alongside the overall 3L+ cohort (HR 1.024 (0.685-1.531; log-rank p-value 0.9066). This again is to be expected considering only a very small number of patients went on to receive a subsequent CAR-T, meaning they were never meaningfully contributing to the OS for the overall ITT 3L+ cohort.

Figure 2: 3L+ OS KM data with subsequent CAR-T censored

As a supplementary analysis, Figures 3 and 5 shows PFS data from the [redacted] cut of the EPCORE NHL-1 study for both 4L+ and 3L+ FL, where instead of censoring at the point in which the CAR-T was received, patients who received subsequent CAR-T therapy were censored from the analyses at baseline. For OS (Figures 4 and 6), COVID-unmodified plots were combined with the COVID-unmodified KM data presented above where subsequent CAR-T patients were censored at the point they received the subsequent CAR-T. As can be seen from Figure 3 - 6, survival did not differ according to whether the full ITT population was considered, or whether patients were censored at baseline or at the point of receiving subsequent CAR-T.

Figure 3: 4L+ PFS KM data, patients with subsequent CAR-T censored at baseline

Figure 4: 4L+ OS KM data with subsequent CAR-T censored and removed at baseline – COVID-unmodified

Figure 5: 3L+ PFS KM data, patients with subsequent CAR-T censored at baseline

Figure 6: 3L+ OS KM data with subsequent CAR-T censored and removed at baseline – COVID-unmodified

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. 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):	Lymphoma Action

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

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.	• AbbVie £40,000 towards our information provision, helpline, workshops and preparing for treatment project • Bristol Myers Squibb £18,000 towards our support groups and our mission and objectives • Roche £40,000 towards our helpline, information provision, preparing for treatment project and peer support services
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 ……..
1	Whilst we understand that this decision has been reached based on the difficulty in determining cost-effectiveness due to uncertainties in the economic model and clinical evidence,

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

	we very much hope that any further discussions will take the patient experience into account and that every effort will be made to resolve these difficulties. The guidance rightly identifies the "profound psychological impact" of follicular lymphoma, as a progressive and incurable condition, on both patients and their families and carers. We are concerned that the recommendation has not properly considered the psychological burden and mental strain that comes with the fear that there will be no suitable treatments available. There have been no new follicular lymphoma treatments recommended by NICE since 2020 and the unmet need for further treatments being made available is not in dispute. The knowledge that as many different treatment options as possible are made available is crucial to patients and their carers.
2	We are especially concerned with the unmet need for more accessible and better-tolerated treatments. Patient experts cited in our original submission noted clear advantages for epcoritamab over current therapies in both categories and we feel it is important that this is considered.
3	
4	
5	
6	

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. 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):	

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

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

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	Epcoritamab is urgently needed for FL patients and particularly for the 20% with difficult to treat disease who eventually run out of current treatments and with decreasing effectiveness in the later stages. Does the methodology here of comparing new treatment

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

	to existing treatment really work for these patients when existing treatments have run out? Surely Epcoritamab would be cost effective in the 'end of life' disease situation? For example; I am in contact with an early 40s FL patient in a very difficult situation. Their first line treatment was RCHOP which relapsed within 24 months. R2 was next and failed, as did RGDP. Bendamustine is now being tried with a view to allogenic stem cell transplant. The patient has been treated in hospital for several weeks. Surely now the most cost-effective possibility instead would be to try Epcoritamab? (Ideally with Lenalidomide perhaps?) The comparison here therefore is either a course of Epcoritamab versus perhaps weeks more in hospital with increasingly desperate treatment efforts. Epcoritamab would surely be a much lower cost option to try than that? Two or three months would be enough to see if the Epcoritamab is working and the patient might even be out of hospital much sooner than that. I worry that the NICE process and methodology in the draft guidance will mean the Committee won't be able find a way to prove cost effectiveness for patients at third or fourth line until further studies are available. Hopefully it will, but if not, I really hope the Committee can find some way to give immediate help with Epcoritamab for those patients in desperate need. That could have been me if I hadn't randomised for Epcoritamab on the REFRACT trial.
2	
3	
4	
5	
6	

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. 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):	

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

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.	Abbvie, £16,500, speakers fees - unrelated, ceased; travel expenses - unrelated,ceased; steering committees - unrelated, ongoing; advisory board - related, ceased; consultancy – related, ongoing Blood Cancer UK and Follicular Lymphoma Foundation, £379,721, research funding, unrelated, ongoing Cancer Research UK, £1,462,949, research funding, unrelated, ongoing NHS England, £1,294,330, research funding, unrelated, ongoing
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	Kim Linton

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 ……..

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

1	**Has all of the relevant evidence been taken into account?** Any access to epcoritamab would be preferable to no access at all. Evidence of comparator data at 3L is already available from the HMRN dataset and will be available in Q4 2025 from the Foundation UK registry. Evidence from an additional two data sources may support the company's decision to present Covid-adjusted analyses: 1) Data from the optimisation cohort of the EPCORE NHL-1 - which largely recruited in the post-pandemic period - provides more reliable evidence of the expected outcomes of epcoritamab in current (post-pandemic) clinical practice. 2) Data from the UNCOVER Blood cancer health data research programme of >17,500 FL patients in the NCRAS dataset from 2014-2021 reported a 14% increase in mortality for FL patients diagnosed after 2020. This data, presented at the 2015 International Conference on Malignant Lymphoma, provides high quality, population-level evidence of the impact of the Covid-19 pandemic on mortality rates in FL patients.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The assertion that the HMRN dataset was not specific for relapsed or refractory follicular lymphoma is not true. The UK doesn't have access to treatments such as CAR-T therapy and other bispecific antibodies and real-world UK data show that the UK is lagging behind other countries for FL outcomes. UK real-world outcomes, such as from HMRN, reflect the paucity of treatment options in the UK. Datasets (such as LEO CREWE) from other countries capture outcomes for patients treated with CAR-T therapy and bispecific antibodies and clearly show superior outcomes when these treatments are included.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The recommendations are not a suitable basis for guidance to the NHS as alternative sources of UK-only comparator data have not been considered.
4	
5	
6	

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Wednesday 22 October 2025**. Please submit via NICE Docs.

information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

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

Please return to: **NICE DOCS**

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	None
Conflict	None
Comments on the DG:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations to withold treatment leaves many patients without treatment options apart from palliative care for a terminal disease.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comments on the Draft Guidance:

The recommendations to withold treatment leaves many patients without options apart from palliative care for a terminal disease.

The Committee discussion does not explain the limited treatment options for many high risk follicular lymphoma patients clearly.

In the first line, patients' options are

a) bendamustine or
b) CHOP or
c) CVP
with a CD20 antibody.

Second line options are the same as for the first line and lenalidomide with a CD20 antibody.

Third line options are the same as second line options and exhaust the available options other than retreating with a regime from which the patient has already relapsed or proved refractory. Clearly this retreatment is going

to be toxic and have a low probability of success. Options are therefore exhausted after third line.

Fourth line treatment then is limited to retreatment with a regime which has already been given and from which the patient has relapsed. This is likely to be unsuccessful due to the resistance induced during prior treatment.

This was the situation of the patient expert who gave evidence to the committee. He received epcoritamab in a clinical trial at fifth line and would probably not be alive to give evidence if he had not been in the epcoritamab arm of the REFRACT trial. He is living proof of the need for an effective treatment such as epcoritamab.

Best supportive care once these options are exhausted is not really a treatment option; it is palliative care for a terminal patient.

External Assessment Group (EAG) Response to Draft Guidance Comments- Final Report

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Christiana Anyebe, Research Associate, University of Birmingham Mubarak Patel, Research Fellow, University of Birmingham Angela Mwape, Research Fellow, University of Birmingham Emma Loveman, Systematic Review Consultant, Effective Evidence LLP Jill Colquitt, Systematic Review Consultant, Effective Evidence LLP Anna Brown, Information Specialist, University of Birmingham Mandy Maredza, Health Economist, University of Birmingham
Correspondence to	Dr Mandy Maredza, m.maredza@bham.ac.uk
Date completed	Date completed (04/12/2025)

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 17/54/94.

Declared competing interests of the authors

None.

Acknowledgements

We thank Dr Sunil Lyengar (Consultant Haematologist, The Royal Marsden Hospital), Dr Dima El-Sharkawi (Consultant Haematologist, The Royal Marsden Hospital) and Dr Premini Mahendra (Consultant Haematologist, University

Hospitals Birmingham) for providing expert clinical advice, and Professor Aileen Clarke for quality assessing this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Copyright statement

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

1 Committee draft recommendations and consultation responses

This section summarises elements of the Committee draft recommendation together with responses from the company (AbbVie Inc.).

1.1 Section 1 Draft Guidance Document (DGD): Recommendations

Committee: Epcoritamab should not be used to treat relapsed or refractory follicular lymphoma in adults after 2 or more lines of systemic treatment

1.2 Section 3.2 DGD: Treatment pathway

Committee: Company's treatment pathway was appropriate

1.3 Section 3.3 DGD: Treatment positioning of epcoritamab

EAG Summary: The committee recognised that the company may choose to focus on a narrower population (4L+) but considered its objective to evaluate the technology in its full marketing authorisation (3L+). The committee concluded that treatment positioning of epcoritamab (especially exclusion of third-line treatment) had not been explored in sufficient detail in the company submission. It understood the arguments raised against modelling third line treatments but considered these to be insufficient and not based on a lack of available evidence. The committee further noted that relevant clinical evidence may be available for third-line treatment and that limiting the company's evidence to fourth line and beyond increases uncertainty. It requested cost-effectiveness modelling for the full licensed population (including third line), or—if this was not possible—a full justification with a clear breakdown of the available evidence and a clear definition of the fourth-line-or-later population.

In response, the company provided an economic evaluation in the 3L+ population but maintains that the 4L+ analysis remains the base-case.

EAG Response: The EAG considers the 3L+ population to be the appropriate basis for the base case. Its clinical experts advised that, although the 4L+ population has significant unmet need, the greater clinical need begins at 3L+, which is where clinicians would prefer epcoritamab to be positioned.

1.4 Section 3.4 DGD: Clinical Effectiveness – EPCORE NHL-1

EAG Summary: The committee concluded that EPCORE NHL-1 trial data was suitable for decision-making but noted that data was limited by the single arm nature of the trial. The committee concluded that it would like to see the longer follow-up data for the dose optimisation cohort. In response, the company have provided analyses using data from the dose-optimisation cohort.

EAG Response: The EAG's detailed critique of the analysis is presented in section 3.2.

1.5 Section 3.5 DGD: Comparator data

EAG Summary: The committee acknowledged the clinical experts' views on the limitations of the comparator data sources to inform comparative evidence for epcoritamab. However, it noted that the HMRN data may cover periods before rituximab was routinely used, and that the purpose of fourth-line treatment may have evolved as new options became available. It highlighted inconsistencies between the HMRN dataset and other comparator sources that need further investigation and suggested also examining comparator use in the third-line setting. The committee concluded that all available comparator data should be assessed for feasibility through scenario analyses and used to validate model results, and that a fuller assessment of generalisability is required.

In response, the company reassessed the publications included in the SLR conducted as part of its original submission (see Appendix 5: company DG response). The company concludes that "none of the excluded publications are appropriate for informing a comparison with epcoritamab" i.e., none can be used to inform an indirect treatment comparison (ITC) in 3L+ or 4L+ FL. The company further concluded that HMRN dataset remains the appropriate dataset for informing comparative efficacy of epcoritamab.

EAG Response: Exploration of alternative comparator sources

The EAG has cross checked the publications of the potential comparator sources that the company lists in Section 5 and Appendix 5 of the response to the draft guidance. All relevant studies were included, except the company appears to have identified the wrong reference for one publication of the Johnson 2025 study.[1] In the EAG targeted searches reported in the original EAG report we identified two publications from the Johnson 2025 study. However, as a study overall the EAG agrees that Johnson 2025 does not have relevant data for an alternative comparator; the Johnson publications were originally identified by the EAG as of possible use for HRQoL.[2, 3]

The EAG has checked the details of the remaining eight studies, and for five of these the EAG agrees with the company that they are not appropriate as alternative sources of comparator data. The remaining three studies are considered by the EAG as of potential relevance as alternatives to, or as validation of, the HMRN data. The EAG has tabulated key details from these three studies below and a brief overview of the rationale of the EAG follows. The EAG is unable to use these in exploratory analyses due to time constraints. There may also be additional studies published since the last update of the company searches for the SLR.

Similarly to the HMRN data, all three studies are single arm studies. Wasterlid 2024[4] is a large cohort study from Sweden. The EAG clinical experts considered that this study was the most likely of the three studies to be used as a comparator because the treatment landscape for FL in Sweden is generally similar to that in the UK. The study has a long follow-up and there are data available by line of therapy (3L+ and 4L+). The EAG agrees with the company that the baselines characteristics for the study cohort are not presented by line of therapy, however the EAG would not exclude on this basis without an attempt to contact the study authors for the baseline data. It doesn't appear that the company has requested these data.

The Record-FL study (Salles 2022)[5] was excluded by the company as no PFS was reported and the cohort was deemed to be healthier than those expected in UK clinical practice. The EAG notes that the study included European FL patients and that the majority (80%) were at 3L. While the EAG agrees there are no PFS data the study does report event free survival (EFS) rates which could be used as a proxy for

PFS. Also, based on the ECOG scores at baseline the EAG does not believe the population is significantly healthier; while the Record-FL study excluded those with ECOG score greater than one, there were only a small proportion with ECOG greater than one in EPCORE-NHL-1. The EAG agrees with the company that the Leo cohort (Casulo 2022)[6] is US based, however the baselines are from index therapy which is at the point of 3L+ initiation, with 94% at 3L. The EAG agrees that there was heterogeneity in the treatments used but this is also true of the HMRN dataset, and the use of 'experimental treatments' in about [redacted] is not a reason to fully exclude this study.

Table 1. Summary overview of the three studies of relevance

Study design	**Wasterlid 2024[4]**	**Salles 2022[5]**	**Casulo 2022[6]**
Population	FL (3L+ and 4L+)	FL 3L+	FL 3L+
Sample size	1772 (3L = 224, 4L = 88)	187	41
Start date	2007	1998	2002
End date	2014	2019	2018
Data cut-off	2020	December 31, 2020	Not specified
Median follow-up	6.8 years	NR	71 months (IQR: 64 to 79)
Study design	National, population-based, retrospective cohort study	Retrospective	Observational
Treatment	Various	Various	Various
Key inclusion criteria			
FL grades	1-3A	1-3A	1-3A FL
Age	Not reported	Adults	≥ 18 years
Line	Analyses 1st to 4th line	3L+	3L+
Location	Sweden	7 countries including Europe	United States

Funding	Swedish Cancer Society; Karolinska Institute; Janssen	Novartis	Genentech and NCI
Outcomes			
PFS	Time to next treatment used as proxy	Yes - EFS	Yes
OS	Yes	Yes	Yes
TTD	Time to next treatment used as proxy	Time to next treatment reported	NR

1.6 Section 3.6 DGD: Adjusting survival data for COVID-19 deaths

EAG Summary: The committee acknowledged that, in principle, the impact of COVID-19 should be accounted for in EPCORE NHL-1. However, they also noted that the company's approach to censor COVID-19 deaths was an optimistic approach and that cost-effectiveness outcomes were very sensitive to COVID-19 censoring. The committee concluded that: (i) the company had not sufficiently explored alternative options for accounting for COVID-19 deaths and (ii) it would like to see more complex methods of accounting for COVID-19 deaths, e.g. using causal inference. In response, the company explored alternative options for accounting for COVID-19 deaths as requested by the Committee, and concludes that full censoring of patients with COVID resembles the current clinical setting most accurately.

EAG Response: The EAG's detailed critique of the options presented by the company for accounting for Covid-19 deaths is presented in section 3.3

1.7 Section 3.7 DGD: Indirect treatment comparison (ITC)

EAG Summary: The committee concluded that the company's technical approach to its ITC for the fourth-line plus population was appropriate but noted that it would like to see a simulated treatment comparison (STC) to validate the matching adjusted ITC. Referring to the uncertainty posed by choice of comparator data (explained above in section 1.5), the committee further stated that it would like to see an updated ITC using alternative comparator data sources.

The company responded that, due to time constraints, it was not possible to conduct an STC because other analyses had to be prioritised. They were only able to partially address the committee's request for an updated ITC using alternative comparator data sources, as they determined that no other UK-relevant data sources were available. Instead, they provided a set of scenario analyses reflecting different approaches to modelling HMRN survival.

EAG Response: The EAG's detailed critique of the company's narrative on inability to conduct STC is presented in section 3.1

1.8 Section 3.8 DGD: Company's modelling approach

Committee: The company's modelling approach is appropriate.

1.9 Section 3.9 DGD: Modelling of comparator efficacy

EAG Summary: The committee concluded that the company's modelling of comparator efficacy lacked robustness. Verification relied largely on aligning estimates with expert-predicted survival, and the method of applying indirect-comparison hazard ratios to unadjusted epcoritamab data was considered unusual. The committee preferred hazard ratios to be applied to comparator survival curves instead and requested stronger justification of the chosen approach, including an examination of underlying hazards and statistical fit.

In response, the company provided additional MAIC analyses with further exploration of prognostic factors where feasible. The company concluded that the analyses robustly demonstrate that epcoritamab has improved efficacy compared with current standard of care.

EAG Response: The EAG's detailed critique of the company's additional MAIC analyses is presented in section 3.1.2

1.10 Section 3.10 DGD: Utility values

EAG Summary: The committee considered the EAG's utility values—which did not vary progression-free utility by complete response status—to be more appropriate for decision making. It noted that the company's approach of adjusting utilities based solely on complete response status failed to account for other relevant factors, such as duration of complete response and adverse events, which could bias the results.

In response, the company updated the base case assumptions for PFS utility to align with the Committee's preferred assumptions.

EAG Response: The EAG agrees with the change.

1.11 Section 3.11 DGD: Subsequent treatment costs

EAG Summary: The committee considered the EAG's request for the company to run scenario analyses that fully removed people who had CAR-T therapy from efficacy estimates, or included the associated costs for people who had CAR-T therapy in efficacy estimates.

The company responded by providing additional analyses exploring the effect of removing patients who received subsequent CAR-T therapy or including associated costs to the economic model in Appendix 7 of the DG responses. The company acknowledges that a small number of patients in EPCORE NHL-1 receive subsequent CAR-T therapy but argue that removing these patients may introduce additional bias and uncertainty.

The company presented Kaplan-Meier plots of OS where patients with subsequent CAR-T were censored, PFS where patients with subsequent CAR-T were censored at baseline, and OS where patients with subsequent CAR-T were censored and removed at baseline in the COVID-unmodified cohort, both for 4L+ and 3L+ populations of EPCORE NHL-1. In all cases, there is little divergence between the original KM plots and the ones where patients with subsequent CAR-T therapy were censored.

EAG Response: Although the KM curves appear to overlay almost entirely, this does not exclude the possibility of informative censoring, particularly if patients

selected for subsequent CAR-T differed systematically from other trial participants. Furthermore, the similarity of full OS KMs does not directly demonstrate that post-progression survival (PPS) is unaffected. Given that CAR-T is administered post-progression, its influence would be more specific to PPS. The company did not provide PPS-specific KM curves or hazard estimates. Another point is the small number of patients who were on subsequent CAR-T; the very small number limits the ability of these analyses to detect any meaningful difference, and thus the absence of divergence in KM curves cannot be interpreted as evidence of no effect.

Overall, while the results provide some reassurance that subsequent CAR-T may not materially influence OS, a degree of residual uncertainty remains.

1.12 Section 3.12 DGD: Resource use costs

EAG Summary: The committee considered the EAG's assumptions on frequency of haematologist visits—i.e., weekly haematologist visits for the first month and monthly visits thereafter—to be more appropriate for decision making. The committee also concluded that it would consider both scenarios with and without 12-monthly PET scans in its decision making

The company updated its base case to align with the committee's preferences on frequency of haematologist visits i.e., haematological consultations to take place weekly for the first month, before reducing to monthly.

EAG Response: The EAG is satisfied with the change.

1.13 Section 3.13: Adverse events costs

EAG Summary: The committee concluded that the EAG's approach—weighting the adverse-event rates for the treatments included in the comparator basket (lenalidomide plus rituximab, obinutuzumab plus bendamustine, and R-CHOP)—was more appropriate than the company's approach, which applied R-CHOP adverse-event rates to the entire comparator basket. The committee agreed that the company's approach (excluding cytokine-release syndrome costs) was appropriate.

In response, the company updated its base case to align with the committee's preference for weighting adverse-event rates according to the relative use of each treatment.

EAG Response: The EAG is satisfied with the change.

2 EAG's critique of company's 3L+ analyses

2.1 Comparator data

The company uses the HMRN dataset for use as a comparator in a 3L+ population, [redacted]. A confidential report was provided by the company.[7] The datasets presented do not state the time period for the data cut or the eligibility criteria of participants with the exception of the data being in those who had received at least their 3rd line of chemotherapy. Participant characteristics were reported in Table 11 of Appendix 2 in the company DG response document. The EAG has cross-checked these data against the HMRN data tables.[7] These generally align; the EAG has a noted a few observations which mostly relate to missing data. Disease stage III-IV (at diagnosis) is reported in the company Table 11 to be [redacted]. This proportion was calculated from those with data, some [redacted] had missing data. The EAG notes that there is an unexplained footnote in the company DG response Table 11 for their reported data for disease stage. Progression within 24 months after 1st line CIT differs from the data in the HMRN. In the HMRN this was [redacted] (based on [redacted] that had CIT at first line).

Table 2. Baseline characteristics from the HMRN 3L+ population

	HMRN 3L+ (n=[redacted])
Age ≥ 60	[redacted]
Male	[redacted]
Disease stage III-IV (At baseline for EPCORE, at diagnosis for HMRN)	[redacted]
Prior ASCT	[redacted]
Prior CAR T	[redacted]
Progression within 24 months after 1st line CIT	[redacted]

Refractory to last prior therapy	[redacted]
Refractory to any Anti-CD20 and an alkylator	[redacted]
Prior lines of therapy ≥ 3	[redacted]
Prior treatment with R[2]	[redacted]

Based on Company draft guidance response Table 11

2.1.1 Composition of treatment basket

The company assumes that, at third line, the comparator comprises a basket of care; the same approach was used for the base case (4L+ analysis). The composition of the treatment basket is shown below.

Table *3*. Comparator treatment basket at third line-plus

Sub-basket	Chemoimmunotherapy costed in model as:	Market share
R-Chemo	R-Benda	[redacted]
Chemotherapy	Chlorambucil	[redacted]
R2	R2	[redacted]
Other immuno-chemotherapies	Bendamustine + obinutuzumab	[redacted]

EAG Comment: The EAG's clinical experts noted that whilst the sub-basket options align with the treatments that would be offered at 3rd line plus, chlorambucil is an older treatment that is now rarely offered as an option. The EAG experts considered that chlorambucil would likely have 10-15% of market share based on current clinical practice and they would expect R-CVP/R-CHOP to be more dominant (i.e., represent the remaining share currently costed as chlorambucil. The dominance of chlorambucil in the company's analysis is likely a consequence of the longer timeframe over which the HMRN data collection period covers. The EAG could not fully explore the impact of changing the treatment basket options due to limitations in the company's current model structure (which does not allow easy adaptation to alternative assumptions for the basket of care). However, implementing this analysis would have likely shifted the ICER [redacted] epcoritamab due to the price differences between chlorambucil and R-CHOP/R-CVP.

2.2 Company approach to survival modelling

The company provided their base case and scenario analysis survival models for the 3L+ and 4L+ populations in EPCORE NHL-1 and the HMRN report in Table 1 of Appendix 1 of the draft guidance responses. The company were consistent in their approach in this response as they were in the original CS, modelling PFS and OS using the epcoritamab arm of EPCORE NHL-1 and using the MAIC-derived hazard ratio to derive PFS and OS extrapolation for HMRN. Furthermore, as the EAG and committee both expressed a preference to see survival modelling based on the HMRN report and use the inverse-HR from the MAIC to derive extrapolations for EPCORE NHL-1, the company also fit models to the HMRN outcomes. TTD was modelled separately, consistent with the original CS. The company presented models for the COVID-adjusted (base case), COVID-unadjusted, and Omicron-adjusted populations to make a total of 36 survival models.

2.3 EAG Survival modelling

The EAG digitised the OS and PFS figures from Appendix 3 to generate pseudo-IPD and fit parametric survival models. Proportional hazards assumption tests results in no violation of the Ph assumption, consistent with the company.

EPCORE NHL-1

The company presented the base case survival analysis of the 3L+ cohort of EPCORE NHL-1 in Appendix 2, following a consistent approach to the original submission (modelling epcoritamab and applying the MAIC HR to derive the HMRN survival extrapolation). The company fit parametric survival models to the observed OS and PFS data, choosing the base case model based on goodness-of-fit (lowest AIC or BIC), visual hazards fit, plausibility of long-term extrapolations and how they align with clinical opinion. The log-normal model was chosen for OS, PFS and, TTD.

The EAG preferred the log-logistic model for OS and the generalised gamma model for PFS. These were chosen based on statistical fit and conformity to the company's expert's estimates. The EAG sought clinical expert views on the plausibility of the company's estimated survival percentages. The experts indicated that, although some estimates were reasonable, the lower plausible limit for 10-year OS in both

arms of the 3L+ population was the most likely value. In other words, the company's clinicians appear to have overestimated the most likely 10-year OS.

HMRN

Responding to committee's request, the company presented the results of modelling the 3L+ cohort of the HMRN dataset and then applying inverse-HRs to inform outcomes in the epcoritamab arm as a scenario analysis in Appendix 1. The company's preferred models were the Weibull model for PFS, log-normal for OS, and log-logistic for TTD. While the company's Weibull model had the lowest AIC/BIC and good fit to the observed PFS data, the Gompertz model had the best statistical fit to the observed OS data but produced extrapolations deemed not clinical plausible, being too optimistic, thus the log-normal model was chosen.

The EAG digitised the OS and PFS figures in Figure 7 of Appendix 2 and agreed with the company's choice of log-normal for OS and chose the generalised gamma model as the base case for PFS as it was the best statistically-fitting model, with no other model was statistically similar. The 3L+ survival models are presented in **Table *4***.

Table 4. EAG's preferred survival models in the 3L+ populations of EPCORE NHL-1 and the HMRN report

	EAG			
Study	Outcome	Base case	Justification	Company
EPCORE NHL-1	OS	Log-logistic	All models similar fit Log-logistic most in line with company's experts (Table 3; Appendix 2)	Log-normal
	PFS	Generalised Gamma	Generalised Gamma best fit and most in line with Table 6 in Appendix 2 Log-normal also good fit	Log-normal
HMRN	OS	Log-normal	Best fitting model	Log-normal
	PFS	Generalised Gamma	Statistically best-fitting model	Weibull

2.4 Matching-adjusted indirect comparison

Table 10 of Appendix 2 in the company's DG responses presents the selection of prognostic factors and TEMs for adjustment in the 3L+ MAIC, similar to that of the 4L+ cohort in the original submission. The chosen TEMs were also the same as those in the 4L+ MAIC, excluding FLIPI and ECOG PS since these were measured at diagnosis in HMRN and not at the start of third-line treatment. However, as with the 4L+ MAIC, excluding these two TEMs introduces a risk of residual confounding. Furthermore, the selection of TEMs appears to be more driven more by data availability, being the same as 4L+, rather than a full exploration of 3L-specific modifiers.

Table 11 of Appendix 2 in the company's DG responses presents a comparison of the baseline characteristics of the TEMs before and after MAIC adjustment, with the effective sample size (ESS) decreases from 128 in the unadjusted EPCORE NHL-1 3L+ population to 79, a reduction of 38%, matching each TEM to HRMN to one decimal place. The reduction of ESS in this MAIC is less than the [redacted] reduction in the 4L+ MAIC, which appears to be a modest reduction, but this can reflect the limited number or choice of available covariates rather than improved cross-trial similarity.

Results of the 3L+ MAIC-adjusted analyses are presented in Figure 7 and the accompanying table in of Appendix 2 in the company's DG responses and presented below in Table 5. After adjustment, the HRs for OS and PFS [redacted] compared to the unadjusted HRs. The company explained this in the 4L+ MAIC during AC1 that the adjustment process down-weighted the patients in EPCORE NHL-1 with [redacted], resulting in the HRs [redacted] of epcoritamab, and while it is not unreasonable to assume this happened again in the 3L+ setting, it highlights that the adjusted results depends heavily on which prognostic factors were available for weighting and the direction of imbalance across these factors.

Table 5. Results of the 3L+ MAIC-adjusted analyses

Epcoritamab vs current-care in 3L+ setting	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]

2.5 Covid-19 adjustment impact in 3L+ population

The company presented scenario analyses comparing the results using the COVID-modified 3L+ cohort to COVID-unmodified and Omicron-modified populations. These results are presented in Appendix 1 of the company's DG response and summarised below.

Table 4 of Appendix 1 presents the number of COVID-19 and Omicron-related deaths in the dose expansion cohort for the 4L+ and 3L+ settings. In 3L+, there were a total of [redacted] deaths classified as COVID-19 deaths, [redacted] of which occurred during the Omicron wave. Furthermore, there were [redacted] COVID-related deaths in the HMRN report, compared to [redacted] in the 4L+.

Table 6 presents the HRs for different COVID-adjustments, comparing the COVID-modified HRs for OS and PFS to the scenarios where only the [redacted] COVID deaths that occurred during the Omicron wave were censored, and when none of them were censored. The COVID-modified and Omicron-modified analysis resulted in [redacted] with the [redacted] resulting in [redacted] in [redacted] of epcoritamab. The COVID-unmodified HRs results in [redacted] HRs in comparison. Since the HMRN cohort had [redacted] COVID-deaths, the company argues that a MAIC using the COVID-unmodified dataset would not create a like-for-like comparison.

The company also presented results of the IPCW-adjusted methods in the 3L+ cohort, and these results were [redacted] the COVID-adjusted analyses. IPCW methods can adjust for informative censoring only if all relevant predictors of censoring are correctly specified in the weighting model. The

company did not present a comparison of baseline characteristics between patients who died of COVID and those who did not, thus the EAG could not determine whether COVID deaths occurred disproportionately, so while the IPCW analysis and reported weight diagnostics offer some reassurance, they do not eliminate this concern.

Table 6. Hazard ratios for epcoritamab vs current care in 3L+ exploring different COVID adjustments

Adjustment	OS HR (95% CI)	PFS HR (95% CI)
COVID-modified	[redacted]	[redacted]
Omicron-modified	[redacted]	[redacted]
COVID-unmodified	[redacted]	[redacted]

The accompanying ICERs are presented in Table 5 of Appendix 1 of the DG responses, with the HRs from the analysis on the COVID-modified populations resulting on the [redacted] ([redacted]), as was the Omicron-modified results. The results using the COVID-unmodified HRs resulted in an ICER [redacted]. Thus, the EAG considers that the cost-effectiveness outcomes are highly sensitive to the method for adjusting Covid-19 deaths in the 3L+ population

2.6 Relevance of new data for dose optimisation part: 3L+

A further data cut from the dose optimisation part of EPCORE NHL-1 has become available. The length of follow-up for the 3L+ Dose optimisation cohort at the 9th December data cut was [redacted]. The company does not provide comment on the similarity of the data to the Dose expansion cohort COVID-19 adjusted/unadjusted data. The EAG considers that the limitations regarding the evidence base from the dose optimisation part that were raised in the EAG report remain when interpreting these data.

Median PFS was [redacted] months (95% CI [redacted]). This is similar to the Dose expansion part COVID-unmodified analysis, [redacted], whereas in the COVID-19 adjusted analyses the median PFS was [redacted]

[redacted] (95% CI [redacted]). At 18 months, [redacted] of participants in the Dose optimisation cohort remained progression free. The EAG considers this is more similar to the COVID-unadjusted data from the Dose expansion part [redacted] than to the COVID-modified data [redacted] (CS Table 69).

Median OS was [redacted] (95% CI [redacted]). In the original Expansion dose part, median OS was [redacted] (95% CI [redacted]) in the COVID-unmodified analysis and [redacted] (95% CI [redacted]) in the COVID adjusted analysis. At 18 months, [redacted] of patients remained alive (95% CI [redacted]). This is higher than both the unadjusted data ([redacted]) and the COVID-modified data from the Dose expansion cohort ([redacted]) (CS Table 70), but more similar to the latter.

Table 7. Overview of key efficacy outcomes (unadjusted data): 3L+

	3L+ (n=86)
Deaths	[redacted]
Deaths related to COVID-19 during extended follow-up	0
PFS	
Number of events	[redacted]
Number censored	[redacted]
Median follow-up[a]	[redacted]
Median PFS	[redacted]
OS	
Number of events	[redacted]
Number censored	[redacted]
Median follow-up[a]	[redacted]
Median OS	[redacted]

[a] Based on reverse Kaplan-Meier estimate. NR, not reached.

Summary of serious Grade 3 and 4 TEAEs, Dose Optimisation 3L+ Cohort

A summary of serious grade 3 and 4 TEAEs in the 3L+ cohort is presented below, these are similar to the 4L+ dose optimisation cohort.

Table 8. Serious Grade 3-4 TEAEs (frequency >2%): 3L+

	3L+ (N86)

TEAEs leading to treatment discontinuation	[redacted]
Serious Grade 3-4 TEAEs	
Infections and infestations	[redacted]
COVID-19	[redacted]
Gastrointestinal disorder	[redacted]
Metabolism and nutrition disorders	[redacted]
Investigations	[redacted]
Immune system disorders	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Blood and lymphatic	[redacted]
Nervous system disorders	[redacted]
Neoplasm benign, malignant and unspecified	[redacted]

3 Critique of 4L+ efficacy data

3.1 MAIC

3.1.1 Justification for not conducting a simulated treatment comparison

In the draft guidance, NICE requested the company to conduct a simulated treatment comparison (STC). In the response, the company did not conduct one, justifying this choice in the DG responses.

The company emphasises that few events in EPCORE NHL-1 limit the number of covariates that can be included in a regression-based STC, which is methodically correct, but the company did not provide a full quantitative feasibility assessment, such as the number of covariates required or whether an exploratory STC was attempted with a reduced batch of covariates or semi-parametric. Furthermore, reference to previous NICE appraisals is not a substitute for assessing feasibility.

The company further argues that the MAIC is preferable because covariate overlap is 'high', but it could be argued that this is not definitely demonstrated. ESS reductions of [redacted] indicate moderate rather than high overlap, meaning that arguing that the MAIC is inherently superior in this context is not fully substantiated.

Given that the MAIC itself results in a [redacted] and produces [redacted] of the treatment, an STC could have served as a useful validation check even with fewer covariates.

3.1.2 Exploration of refractory variables in the MAIC

Refractory status was included in the base case MAIC in the original submission. In response to clarification question A24, the company investigated whether varying the definition for refractory status would impact the results of the MAIC:

Base case MAIC: refractory to most recent anti-lymphoma therapy, and to both anti-CD20 and an alkylator.

Sensitivity analysis 2: primary refractory, and refractory to any prior anti-CD20 therapy.

Sensitivity analysis 3a: inclusion of all four refractory variables in 4L+ setting

Sensitivity analysis 3b: all refractory variables in 3L+ setting

Sensitivity analysis 2 and 3a (4L+)

Table 2 of Appendix 6 in the company's DG responses presents the baseline characteristics of the patients on epcoritamab from EPCORE NHL-1 before and after MAIC adjustment. From an original sample size of 81, the MAIC-adjusted epcoritamab arm has an ESS of 31, a reduction of 63% for sensitivity analysis 2 which redefined refractory patients, and an ESS of 26 when including all four refractory variables. After adjustment, both matched populations aligned to one decimal place across the included covariates, suggesting that the re-weighting process was able to achieve balance even under the alternative refractory definitions. However, such close numerical alignment should be interpreted cautiously given the substantial ESS loss, which indicates that the matching relies on a small effective subset of the EPCORE NHL-1 population, limiting the robustness of conclusions drawn from the sensitivity analysis.

Compared to the base case, the MAIC-adjusted HRs for epcoritamab were [redacted] implying a [redacted] treatment effect for both scenarios conducted on the 4L+ patients (Table 9).

Sensitivity analysis 3b (3L+)

The 'all refractory variables" sensitivity analysis was also performed for the 3L+ population, results included in Table 9. Table 6 of Appendix 6 in the company's DG responses presented the baseline characteristics before and after MAIC-adjustment after included all four refractory variables, where the ESS reduced from 128 to 63 (a 51% reduction). As with the 4L+ population, the results of the MAIC-adjusted analyses [redacted] HRs in [redacted] of epcoritamab.

While the results of these sensitivity analyses suggest that the choice of refractory variables did not introduce bias, the substantial ESS reduction

raises concerns about robustness. With only 26 to 31 effective patients (62-68% reduction) in 4L+ and 63 patients (51% reduction) in the 3L+ setting between the different scenarios, the sensitivity MAIC results may be less reliable, and the [redacted] of the treatment effect indicates that conclusions drawn from these analyses should be interpreted with caution. Nonetheless, the analyses demonstrate that varying refractory definitions does not materially change the direction of the treatment effect.

Table 9. Results of the sensitivity MAIC after varying the definition of refractory

Epcoritamab vs current-care	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
4L+ cohort		
Base case (N = 81)		
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]
Sensitivity analysis 2 (ESS = 31)		
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]
Sensitivity analysis 3a (ESS = 26)		
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]
3L+ cohort		
Base case (N = 128)		
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]
Sensitivity analysis 3b (ESS = 63)		
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]

3.2 4L+ dose optimisation cohort

3.2.1 New data for Dose optimisation Cohort

Since the original CS, a further data cut has become available (9th December 2024). The EAG has checked the data in the company's Draft Guidance Response against data tables provided by the company, and has checked the company's statements regarding similarities to the Dose expansion COVID-modified data. The company reports that there were no COVID-19 deaths or COVID-19 Grade 3-4 TEAEs in the Dose optimisation cohort. The company has provided updated data for PFS, OS and Grade 3 and 4 TEAEs only. The EAG considers that the limitations regarding the evidence base that were raised in the EAG report remain. EPCORE NHL-1 is an ongoing, single-arm, open-label trial. The data are from subgroups relating to number of prior lines of treatment and some data are not available at the latest data cuts. PFS was investigator assessed, without blinded independent central review. The generalisability of the findings to the broader population of patients with relapsed/refractory FL in routine clinical practice is uncertain.

New data for Dose optimisation part: 4L+

Follow-up at the latest data cut (9th December 2024) was median [redacted] (wrongly stated as [redacted] months on p.53 of the company's Draft Guidance Response but correct elsewhere). Follow-up in the original CS was 5.7 months.

Median PFS was [redacted] months (95% CI [redacted], [redacted]). The company states that this aligns with the COVID-modified Dose Expansion cohort. However, the EAG considers that the outcome is more similar to the COVID-unmodified analyses [redacted] than the COVID-adjusted analyses [redacted]. The company notes that the proportion of patients remaining progression-free at 18 months was not available due to the lack of follow-up.

Median OS was [redacted]. At 18 months, [redacted] of patients remained alive. The company notes that this outcome is better than in the COVID-modified Dose Expansion cohort at 18 months at the earlier data cut ([redacted]).

Table 10. Overview of key efficacy outcomes (unadjusted data): 4L+

	4L+ (n=41)
Deaths	[redacted]
Deaths related to COVID-19 during extended follow-up	0
PFS	
Number of events	[redacted]
Number censored	[redacted]
Median follow-up[a]	[redacted]
Median PFS	[redacted]
OS	
Number of events	[redacted]
Number censored	[redacted]
Median follow-up[a]	[redacted]
Median OS	[redacted]

[a] Based on reverse Kaplan-Meier estimate. NR, not reached.

Summary of serious Grade 3 and 4 TEAEs: Dose optimisation 4L+

Serious Grade 3 and 4 TEAEs are presented in Table 11. The company states that TEAEs reported at the 9 December 2024 data cut were reported at similar or lower rates than those reported in Dose expansion Part of the trial (CS section 2.13.3). However, the EAG notes that blood and lymphatic system disorders appear higher at [redacted] in the Dose optimisation cohort, compared with [redacted] in the Dose expansion part. The EAG also notes the follow-up period is shorter in the Dose optimisation part (median [redacted] months) than in the Dose expansion part (median [redacted] months), limiting the comparison. These observations may relate to the general limitations of the evidence base.

Table 11. Serious Grade 3-4 TEAEs: 4L+

	4L+ (N= 41)
TEAEs leading to treatment discontinuation	[redacted]
Serious Grade 3-4 TEAEs	
Infections and infestations	[redacted]

COVID-19	[redacted]
Gastrointestinal disorder	[redacted]
Metabolism and nutrition disorders	[redacted]
Investigations	[redacted]
Immune system disorders	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Blood and lymphatic	[redacted]
Nervous system disorders	[redacted]
Eye disorders	[redacted]
Neoplasm benign, malignant and unspecified	[redacted]

3.2.2 Efficacy results

The company provided results from the 4L+ dose optimisation cohort in section 1 of Appendix 3 of the DG responses, data cut 09/12/2024. Results up to 08/01/2024 were provided in the original submission. This was provided to give extra context of the efficacy of epcoritamab outside of the Omicron wave of the COVID-19 pandemic. As of the December 2024 data cut, the median follow-up was [redacted] months.

Table 12 presents the PFS and OS results of the data optimisation cohort from the January 2024 data cut in the original submission, and the new December 2024 data cut reported in the DG response. The company state that the results of this cohort follow a similar trend to the dose expansion cohort used in the base case, where many outcomes happened early on, and then a flattening of the curve. On investigating the relevant Kaplan-Meier plots, the EAG agrees with this conclusion.

Table 12. Results of the data optimisation cohort

Data cut	Jan-24	Dec-24
PFS		

Events	[redacted]	[redacted]
Median	[redacted]	[redacted]
OS		
Events	[redacted]	3 (7.3%)
Median	[redacted]	NR (18.7, NR)

3.2.3 Validating the base case using the dose optimisation cohort

In section 3 of the main table in the company's DG response, the company present their chosen log-normal OS and PFS curves with the Kaplan-Meier plot of the dose optimisation cohort. The result of the extended follow-up provides additional reassurance about the plausibility of the company's base case extrapolations for OS and PFS, with observed outcomes in this post-peak pandemic cohort generally consistent, or slightly better, than the COVID-modified dose expansion cohort, supporting the approach of censoring COVID-19 related deaths, which the EAG notes was the preferred approach form the clinical experts during AC1.

The dose optimisation cohort is small with [redacted] follow-up. While early trends suggest the base case extrapolations are conservative and reasonable, there remains residual uncertainty for longer0term outcomes beyond the follow-up period.

3.3 COVID-19 adjustment impact

Section 4 of the main table in the company's DG response explores alternative scenarios for adjusting for COVID-19 in the 4L+ population. In the original submission, [redacted] deaths were identified as COVID-related and censored at the date of event, resulting in the COVID-modified population used to derive the 4L+ OS and PFS outcomes for epcoritamab. The company argued that this adjustment was required to estimate survival in a contemporary, post-pandemic setting. To address this issue, the company implemented the following scenario analyses to explore the results of the base-case COVID-modified analysis.

COVID-unmodified analysis where conducted where COVID-related deaths were not censored, representing the observed outcomes from the dose expansion cohort during the pandemic. Omicron-modified analysis where deaths only after the emergence of the Omicron-variant of COVID-19 ([redacted] deaths counted as events, [redacted] censored) were censored, described as a 'middle ground' by the company between the COVID-modified and COVID-unmodified analyses. The company also uses post-pandemic dose optimisation cohort as supporting evidence since this cohort was recruited predominantly after the peak of the pandemic and reported no COVID-related deaths. These data were presented as supportive evidence that censoring COVID-19 deaths leads to survival outcomes [redacted] with post-pandemic expectations, while the COVID-unmodified cohort produced results [redacted] (Figure 5 in DG responses).

Causal inference using inverse probability of censoring weighting (IPCW) where weights were applied based on estimated probabilities of remaining uncensored, and weighted Kaplan-Meier curves were produced. The company reported that IPCW-adjusted curves were similar to those obtained using the COVID-modified approach (Figure 6 in DG responses).

Results of the MAIC-unadjusted and MAIC-adjusted OS and PFS outcomes for the COVID-modified, COVID-unmodified, and Omicron-modified populations in Table 3 of the DG responses. In all three populations, the MAIC-adjusted OS and PFS HRs are [redacted] in favour of epcoritamab, with the COVID-modified HRs showing the [redacted] for epcoritamab ([redacted]), then Omicron-modified, and then COVID-unmodified. There were [redacted] in the HRs between these three populations. The accompanying ICERs are presented in Table 4 of the DG responses, with the HRs from the analysis on the COVID-modified populations resulting on the [redacted] ([redacted]), as was the Omicron-modified results. The results using the COVID-unmodified HRs resulted in an ICER [redacted].

Given that the [redacted] but the [redacted] across all three datasets, it appears that whilst the choice of COVID-adjustment increases uncertainty in cost-

effectiveness outcomes, the impact is less than that for the 3L+ population (see section 2.5).

3.3.1 Company's IPCW analyses

The company presented an inverse probability of censoring weighting (IPCW) analysis to adjust for potential bias introduced by censoring COVID-related deaths. IPCW aims to recreate the survival experience that would have been observed had no informative censoring occurred by up-weighting individuals who remain uncensored but share characteristics with those who were censored. While this approach can provide an unbiased estimate of survival under a hypothetical scenario in which censoring is unrelated to prognosis, it requires specification of the model used, appropriate selection of adjustment variables, stabilisation of weights, and detailed diagnostic reporting to ensure that the weighted cohort is representative and suitable for interpretation.

The company implemented IPCW using a pooled logistic regression to estimate the probability of COVID-related mortality at each weekly interval. The variables that were included in the model are presented in Table 2 of Appendix 4 of the company's DG responses and were chosen based on whether clinicians believed the variables were "associated" with progression/death and COVID-mortality. No causal framework was presented to demonstrate why only the presented variables are sufficient, nor was there any discussion of potential confounders.

The probability of COVID-19 mortality was estimated from the date of the first COVID-19 infection, rather than restricting estimation to the period in which patients were actively COVID-positive. Patients received a weight of one up to the date of their first COVID infection, after which they receive a weight equal to the inverse of the model-estimate probability of COVID-related mortality. This approach assumes the risk of COVID-19 mortality continues after COVID-19 infection ends, which may or may not be appropriate, and it assumes no differential COVID-19 mortality risks pre-infection, which is unlikely given baseline factors that influence both risk of COVID-19 and death.

3L+ population

The COVID-19 mortality model uses a binomial logistic regression model with time-varying covariates. Table 3 of the DG responses presents the results for OS, where age was the only variable that was statistically significantly associated with COVID-19 mortality. Table 4 presents the results for PFS, where age and country=France were significantly associated with COVID-19 mortality.

The weights appear small (mean = 1.41 for OS model, 1.24 for PFS model), indicating limited rebalancing and suggesting the model only weakly predicts censoring. The mean of stabilised weights was close to 1 for both models and reduced the range of the weights. KM curves overlap nearly perfectly between the IPCW-adjusted datasets and the COVID-modified datasets

4L+ population

The COVID-19 mortality model uses a binomial logit link regression model with time-varying covariates. Table 7 of the DG responses presents the results for OS, where country=France, corticosteroid use=True, Sex=Male were statistically significantly associated with COVID-19 mortality. Table 8 presents the results for PFS, where age and country=France were significantly associated with COVID-19 mortality.

The weights appear small (mean = 1.41 for OS model, 1.11 for PFS model), indicating limited rebalancing and suggesting the model only weakly predicts censoring. The mean of stabilised weights was close to 1 for both models and reduced the range of the weights. KM curves again overlap nearly perfectly between the IPCW-adjusted datasets and the COVID-modified datasets

EAG Comments:

Post-PMB the EAG was requested to produce ICERs reflective of the IPCW analysis. This analysis will be submitted as part of a supplementary addendum.

4 EAG exploratory analysis using Chihara et al. 2025

NICE requested the EAG to perform a scenario analysis based on the recently published study by Chihara et al which aimed to characterise real-world treatment patterns and outcomes in older patients with FL, using population-based registry data in the USA.

Median event-free and overall survival was extracted from Figure 3 of the Chihara et al. 2025 paper,[8] shown in Table 13.

Table 13. Median survival in months (95% CI) from Chihara et al. 2025

Line of treatment	Event-free survival	Overall survival
1L+	33.1 (31.6 to 34.6)	79.6 (76.9 to 82.2)
2L+	19.3 (18.1 to 20.7)	47.5 (44.3 to 50.9)
3L+	15.5 (13.9 to 17.0)	32.8 (29.0 to 36.9)
4L+	13.0 (11.9 to 14.2)	26.1 (22.1 to 30.3)
5L+	10.7 (9.6 to 12.3)	21.9 (9.2 to 27.6)
Source	Figure 3A	Figure 3B

Assuming proportional hazards between lines of treatment, the EAG calculated the hazard ratios between groups by dividing the median survival of one group by the median of the preceding group which is used as the reference (Table 14). HR >1 indicates a higher hazard for the latter line of treatment, which is expected.

Table 14. Hazard ratios calculated from median survival time

Hazard ratio	Event-free survival	Overall survival
2L+ vs 1L+ (reference)	1.72	1.68
3L+ vs 2L+ (reference)	1.25	1.45
4L+ vs 3L+ (reference)	1.19	1.26
5L+ vs 4L+ (reference)	1.21	1.19

The EAG used the 4L+ vs 3L+ HR on the company's base case in the 4L+ setting to estimate survival outcomes in the 3L+ setting. Applying the same HR to both epcoritamab and HMRN 4L+ curves would scale survival equally in both arms and therefore would have minimal impact on the incremental outcomes and the resulting ICER. To ensure the scenario explored the potential change in the relative benefit of epcoritamab in a 3L+ population, the EAG applied the HR to the epcoritamab arm only, deriving HMRN outcomes using the MAIC HR.

This approach is purely exploratory and subject to the following limitations. The SEER-Medicate database might not be representative of the UK FL population, for example participants in this database start at 65 years which a median around 76 years, and other potential heterogeneity, the assumption of proportional hazards and the use of medians to obtain hazard ratios was not formally tested, the SEER-Medicare all-cause survival includes non-cancer deaths, so comparisons to trial data with different censoring need care, and Chihara et al. 2025 shows survival improved over calendar periods, and applying simple multipliers ignores temporal changes in care and new treatments.

5 EAG Tentative Preferred Base Case

Based on all considerations summarised throughout this report, the EAG defined a tentative preferred base-case analysis for the 3L+ population, starting from the company's base-case analysis. The EAG could not fully explore the impact of alternative comparator data sources due to limitations in the company's current model structure (which does not allow easy adaptation to alternative sources) and time constraints. The same applied for changing the composition of treatment basket to reflect EAG clinical expert opinion.

The company maintains its MAIC approach and, in the absence of any additional analyses—such as the standard treatment comparison requested by the committee—to validate the MAIC, the uncertainty around this approach remains.

The EAG base-case results should therefore be interpreted with these limitations in mind.

5.1 Justification for the tentative preferred base case

The EAG prefers to model OS and PFS from the HMRN 3L+ population and using the 1/HR from the MAIC performed on the Omicron-adjusted population to derive OS and PFS for epcoritamab, modelling TTD using the same models as the company. Data from the HMRN are more mature and representative of the real-world UK population, providing a more robust basis for extrapolation. While the MAIC does have some limitations, such as the reduced ESS and [redacted] of treatment effect, using the inverse-HR from the MAIC preserves the PH assumption and maintains with NICE methodological practice to derive extrapolations from the most reliable data available and minimising bias.

To reiterate, the committee explicitly noted that the company's method of applying MAIC-adjusted HRs to unadjusted epcoritamab survival curves was unusual. Standard practice is to use the comparator dataset (in this case, HMRN) as the baseline survival function and then apply the relative treatment

effect from the MAIC to obtain the epcoritamab curves (see previous section 1.9).

The EAG's base case - fitting survival models to HMRN 3L+ and applying inverted MAIC HRs to derive epcoritamab outcomes - aligns with standard practice whereas the company's approach risked double-adjustment and obscured the construction of comparator survival, relying more on expert-predicted face validity rather than the empirical assessment of hazards and statistical fit (see Table 15).

Table 15. Summary of tentative EAG preferred base case assumptions

Analysis (population)	**EPCORE NHL-1**	**HRMN**
3L+ omicron-adjusted Fit on HMRN, use inverse HR for epco from base case MAIC	OS: Apply inverse-MAIC HR = 1/[redacted] PFS: Apply inverse-MAIC HR = 1/[redacted] TTD: Same as company	OS: Same as company PFS: Same as company TTD: Same as company

5.2 Survival curves – tentative EAG base case

Figure 1. Survival curves for epcoritamab, tentative EAG base case

Figure 2. PFS - epcoritamab vs. current 3L+care, tentative EAG base case

Figure 3. Overall survival - epcoritamab vs. current 3L+care, tentative EAG base case

5.3 EAG Tentative Preferred base case results

Table 16. Deterministic cost-effectiveness results- tentative EAG base case 3L+ population, no severity modifier

Technology	Total discounted costs	Total discounted QALYs	Mean LYG	ICER
Epcoritamab	[redacted]	7.594	17.161	-
Current 3L+ Care	[redacted]	2.537	4.225	-
Difference	[redacted]	5.057	12.935	[redacted]

***Threshold for severity weighting not reached**

5.4 Probabilistic cost-effectiveness results- tentative EAG base case

Table 17. Probabilistic cost-effectiveness results - tentative EAG preferred base case

Technology	Mean total discounted costs	Mean total discounted QALYs	ICER
Epcoritamab	[redacted]	7.566	-
Current 3L+ Care	[redacted]	2.534	-
Difference	[redacted]	5.032	[redacted]

The cost-effectiveness acceptability curve indicates that probability of cost-effectiveness of epcoritamab varies between [redacted] and [redacted] for the £20,000 and £30,000 thresholds respectively.

Figure 4. Cost-effectiveness acceptability curve (epcoritamab vs. current 3L+ care)

5.5 Scenario analyses – 3L+

The EAG's base case differs from the company's chosen base case. As a result, the EAG has conducted only two exploratory analyses for the 4L+ population: (1) implementing a 15-year survival cap, and (2) exploring the impact of censoring patients who received subsequent CAR-T therapy in the

EPCORE NHL-1 trial. The results of the latter will be presented in supplementary appendix. The EAG has focused primarily on the 3L+ population, as this aligns with the chosen base case (see **Table 18**).

Table 18: Summary of EAG's scenario analyses on EAG's base case

Scenario analysis number	EAG's base-case assumption	EAG's scenario
1	Population: Omicron adjusted	Covid-adjusted (fully censored) population
2	Population: Omicron adjusted	Covid unadjusted population
3	Inverse hazard ratios (HRs) from the matching adjusted indirect comparison (MAIC) are applied to the extrapolated HMRN curve to derive Epcoritamab survival curves (except TTD)	MAIC is used to derive HMRN outcomes, hazard ratios are applied to the MAIC-reweighted epcoritamab survival (except TTD) as per company base case
4	No additional resource use for PET scans	Once yearly PET scans
5*	Population: Omicron adjusted	IPCW Weighted survival analysis to adjusted for covid-related censoring deaths
6*	No CAR-T censoring	CAR-T censoring

*Analyses will be included as a supplement

The deterministic results of the additional scenario analyses (on EAG's base case) are presented in **Table 19**.

.

Table 19. Scenario analyses deterministic cost-effectiveness results on EAG base case

Scenario analysis number	Scenario Applied to EAG Base Case	Total costs		Total QALYs		Incremental costs (£)	Incremental QALYs No severity weighting	ICER £/QALY No severity weighting
		Epcoritamab	Current 3L+ care	Epcoritamab	Current 3L+ care			
Not applicable	EAG's base case	[redacted]	[redacted]	7.594	2.537	[redacted]	5.057	[redacted]
1	Covid-adjusted (fully censored) population	[redacted]	[redacted]	8.217	2.614	[redacted]	5.603	[redacted]
2	Covid unadjusted population	[redacted]	[redacted]	5.904	2.453	[redacted]	3.451	[redacted]
3	MAIC is used to derive HMRN outcomes, hazard ratios are applied to the MAIC-reweighted epcoritamab survival (except TTD) as per company base case	[redacted]	[redacted]	5.635	1.791	[redacted]	3.844	[redacted]
4	Once yearly PET scans as additional resource use	[redacted]	[redacted]	7.594	2.537	[redacted]	5.057	[redacted]

*The severity weighting threshold is not reached for all analyses

5.6 Scenario Analysis:4L+ population

The EAG applied a 15-year survival cap to the comparator OS curve, aligning with the views of the clinical experts at ACM1 and the EAG clinical experts, who agreed that applying a survival cap to the OS curve was a valid assumption. All other assumptions remain as per the company's chosen base case.

Table 20. Scenario analysis, OS cap at 15 years for current 4L+care - company base case

Technology	Total discounted costs	Total discounted QALYs	Mean LYG	ICER (no severity)	ICER (x1.2 severity applied)
Epcoritamab	[redacted]	5.999	9.275		
Current 4L+ care	[redacted]	1.538	1.973		
Difference	[redacted]	4.461	7.302	[redacted]	[redacted]

EAG Comments: The results of the EAG's tentative preferred base case, excluding confidential comparator discounts, indicate that the ICERs for both the base case and the scenarios presented fall below, or within, the £20,000 to £30,000 per QALY threshold range. However, as noted at the beginning of Section 5, these results should be interpreted with caution.

6 References

1. Johnson PC, Abramson JS, LaCasce AS, Armand P, Barnes J, Merryman RW*, et al.* Longitudinal patient-reported outcomes in older adults with aggressive lymphomas receiving chemoimmunotherapy. *J Natl Compr Canc Netw* 2025;**23**(3). http://dx.doi.org/10.6004/jnccn.2024.7082
2. Johnson PC, Bailey A, Ma Q, Milloy N, Biondi E, Quek RGW*, et al.* Quality of life evaluation in patients with follicular cell lymphoma: a real-world study in Europe and the United States. *Adv Ther* 2024;**41**(8):3342-61. http://dx.doi.org/10.1007/s12325-024-02882-1
3. Johnson PC, Dueck A, Ghione P, Major A, Wang A, Alshreef A*, et al.* Patient-reported outcomes in patients with relapsed/refractory follicular lymphoma treated with epcoritamab within the entire study cohort and in patients with symptoms at baseline. Paper presented at: EHA2025; Milan, Italy, 14 June 2025. URL: https://library.ehaweb.org/eha/2025/eha2025-congress/4160972/p.connor.johnson.patient-reported.outcomes.in.patients.with.relapsed.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D2%2Asearch%3Depcoritamab (Accessed 18 June 2025).
4. Wästerlid T, Dietrich CE, Oksanen A, Spångberg LD, Wahlin BE, Enblad G*, et al.* Treatment sequencing and impact of number of treatment lines on survival in follicular lymphoma: a national population-based study. *eJHaem* 2024;**5**(3):516-26. https://doi.org/10.1002/jha2.904
5. Salles G, Schuster SJ, Fischer L, Kuruvilla J, Patten PEM, Von Tresckow B*, et al.* A retrospective cohort study of treatment outcomes of adult patients with relapsed or refractory follicular lymphoma (ReCORD-FL). *Hemasphere* 2022;**6**(7):e745.
6. Casulo C, Larson MC, Lunde JJ, Habermann TM, Lossos IS, Wang Y*, et al.* Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study. *Lancet Haematol* 2022;**9**(4):e289-e300.
7. Haematological Malignancy Research Network. *Clinical management and outcome in follicular lymphoma to understand survival outcomes, clinical characteristics, and management of patients with relapsed/refractory follicular*

lymphoma (FL) receiving at least their third-line standard of care [Data on File]. Unpublished; 2025.

8. Chihara D, Yang S, Bains Chawla S, Zhang G, Wang A, Yu J*, et al.* Real-world treatment patterns and clinical outcomes in patients with follicular lymphoma: a SEER-Medicare analysis. *Blood Neoplasia* 2025;**2**(2):100080. http://dx.doi.org/10.1016/j.bneo.2025.100080

Introduction

This addendum presents the cost-effectiveness results for the two analyses requested post-PMB:

Scenario 1: Implementation of CAR-T censoring

Scenario 2: IPCW-weighted survival analysis to adjust for COVID-related censoring deaths (applied to the EAG base case)

These scenario analyses should be interpreted with caution, and as conservative estimates for several reasons:

- **Curve digitisation challenges:** The published survival curves lacked clarity and several curves overlapped, making accurate digitisation difficult.
- **Analytical constraints:** The EAG was limited to reproducing only what the company had implemented; for example, the CAR-T censoring could only be applied to the ITT population rather than the COVID-adjusted populations.
- **Time limitations:** Time constraints prevented a full investigation of apparent inconsistencies in the results (e.g., the slightly earlier-than-expected crossing of the PFS curve with the current 3L+ care curve for CAR-T censoring).

Scenario 1: Implementation of CAR-T censoring

The company's CAR-T censoring analysis was conducted on the ITT population. Consequently, this scenario analysis has been implemented using the COVID-unadjusted population, while retaining all other parameters from the tentative EAG base case. The ICER for the EAG base case (using COVID-unmodified data) was [redacted]; implementing CAR-T censoring increases the ICER to [redacted].

Table 1. CAR-T censoring scenario analysis

Technology		Total discounted costs	Total discounted QALYs	Mean LYs	ICER
Epcoritamab		[redacted]	4.727	8.483	-
Current 3L+ Care		[redacted]	2.403	3.624	-
Difference		[redacted]	2.324	4.859	[redacted]

[redacted]

Scenario 2: IPCW weighted analysis

Table 2. IPCW Scenario analysis on EAG base case

Technology	Total discounted costs	Total discounted QALYs	Mean LYG	ICER (no severity modifier)
Epcoritamab	[redacted]	7.588	17.161	-
Current 3L+ Care	[redacted]	2.535	4.225	-
Difference	[redacted]	5.053	12.935	[redacted]

The EAG base case ICER changed from [redacted] to [redacted]; that is a very negligible change when the IPCW analysis was run.

[redacted]

Introduction

This addendum presents the cost-effectiveness results for the Wasterlid 2024[1] exploratory scenario analysis requested post-PMB.

Overall survival for a pseudo third-line population was estimated using digitised survival data from the third-line-plus population reported in the Wasterlid et al. publication. The extrapolated curves indicated that survival remained at approximately 20% beyond 18 years. The EAG considered this long-term plateau to be clinically implausible for the comparator arm. To avoid producing comparator survival estimates that exceeded those of the epcoritamab curve, the pseudo third-line-plus OS curve was constrained (bounded) by the epcoritamab curve such that the comparator survival probability was never higher than the epcoritamab survival probability at any time point in this exploratory analysis.

This scenario analysis should therefore be interpreted with considerable caution and regarded as purely exploratory.

Scenario 1: Cost-effectiveness results (non-cPAS), epcoritamab vs. pseudo third line plus population

Technology	Total discounted costs	Total discounted QALYs	Mean LYs	ICER
Epcoritamab	[redacted]	6.217	12.628	-
Current 3L+ Care	[redacted]	4.059	9.054	-
Difference	[redacted]	2.158	3.574	[redacted]

1. Wästerlid T, Dietrich CE, Oksanen A, Spångberg LD, Wahlin BE, Enblad G*, et al.* Treatment sequencing and impact of number of treatment lines on survival in follicular lymphoma: a national population-based study. *eJHaem* 2024;**5**(3):516-26. https://doi.org/10.1002/jha2.904