Epcoritamab for treating relapsed or refractory large B-cell lymphoma [ID4045]

For committee – contains AIC information

Technology appraisal committee C [12 December 2023]

Chair: Steve O'Brien

Lead team: Pedro Saramago Goncalves, Andrew Renehan, Stella O'Brien

External assessment group: BMJ

Technical team: Heather Stegenga, Lizzie Walker, Ross Dent

Company: AbbVie

Key issues*

Key issues	Resolved?	ICER impact
1. Long-term outcomes		
- long-term remission assumption (for epcoritamab)	No, to discuss	Large
- partially adjusted or fully adjusted MAICs	No, to discuss	Moderate
- OS, PFS, and TTD	No, to discuss	Large
2. Treatment costs and resource use		
- resource use in progression-free state	No, to discuss	Moderate to large
- treatments used post-progression	No, to discuss	Moderate

*See appendix for other issues

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

- ✓ **Recap from ACM1**
- ❑ Consultation responses
- ❑ Summary

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Summary of committee conclusions at ACM1

Epcoritamab is not recommended

Committee preferences:

- Include Pola + BR as a comparator
- Use the 9/10 partially adjusted MAICs for comparison with R-based CIT
- Apply long-term remission assumption for all comparators
- Apply a reduced follow-up intensity for people who had a complete remission while taking epcoritamab

Key areas of uncertainty:

- Appropriateness of the MAICs, including whether should do partially or fully adjusted MAICs
- Poor fitting of extrapolations for OS, PFS and TTD to trial data
- Appropriateness of applying long-term remission assumption
- Subsequent treatments received after progression
- Follow-up costs for people having epcoritamab

Abbreviations: MAIC, matched adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; Pola+ BR, polatuzumab vedotin with rituximab and bendamustine; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time-to-treatment discontinuation

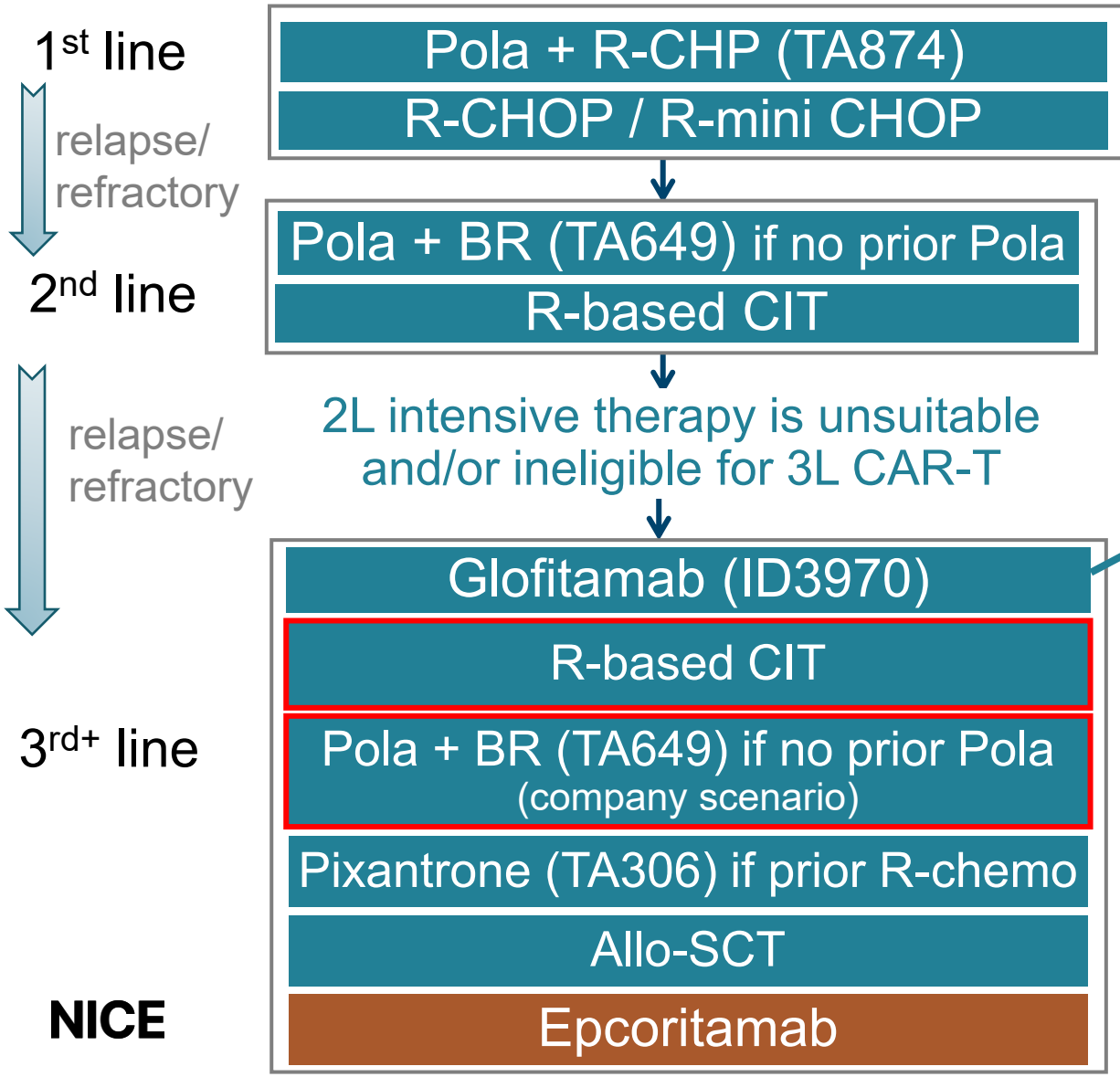
Epcoritamab (Tepkinly®, AbbVie)

Marketing authorisation	• Adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy
Mechanism of action	• Humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B-cells and to CD3 on T cells • Similar mechanism of action to glofitamab (recommended by NICE in October 2023 [TA972])
Administration	• Subcutaneous injection • Administered until progression or unacceptable toxicity

Price	• List price: £6,568 (48 mg vial) and £547.33 (4 mg vial)
	• Confidential simple patient access scheme in place
	• Average cost of a course of treatment [a]:
	  • Between £84,561 and £75,877 for people not eligible for, or choose not to have, intensive treatments (population A)
	  • £94,831 for people eligible for intensive treatments (population B)

[a] provided by company and based on modelled time to treatment discontinuation within the company's analyses updated after consultation

Treatment pathway for DLBCL – intensive Rx unsuitable (population A)



Included in company submission as relevant comparators

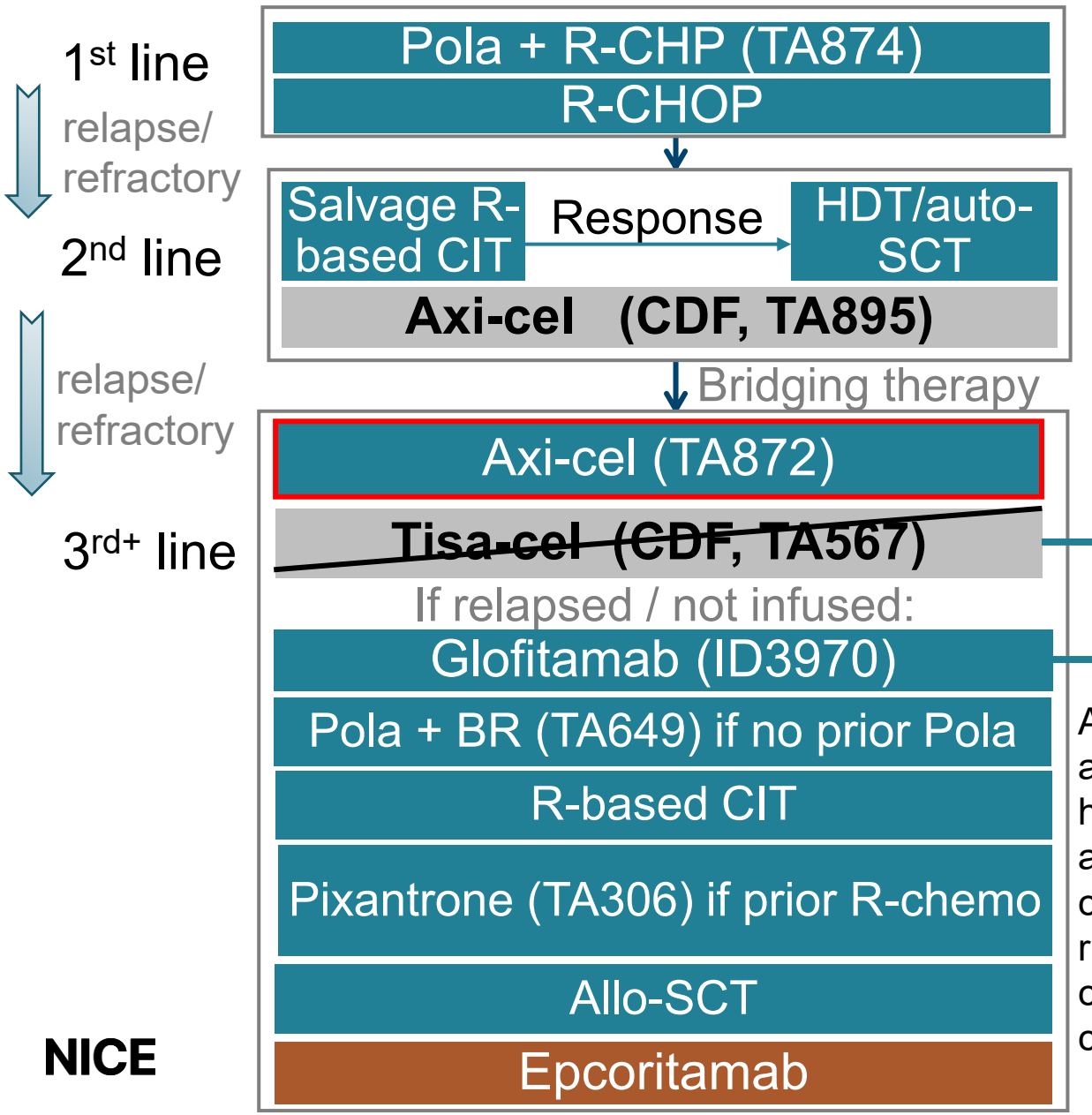
Published October 2023

Loncastuximab tesirine (ID3943) is currently under appraisal

Abbreviations: allo-SCT, allogeneic stem cell transplant; Pola + BR, polatuzumab vedotin with rituximab and bendamustine; Pola + R-CHP, polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisolone; R-based CIT, rituximab-based chemoimmunotherapy; R-mini CHOP; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Treatment pathway for DLBCL – intensive Rx suitable (population B)

Recap



Included in company submission as relevant comparator

CDF drugs not considered in appraisal

Terminated Nov 2023

Published October 2023

Loncastuximab tesirine (ID3943) is currently under appraisal

Abbreviations: allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; CDF, Cancer Drugs Fund; HDT, high dose therapy; Pola+ BR, polatuzumab vedotin with rituximab and bendamustine; Pola + R-CHP, polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisolone; R-based CIT, rituximab-based chemoimmunotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; tisa-cel tisagenlecleucel

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

- ❑ Recap - overall
- ✓ **Consultation responses and key issues**
- ❑ Summary

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Consultation comments*

Comments from Blood Cancer UK, professional groups, clinical expert

Unmet need

- Physical and mental burden for patients and carers from disease and toxicity of current treatments
- Less intensive treatment needed; impacts quality of life of patients and carers

Mode of administration of epcoritamab

- Subcutaneous delivery may be preferred; improves accessibility. Can be delivered in day setting locally

Epcoritamab and glofitamab

- Efficacy and safety profiles are very similar – glofitamab has been recommended by NICE
- Possible that people in EPCORE NHL-1 were higher risk than glofitamab. Real-world evidence needed to compare long-term outcomes → not recommending epcoritamab will limit ability to do this
- **EAG comments:** Glofitamab not a comparator for this appraisal, so not able to comment on comparability

Validity of comparison with pola-BR

- Clinically not relevant because polatuzumab used 1st line (and not subsequently) and bendamustine avoided because may reduce CAR-T efficacy

Validity of cross-trial comparisons

- EPCORE NHL-1 population heavily pre-treated and higher risk that other trial populations
- **EAG comments:** Acknowledges EPCORE NHL-1 population may have worse prognosis than those seen in clinical practice. Considers appropriate to exclude group with prior CAR-T to better match comparator studies and conduct matching to reduce other between trial differences

*See more detail of responses in appendix

Consultation comments*

Comments from Gilead, comparator company for axi-cel

Bridging to axi-cel

- Bridging therapy not mandatory: no bridging (or corticosteroids only) in 11% of UK patients in 2020 to 2022

ZUMA-1 vs EPCORE NHL-1 population

- Unreasonable to assume axi-cel population in ZUMA-1 healthier than epcoritamab population in EPCORE NHL-1, because 'people who could not wait long enough for treatment unlikely to have been referred to axi-cel'
- 94% in ZUMA-1 had stage 3 or 4 disease at baseline compared with 73% with DLBCL in EPCORE NHL-1

Question definition of population A and B

- Not appropriate to do separate analyses based on eligibility for ASCT or CAR T
- Should be based on NICE recommended criteria not trial inclusion (i.e. CAR-T may be considered for ECOG 2)
- **EAG comments:** considers division reasonable. Eligibility for CAR-T includes those with ECOG 2

RWE on axi-cel not considered

- Efficacy and safety results from UK RWE study (Boyle 2023) not considered
- **EAG comments:** acknowledges only ZUMA-1 considered, but limitations comparing trial data with RWE

*See more detail of responses in appendix

Key issue: Long-term remission in model

Unclear if appropriate to apply long-term remission assumption for epcoritamab

Company response to DG

- Applied long-term remission (LTR) for people progression-free 36 months after treatment initiation (in line with committee's preferred assumptions for TA927, glofitamab)
- UK clinical experts stated that some people may discontinue epcoritamab after a prolonged complete response. So, did scenario where people discontinue epcoritamab when entering LTR

EAG comments

- Glofitamab is given for a fixed duration of 12 cycles or until disease progression or toxicity. Epcoritamab is given until disease progression or toxicity
- Clinically implausible that people would enter LTR and be discharged from follow-up while still on treatment with epcoritamab
- EAG base case includes LTR assumption for epcoritamab. Did scenario with no LTR for epcoritamab and LTR at 36 months after initiation for comparators → large impact on ICER

Clinical experts input before committee

- LTR assumption appropriate for epcoritamab: relapse after 3 years unlikely; 90% occur within 2 years
- 50% of patients in LTR likely to discontinue epcoritamab at 3; proportion discontinuing likely to increase over time as data emerges

Should long-term remission assumption be applied for people having epcoritamab? Would people discontinue epcoritamab when entering long-term remission?

Abbreviations: ICER, incremental cost-effectiveness ratio; LTR, long-term remission

Key issue: Adjustment in MAICs

Company provide fully adjusted MAICs but maintain preference for partially adjusted MAICs; EAG preferred fully adjusted for comparison with pola+BR and axi-cel

Background

- Committee requested scenario analyses with fully adjusted MAICs for comparisons with pola+BR and axi-cel.
- Company prefer partially adjusted MAICs. EAG note some reported characteristics not adjusted for, so prefer fully adjusted MAICs. Company provided scenarios with fully adjusted MAICs at draft guidance consultation

Company

- Fully adjusted MAICs have high degree of uncertainty (very low numbers of patients) and issues with over-adjustment as UK clinical experts confirm some variables correlated (i.e. disease stage and IPI score)

EAG comments

- Prefer fully adjusted MAICs for pola+BR and axi-cel, partially adjusted MAIC (9/10 variables) for R-based CIT
- Adjustment for factors in unanchored comparisons important (TSD18); adjustment for all reported variables appropriate – those omitted identified as potentially prognostic originally and not adjusted for due to potential overlap/other reasons, but EAG does not consider rationale provided is sufficient
- Number of patients in the analyses (precision) reduces, but less precise and potentially more accurate estimates preferred to more precise estimates that are likely less accurate
- Differences between studies may be too great to adjust for → has large impact on cost-effectiveness results

Which MAICs do the committee prefer to use for cost-effectiveness modelling?

Abbreviations: MAIC, matched adjusted indirect comparison; TSD, Technical Support Document

Key issue: Use of flexible survival models

Company conduct scenarios with piecewise models; EAG: piecewise models implemented incorrectly but prefer over parametric in EAG base case

Background

- Company used parametric models for long-term extrapolations for OS, PFS and TTD
- EAG: curves do not fit data well; more flexible models should be explored to see if better fit
- Committee requested scenario analyses with more flexible models

Company

- Insufficient evidence to implement spline and mixture-cure models
- Did scenarios with piecewise models for all comparisons: using KM data for first 24 months (except scenario using Northend RWE for pola+BR which used 12 months because study was only 14 months) and then fitted parametric extrapolated curves

EAG

- Agree spline and mixture-cure models not appropriate.
- Piecewise models implemented incorrectly – should represent only initial section of KM data; timepoint of 24 months not justified and no scenarios with alternative timepoints
- If committee consider LTR assumption does not apply to epcoritamab, more robust application needed
- Despite concerns, EAG consider piecewise models best current alternative and use in base case

Are piecewise models preferred?

KM, Kaplan-Meier; LTR, long-term remission; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

Population A – comparison to R-based CIT*

EAG and company differ on preferred MAICs + most extrapolations

	Company	EAG
MAIC	Partially adjusted: 7/10 variables adjusted to Neelapu et al	Partially adjusted: 9/10 variables adjusted to Neelapu et al
OS	**Epcoritamab:** Lognormal **R-based CIT:** Lognormal	**Epcoritamab:** KM then exponential *(best-fitting)* **R-based CIT:** KM then Gen. gamma *(2nd best-fitting)*
PFS	**Epcoritamab:** Gen. gamma **R-based CIT:** Based on OS HR from 7/10 adjusted MAIC ([redacted])	**Epcoritamab:** KM then gen. gamma *(best-fitting)* **R-based CIT:** Based on OS HR from unadjusted, no prior CAR-T MAIC ([redacted])
TTD	**Epcoritamab:** Exponential **R-based CIT:** TTD=PFS	**Epcoritamab:** KM then lognormal *(best-fitting)* **R-based CIT:** TTD=PFS; adjusted for 10% discontinue for reasons other than progression

Company rationale for preferred extrapolations:

- OS: Broadly aligned with SCHOLAR-1 and clinical expert opinion
- PFS: Results clinically plausible and do not over-estimate epcoritamab, but uncertain
- TTD: Clinical expert opinion says very few patients on treatment after 5 years, so used exponential

EAG comments:

- Prefer to use for best fitting curves which are more clinically plausible
- R-based CIT curve underpredicts long-term OS compared to SCHOLAR-1 KM data (so also underpredicts PFS)
- TTD curve underestimates treatment costs for epcoritamab and overestimates costs for R-based CIT

Which extrapolations should be used in the model?

*See more detail on extrapolations

PFS and TTD extrapolations: epcoritamab vs R-based CIT*

EAG prefer piecewise model using KM data up to 24 months

Company-preferred curves for epcoritamab (using company-preferred MAIC)

EAG-preferred curves for epcoritamab (using EAG-preferred MAIC)

Company preferred MAIC: adjusted for 7/10 reported variables; EAG-preferred MAIC: adjusted for 9/10 reported variables

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Abbreviations: MAIC, matched adjusted indirect comparison; PFS, progression-free survival; R-based CIT, rituximab-based chemoimmunotherapy; TTD, time-to-treatment discontinuation

*See extrapolations for OS in appendix

Population A – comparison to Pola+BR*

EAG and company differ on preferred MAICs and extrapolations

	Company	EAG
MAIC	Partially adjusted: 6/10 variables adjusted to Sehn et al.	Fully adjusted: 10/10 variables adjusted to Sehn et al.
OS	**Epcoritamab:** Gen. gamma **Pola + BR:** Log. logistic	**Epcoritamab:** KM then lognormal *(best-fit)* **Pola + BR:** KM then lognormal (*best-fit)*
PFS	**Epcoritamab:** Gen. gamma **Pola + BR:** Gamma	**Epcoritamab:** KM then lognormal *(best-fit)* **Pola + BR:** KM then gen. gamma *(best-fit)*
TTD	**Epcoritamab:** Exponential **Pola + BR:** TTD=PFS	**Epcoritamab:** KM then lognormal *(best-fit)* **Pola + BR:** TTD=PFS; adjusted for 10% discontinue for reasons other than progression

Company rationale for preferred extrapolations:

- Clinical experts: gen. gamma, loglogistic and lognormal plausible for epcoritamab OS curve; gen. gamma most plausible for epcoritamab PFS; TTD, exponential as very few patients expected on treatment after 5 years

EAG comments:

- In fully adjusted MAIC, epcoritamab and pola+BR OS curves cross at [redacted]; and PFS curves cross at [redacted]. Company's curves do not capture crossing curves; piecewise models do
- OS: log-normal best-fitting and clinically plausible. Company approach underpredicts vs Sehn et al. for Pola+BR
- TTD: Company approach underestimates costs of epcoritamab and over-estimates costs of Pola+BR

Which extrapolations should be used in the model?

*See more detail on extrapolations

PFS and TTD extrapolations: epcoritamab vs Pola + BR

EAG prefer piecewise model using KM data up to 24 months

Company-preferred curves for epcoritamab (using company-preferred MAIC)

EAG-preferred curves for epcoritamab (using EAG-preferred MAIC)

Company preferred MAIC: adjusted for 6/10 reported variables; EAG-preferred MAIC: adjusted for 10/10 reported variables

Abbreviations: MAIC, matched adjusted indirect comparison; PFS, progression-free survival; Pola+BR, polatuzumab vedotin with rituximab and bendamustine; TTD, time-to-treatment discontinuation

*See extrapolations for OS in appendix

Population B – comparison to axi-cel*

EAG and company differ on preferred MAIC + most extrapolations

	Company	EAG
MAIC	Partially adjusted: DLBCL, 7/10 variables adjusted to ZUMA-1	Fully adjusted: LBCL, 11/11 variables adjusted to ZUMA-1
OS	**Epcoritamab:** Gompertz **Axi-cel:** Gompertz	**Epcoritamab:** KM then lognormal *(2nd best fit)* **Axi-cel:** KM then Gompertz *(best fit)*
PFS	**Epcoritamab:** Gompertz **Axi-cel:** Gompertz	**Epcoritamab:** KM then lognormal *(best fit)* **Axi-cel:** KM then gen. gamma *(2nd best fit)*
TTD	**Epcoritamab:** Exponential **Axi-cel:** N/A	**Epcoritamab:** KM then lognormal *(best fit)* **Axi-cel:** N/A

Company rationale for preferred extrapolations:

- Clinical experts considered gen. gamma or lognormal plausible for epcoritamab OS extrapolations and gen. gamma or loglogistic for epcoritamab PFS extrapolations. However, Gompertz selected for OS and PFS to align with axi-cel and MAIC. For TTD, very few patients expected on treatment after 5 years, so exponential selected

EAG comments:

- Prefer base case with LBCL population from EPCORE NHL-1 compared with DLBCL used by company
- Company OS curves do not [redacted], and axi-cel and epcoritamab curves converge at around [redacted]
- Company PFS curves do not reflect KM data for epcoritamab adjusted and ZUMA-1 unadjusted PFS curves
- Company base case has [redacted] year difference between mean PFS and mean TTD – unlikely to be clinically plausible and underestimates costs for epcoritamab

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Which extrapolations should be used in the model?

*See more detail on extrapolations

PFS and TTD extrapolations: epcoritamab vs axi-cel

EAG: company extrapolations have large difference between mean PFS and TTD for epcoritamab - underestimates costs for epcoritamab

Company-preferred curves for epcoritamab (using company-preferred MAIC)

EAG-preferred curves for epcoritamab (using EAG-preferred MAIC)

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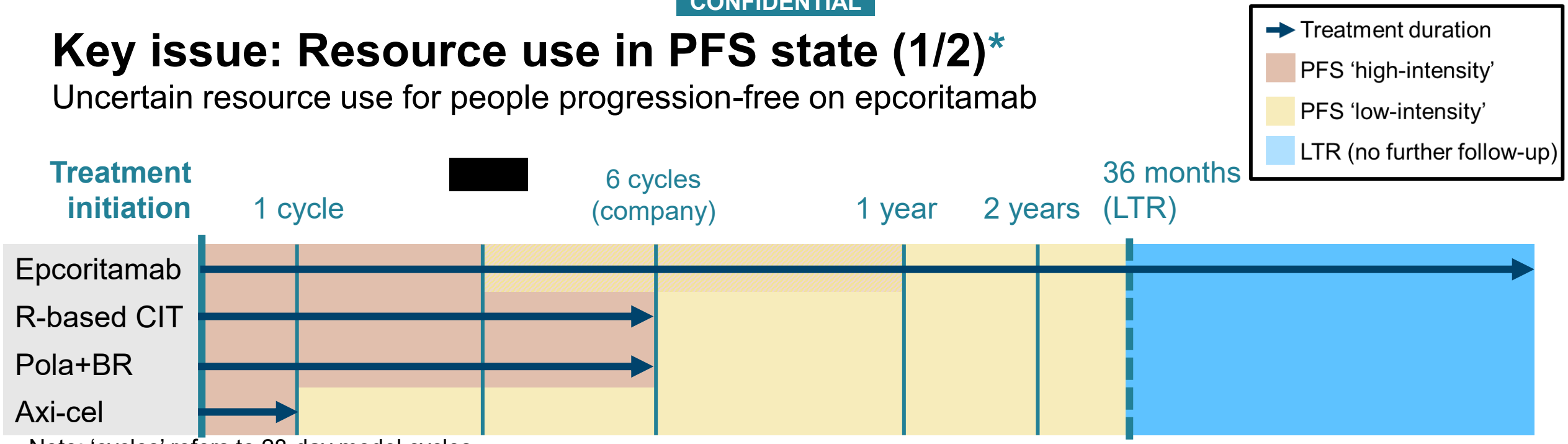
[a] Company-preferred MAIC: DLBCL, 7/10 variables adjusted for; AG-preferred MAIC: LBCL population, 11/11 variables adjusted for

*See extrapolations for OS in appendix

Key issue: Resource use in PFS state (1/2)*

Uncertain resource use for people progression-free on epcoritamab



Note: 'cycles' refers to 28-day model cycles

Company response to DG

- Interviewed 5 clinical experts and revised resource use for **PFS 'low-intensity'** on epcoritamab (reduced blood, liver, immunoglobin and calcium phosphate tests, increased specialist nurse and haematologist time)
- Assumes switch from 'high-intensity' to 'low-intensity' follow-up at [redacted] as this is median PFS from EPCORE NHL-1, when [redacted]
- Updated values for **PFS 'low-intensity'** for epcoritamab were lower than original **PFS 'low-intensity'** values (for epcoritamab and comparators). Not clinically plausible that people still on epcoritamab would have lower resource use than people who had stopped other treatments.
  - So applied updated values for **'low-intensity'** phase for epcoritamab and comparators

Abbreviations: LTR, long-term remission; PFS, progression-free survival

*see appendix for original and updated resource use assumptions

Key issue: Resource use in PFS state (2/2)

Uncertain resource us for people progression-free on epcoritamab

EAG comments

- Company has not provided justification to change from original resource use assumptions
- Not appropriate to use median PFS for partial or complete responders from trial to inform switch from **'high-intensity'** to '**low-intensity'** follow-up. Have done scenarios where switch happens at 1 and 2 years (see dashed box on figure) → large impact on ICERs

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- Unsure if clinically plausible to assume same resource use for:
  - Epcoritamab (on-treatment, after median PFS) and comparators (off-treatment) in **PFS 'low-intensity'** state
  - Epcoritamab (on-treatment) and comparators (off-treatment) in **Long-term remission**
- Company not provided clinical validation of resource use for people in **LTR** on epcoritamab

Clinical experts input before committee

- Follow-up for people taking epcoritamab in LTR ranges; expert 1: every 3 to 4 months in clinic, expert 2: once per year as telephone consultation or nurse-led consultation

- When should people having epcoritamab switch from 'high-intensity' to 'low-intensity' follow-up?
- Should the resource use be the same for people having epcoritamab as for people not having treatment:
  - when on 'low-intensity' follow-up?
  - in long-term remission?

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Abbreviations: LTR, long-term remission; PFS, progression-free survival

Key issue: subsequent treatments*

EAG assume higher proportion of people receive CAR-T after epcoritamab

Company response to DG

- Updated subsequent treatment estimates based on feedback from 4 UK clinical experts

Proportion of patients receiving subsequent treatments after epcoritamab in company and EAG models, and in EPCORE NHL-1

%	Company		EAG		EPCORE NHL-1[1]
	Pop A	Pop B	Pop A	Pop B	
R-based CIT	40.6	32.5	30	30	[redacted]
CAR-T	0.6	8.1	11	30	[redacted]
Radiotherapy	12.5	13.8	25	25	[redacted]
Pola	0	0	0	0	[redacted]
Lenalidomide	0	0	0	0	[redacted]
No tx costs	46.0	40.4	30	12	[redacted]
Other	0	0	0	0	[redacted]

EAG comments

- Prefers estimates from EAG's clinical experts
- Company's revised estimates underestimate use of subsequent CAR-T
- EAG's preferred CAR-T estimates are aligned with EPCORE NHL-1 where [redacted] of patients received subsequent CAR-T
- Maintains view that people receiving R-based CIT or pola+BR should receive subsequent palliative chemotherapy, not R-based chemotherapy

[1] From Table 4 of EAG critique of company response. Company and EAG disagree on correct proportions from EPCORE NHL-1. EAG consider that different denominators were used: company used number of patients who had each subsequent treatment out of total enrolled LBCL patients and EAG used progressed patients with subsequent treatment.

What subsequent treatments should be used in model?

- What percentage of people will receive CAR-T post-progression in clinical practice?
- Would people receive R-based chemotherapy after R-based CIT and pola+BR?

*see appendix for original and updated subsequent treatment assumptions

QALY weighting for severity: Pola + BR*

Background

- Committee concluded severity modifier unlikely to apply to pola+BR; did not apply for TA927 or ID3943.
- Company conclude x1.2 based on 85% proportional shortfall. EAG: does not meet x1.2 modifier criteria

Key for applying severity modifier

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

QALY shortfall analysis

Treatment	Expected total QALYs without disease	Total QALYs with condition, under current treatment	Absolute shortfall	Proportional shortfall	QALY weight
Company base-case assumptions (deterministic)	[redacted]	1.73	[redacted]	85.00%	1.2
Company base-case assumptions (probabilistic)	[redacted]	1.80	[redacted]	84.48%	1
EAG base-case assumptions	[redacted]*	1.75	[redacted]	83.4%	1
Glofitamab company base case assumptions (cure at 3 yrs)	11.62	2.63	8.99	77.36%	1
Loncastuximab tesirine company base case assumptions	11.66	1.82	9.84	84%	1

Abbreviations: QALY, quality-adjusted life year; * using company estimate of 'Expected total QALYs without disease', the QALY weighting is still 1

*See more details in appendix

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

- ❑ Recap - overall
- ❑ Consultation responses
- ✓ **Summary**

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Company and EAG preferred base case after consultation

Assumption	Company base case	EAG base case
MAIC (and number of variables adjusted)	All partially adjusted: R-based CIT: 7 variables Pola + BR: 6 variables adjusted to Sehn et al. Axi-cel: DLBCL, 7 variables	R-based CIT: 9/10 reported variables (*company scenario A.4*) Fully adjusted: Pola + BR: 10 variables adjusted to Sehn (*company scenario A.1)* Axi-cel: LBCL, 11 variables (*company scenario B.1*)
LTR assumption	From 36 month after treatment initiation for all comparators (in line with TA927; glofitamab)	Same as company Scenario removing LTR for epcoritamab
OS, PFS, TTD extrapolation curves	As per slides	Alternative curves for most arms of each comparisons For pop B, applied HR of 1.2 to epcoritamab PFS curve, to estimate epcoritamab TTD curve
Estimation of PFS curve for R-based CIT	Based on OS HR from 7/10 adjusted MAIC ([redacted]*). Scenario using HR between OS and PFS for epcoritamab applied to OS for R-based CIT	Based on OS HR from unadjusted, no prior CAR-T MAIC ([redacted])
Capping of epcoritamab curves	n/a	OS capped to OS for R-based CIT PFS capped to PFS for axi-cel
Follow-up costs for people in complete remission while still taking epcoritamab	Updated estimates of resource use (based on clinical input) after [redacted] months	Company's original reduced follow-up intensity to start 1 year after treatment initiation
Subsequent treatment	Proportions from new expert input Included rituximab costs for CIT	Removed rituximab from R-based CIT EAG's preferred distributions from technical engagement

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

- Company base case ICERs for comparison with R-based CIT are within the range normally considered an effective use of NHS resources when there is a high level of uncertainty; for the comparison with pola + BR, ICERs are higher than the range normally considered an effective use of NHS resources (with and without the severity modifier applied)
- In the company's base case, epcoritamab costs less than axi-cel but produces more QALYs
- EAG base case ICERs for all comparisons are higher than the range normally considered an effective use of NHS resources when there is a high level of uncertainty

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

Supplementary appendix

- Responses to consultation
- Supporting background information
- Supporting information for key issues
- ACM1 slides

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Company response to consultation: summary

MAICs

- Information provided (re: population from EPCORE NHL-1 eligible for intensive therapies), but no scenario requested
- Scenarios:
  - with fully adjusted MAICs
  - with Crump for R-based CIT

Modelling

- Add long-term remission for all comparators in line with glofitamab appraisal (TA927)
- Sought clinical expert opinion to obtain values more representative of UK clinical practice and incorporated in base case:
  - 'low intensity' follow-up costs for people having epcoritamab who are in complete remission
  - subsequent treatment
- Incorporate committee preferred bridging and monitoring costs with EAGs and use updated chemotherapy administration costs
- Scenarios:
  - alternative to estimate PFS for R-based CIT
  - some patients in population A discontinue other than PFS
  - using piecewise approach
- Re-generated shortfall calculations from updated models

Patient group: Blood Cancer UK*

- Disappointed in decision
- Re-iterate key messages from initial submission:
    - significant proportion of patients fail to respond to first two treatments or will relapse after initial response; these patients live with challenges associated with the disease plus treatment toxicities and psychological impacts of ineffective, harsh treatments. Significant impact on quality of life of patients and carers
    - significant unmet need: not all will be cured or have a durable response with current treatment
    - improving quality and length of life is hugely important to patients and their loved ones
    - epcoritamab: easy to administer, well tolerated, more readily available than CAR-T therapy; good option when other options exhausted – even if not curative, additional life years hugely valuable
- Acknowledge difficulties in determining reliable cost effectiveness estimates; patients should be heart of decision-making
- Heavy burden for patients and carers for managing symptoms and toxicities of current treatment; need for kinder treatments
- No widely accessible standard of care at 3rd line – needs more consideration. Nuances of trials differs from clinical practice
- Epcoritamab tolerability and potential clinical benefit with subcutaneous administration are valuable benefits to patients and NHS: administration convenient and avoids disruption to day-to-day life
- At this stage of treatment line, physical and mental burdens are great; CAR-T often not a real option for many
- Epcoritamab has potential to change course of lives – a transformative choice in heavily pre-treated patients with limited options

Professional groups*

Royal College of Physicians, Association of Cancer Physicians, Royal College of Radiologists

- Disappointed in decision
- Easily delivered in day setting – ideal for local treatment
- Subcutaneous attractive for some patients
- Glofitamab has identical response rate and similar adverse event profile; ongoing collection of RWE may help determine if one is superior; concerned if epcoritamab not approved, NHS patients could be denied a potentially superior treatment
- Clinically implausible no advantage over R-chemo which has poor impact on survival in 3rd line and beyond
- GEN-01 study not appropriate to compare with other trials includes heavily pre-treated patients with poor risk, 40% with prior CAR-T, and was conducted during COVID-19.

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Clinical expert - Wendy Osborne*

- EPCORE NHL-1 and pola + BR trial (Sehn et al) not comparable:
    - No patients in Sehn had prior CAR-T because it was not available, compared to 40% in EPCORE NHL-1
    - Patients in EPCORE NHL-1 higher risk:
        - more prior lines of therapy (30% had only 1 prior line in pola+BR study)
        - more efficacious prior treatments (subsequent refractory disease likely worse)
- Comparison with pola + BR not clinically useful:
    - Patients all now have polatuzumab first line – will not be used again if relapse
    - Clinicians now avoid using bendamustine since T-cell engagers now available because there is data bendamustine depletes cells for years, reducing efficacy of CAR-T – will not want to preclude 3rd line use of CAR-T in patients
- 'Fitness' for treatment
    - Autologous stem cell transplant is 'intensive treatment'; all other treatments – including CAR-T are less intensive with same 'fitness' for treatment required

Clinical expert - Wendy Osborne (continued) *

- Expected epcoritamab use in practice
    - 3rd line after CAR-T if relapse within 12 months of treatment (NB: this use of CAR-T is currently in the CDF so cannot be considered in this appraisal)
    - 4th line if relapse after 12 months of treatment (and therefore receive CAR-T in the 3rd line)
    - 3rd line instead of CAR-T because CAR-T not possible earlier (waiting for apheresis or manufacturing / patient choice)
- Intention to treat data
    - ZUMA-1 only assessed infused patients, not patients who did not reach infusion: some patients drop out after apheresis (based on UK data from Kuhnl et al.), are not referred because of rapid progressive disease that could not be wait 6-8 weeks before infusion, or are not referred because of distance from a CAR-T centre.
- Delivery
    - Bispecifics improve access independent of location – many district general hospitals are experienced in delivering, particularly far from CAR-T centres since patients have been choosing treatment closer to home; subcutaneous off-the-shelf administration and hospitals that manage neutropenic sepsis can manage low grade CRS associated with bispecifics

Comparator company comments (Gilead, axi-cel) *

- Bridging therapy not mandatory, may reduce disease bulk and progression while CAR-T cells manufactured: no bridging or corticosteroids only in 11% of UK patients in 2020-2022 (Boyle 2023 RWE study)
- Conclusion that axi-cel population from ZUMA-1 likely healthier than epcoritamab population in EPCORE NHL-1 because ZUMA-1 population excludes those referred but not transfused not substantiated:
    - 94% in ZUMA-1 had stage III or IV disease at baseline compared with 73% with DLBCL in EPCORE NHL-1
- Costs associated with axi-cel need reviewing to ensure costs are not included twice; NHSE tariff includes all costs of care and may include bridging therapy (NB: NHSE Cancer Drugs Lead advised before ACM1 that bridging therapy not included in tariff)
- Agree fully adjusted MAICs needed and that study populations may not be similar enough for valid comparison
    - Number of prior lines important prognostic factor in DLBCL
- Question appropriateness of separate analyses for population A and population B; unclear methodology to define populations; should be based on ECOG status in line with NICE recommendations rather than trial inclusion (i.e. people with ECOG 2 considered for CAR-T)
- Full evidence base for axi-cel not included: efficacy and safety results from UK RWE study (Boyle 2023)

Abbreviations

General

CI	Confidence interval	CR	Complete response	DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group	FACT-Lym	The Functional Assessment of Cancer Therapy	HRQoL	Health-related quality of life
ICANS	Immune effector cell-associated neurotoxicity syndrome	ICER	Incremental cost-effectiveness ratio	IPI	International Prognostic Index
IRC	Independent review committee	ITT	Intention to treat	LBCL	Large B-cell lymphoma
LTR	Long-term remission	MAIC	Matching adjusted indirect comparison	Neff	Effective sample size
OR(R)	Overall response (rate)	OS	Overall survival	PFS	Progression-free survival
QALY	Quality-adjusted life year	TE	Technical engagement	TOT	Time on treatment
TTD	Time to treatment discontinuation	TTNT	Time to next treatment	TTNT	Time to next treatment

Treatment names

ASCT	autologous stem cell transplant	Axi-cel	axicabtagene ciloleucel
HDT	high dose therapy	CAR-T	chimeric antigen receptor T-cell
Pola R-CHP	polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisolone	Pola + BR	polatuzumab vedotin with rituximab and bendamustine
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone	R-based CIT	rituximab-based chemoimmunotherapy
R-GemOX	rituximab, gemcitabine and oxaliplatin	SCT	stem cell transplantation
tisa-cel	tisagenlecleucel		

Equality considerations

Possible initial inequality of access and in the longer term without training and support for smaller centres

Patient organisation:

- epcoritamab may need to be delivered at larger, transplant or CAR-T centres initially before training and support at smaller centres provided: short-lived inequities for patients who live further from centres and cannot afford to pay for travel or are unable to travel longer distances
- potential longer-term inequity if training and support for smaller centres not in place.

Clinical experts (at technical engagement):

- epcoritamab will allow more equality of access and reduce inequalities compared with CAR-T due to geographical limitations of CAR-T and the difficulties that some patients have with accessing CAR-T (social support, economic, travel)

Committee's key conclusions & requests from ACM 1*
Epcoritamab not recommended

Committee conclusions and key issues	Company response	Resolved?	ICER impact
Pola-BR, R-based CIT, and axi-cel are relevant comparators	Pola-BR less relevant but presented	Resolved (ACM1)	n/a
MAICs very uncertain; scenarios with fully adjusted analyses needed	Scenarios provided but prefer partially adjusted	Partially resolved	Large
For population A (comparisons with R-based CIT and Pola + BR):			
Unresolvable uncertainty if results applicable to people who previously had CAR-T	n/a	Unresolvable uncertainty	Unknown
Uncertain if MAICs include people ineligible for intensive treatments. Need: • Baseline characteristics and efficacy outcomes from subgroup in EPCORE TM NHL-1 ineligible for intensive treatments • Scenarios with 'no prior CAR-T, ineligible for intensive therapies' population from EPCORE NHL-1 adjusted to comparator trials	Provide baseline characteristics but not scenarios	Unresolvable uncertainty	Unknown
Do not include QALY adjustment for subsequent use of axi-cel	Removed	Resolved	Unknown
Scenarios needed where treatment is stopped for reasons other than progression	Provided	Resolved	Small

Committee's key conclusions & requests from ACM 1 (cont'd) *

Issue	Company response	Resolved?	ICER impact
For comparison with R-based CIT:			
Scenario needed using data from Crump et al	Provided but prefer Neelapu et al	Resolved	Small
Scenario using hazard ratio between OS and PFS to estimate PFS curve	Provided	No, to discuss	Small
For population B (comparison with axi-cel):			
Scenario needed with fully adjusted MAIC in LBCL population	Provided	Unresolvable uncertainty	Small
Remove additional monitoring costs, use EAG's bridging costs	Done in base case	Resolved	Unknown

Recap

Committee's key conclusions & requests from ACM 1 (cont'd) *

Issue	Company response	Resolved?	ICER impact
Other conclusions about cost-effectiveness:			
Poor fitting of extrapolations for OS, PFS, TTD for all treatments; scenarios using more flexible extrapolations needed	Piecewise scenarios provided	No, to discuss	Large
Long-term remission should be included for all treatments	Done in base case	Partially, to discuss	Large
Subsequent treatment should reflect UK clinical practice or be aligned with EPCORE NHL-1	Clinical input received	No, to discuss	Large
Follow-up costs for people who had a complete remission while taking epcoritamab should have reduced intensity; clinical validation needed	Clinical input received and costs updated	No, to discuss	Large
Other:			
Severity weighting x 1.2 appropriate for R-based CIT comparison but unlikely for pola + BR comparison; need updated shortfall calculations	Update calculations; pola + BR x1.2	No, to discuss	n/a
Committee would accept ICER at lower end of acceptable range due to uncertainty		n/a	n/a

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Comparative Evidence – company base case MAIC (pop A)

Epcoritamab [redacted] OS vs R-based CIT

OS for epcoritamab compared with R-based CIT (DLBCL): company MAIC (7 adjusted factors)

OS for epcoritamab compared with R-based CIT (DLBCL): EAG-preferred MAIC (9/10 reported factors adjusted)

PFS not reported in comparator trial (SCHOLAR-1); modelled based on OS HR

EAG comments:

- Company base case not EAG preferred MAIC (adjust 9/10 reported factors)
- Lack of overlap between trials in MAIC (small sample sizes and factors remain imbalanced). Difference between trials may be too large for robust conclusions

Comparative Evidence – MAIC from scenario (population A)

[redacted] in OS and PFS between epcoritamab and pola + BR

OS for epcoritamab compared with pola + BR: company MAIC (6 adjusted factors)

OS for epcoritamab compared with pola + BR: EAG-preferred MAIC (10/10 adjusted factors)

Company did additional scenarios using data from Liebers (in which only 60% had pola + BR; 40% had pola only) and Northend using subgroup with 3+ prior lines of therapy

EAG comments:

- Company base case does not use fully adjusted MAICs
- Lack of overlap between trials in MAIC (small sample sizes and factors remain imbalanced in partially adjusted MAIC). Difference between trials may be too large for robust conclusions

Comparative Evidence – MAIC from scenario (population A)

[redacted] in OS and PFS between epcoritamab and pola + BR

PFS for epcoritamab compared with pola + BR: company MAIC (6 adjusted factors)

[redacted]

PFS probability

PFS for epcoritamab compared with pola + BR: EAG-preferred MAIC (10/10 adjusted factors)

[redacted]

Company did additional scenarios using data from Liebers (in which only 60% had pola + BR; 40% had pola only) and Northend using subgroup with 3+ prior lines of therapy

Comparative Evidence – company base case MAIC (pop B)

[redacted] in OS and PFS between epcoritamab and axi-cel

OS for epcoritamab compared with axi-cel: company MAIC (DLBCL; 7 adjusted factors)

[redacted]

OS for epcoritamab compared axi-cel: EAG-preferred MAIC (LBCL; 11 adjusted factors)

Survival probability

[redacted]

EAG comments:

- Company base case does not use fully adjusted MAICs
- Prefer MAIC with LBCL population from EPCORE™ NHL-1 (plus adjustment for type of LBCL) to align more closely with ZUMA-1 population
- Lack of overlap between trials in MAIC (small sample sizes and factors remain imbalanced). Difference between trials may be too large for robust conclusions

Comparative Evidence – company base case MAIC (pop B)

[redacted] in OS and PFS between epcoritamab and axi-cel

PFS for epcoritamab compared with axi-cel: company MAIC (DLBCL; 7 adjusted factors)

PFS for epcoritamab compared axi-cel: EAG-preferred MAIC (LBCL; 11 adjusted factors)

OS extrapolations: epcoritamab (adjusted) vs. R-based CIT *

Company-preferred OS curves using company preferred MAIC (7/10 adjusted variables)

OS extrapolations: epcoritamab (adjusted) vs. R-based CIT

EAG prefer piecewise model using KM data up to 24 months, with survival converging between treatment arms after 12 years

EAG base-case curves (EAG-preferred MAIC[a]) – piecewise with KM up to 24 months; long-term remission 36 months for all treatments

EAG base-case curves (EAG-preferred MAIC[a]) – piecewise with KM up to 24 months; long-term remission 36 months R-based CIT only

[a] EAG-preferred MAIC: adjusted for 9/10 reported variables

PFS extrapolations: epcoritamab (adjusted) vs. R-based CIT

Company determine PFS determined by applying HR from MAIC for OS to the PFS epcoritamab curve [a]

Company-preferred curves using company preferred MAIC (7/10 adjusted variables)

[a] HR for OS applied to PFS epcoritamab curve to generate R-based CIT PFS curve: [redacted]

PFS extrapolations: epcoritamab (adjusted) vs. R-based CIT

EAG prefer using HR between OS and PFS for epcoritamab to R-based CIT OS curve [a] and piecewise model using KM data up to 24 months

EAG base-case curves (EAG-preferred MAIC[b]) – piecewise with KM up to 24 months; long-term remission 36 months for all treatments

EAG base-case curves (EAG-preferred MAIC[b]) – piecewise with KM up to 24 months; long-term remission 36 months R-based CIT only

[a] HR between OS and PFS for epcoritamab that is applied to R-based CIT PFS curve: [redacted], 95% CI: [redacted],
[b] EAG-preferred MAIC: adjusted for 9/10 reported variables (company scenario A4)

OS extrapolations: epcoritamab (adjusted) vs. pola + BR*

Company-preferred curves using company preferred MAIC (6/10 adjusted variables)

OS extrapolations: epcoritamab (adjusted) vs. Pola + BR *

EAG: company curves overestimate epcoritamab and underestimate pola + BR survival; prefer piecewise model using KM data up to 24 months

EAG base-case extrapolation (fully adjusted MAIC)[a] – piecewise with KM up to 24 months; long-term remission 36 months for all treatments

EAG base-case extrapolation (fully adjusted MAIC) [a] – piecewise with KM up to 24 months; long-term remission 36 months pola + BR only

[a] 10/10 variables adjusted to Sehn et al

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PFS extrapolations: epcoritamab (adjusted) vs. Pola + BR

Company-preferred extrapolation for epcoritamab

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PFS extrapolations: epcoritamab (adjusted) vs. Pola +BR

EAG: company curves poorly fitted [redacted]; prefer piecewise model using KM data up to 24 months

EAG base-case extrapolation (fully adjusted MAIC) – piecewise with KM up to 24 months; long-term remission 36 months for all treatments

[redacted]

EAG base-case extrapolation (fully adjusted MAIC) – piecewise with KM up to 24 months; long-term remission 36 months pola+BR only

[redacted]

OS extrapolations: epcoritamab (adjusted) vs. axi-cel*

Company-preferred curves using company preferred MAIC (DLBCL 7/10 adjusted variables)

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OS extrapolations: epcoritamab (adjusted) vs. axi-cel *

EAG: company curves do not [redacted]; prefer piecewise model using KM data up to 24 months

EAG base-case extrapolation (fully adjusted MAIC)[a] – piecewise with KM up to 24 months; long-term remission 36 months for all treatments

[redacted]

[a] EAG-preferred MAIC: LBCL population, 11/11 variables adjusted for

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PFS extrapolations: epcoritamab (adjusted) vs. axi-cel

Company-preferred extrapolations for epcoritamab from company-preferred MAIC (DLBCL 7/10 adjusted variables)

PFS extrapolations: epcoritamab (adjusted) vs. axi-cel

EAG: prefer piecewise model using KM data up to 24 months which better captures [redacted]

EAG base-case extrapolation (fully adjusted MAIC)[a] – piecewise with KM up to 24 months; long-term remission 36 months for all treatments

EAG

- Gompertz curve for epcoritamab (company base case) likely provides implausible [redacted] not in trial;
- For axi-cel, best fit (generalised gamma) and second-best (Gompertz – company choice) similar including divergence at 60 months
  - KM curves suggest epcoritamab has higher progression than axi-cel, but limited data after 2 years for epcoritamab to judge this

[a] EAG-preferred MAIC: LBCL population, 11/11 variables adjusted for

PFS extrapolations: epcoritamab (adjusted) vs. axi-cel

EAG: prefer piecewise model using KM data up to 24 months which better captures [redacted]

EAG base-case extrapolation [a] – piecewise with KM up to 24 months; long-term remission 36 months axi-cel only

EAG base-case extrapolation [a] – piecewise with KM up to 24 months; long-term remission 36 months axi-cel only; PFS for epcoritamab allowed to cross the PFS curve for axi-cel

[a] EAG-preferred MAIC: LBCL population, 11/11 variables adjusted for

TTD extrapolations: epcoritamab vs axi-cel

EAG: piecewise models do not address EAG concerns that TTD for epcoritamab underestimated; EAG base case applies HR of 1.2 to PFS curve to estimate TTD for epcoritamab

EAG

- In company base case, there is a difference of just over [redacted] years between mean PFS and mean TTD in model
- EAG considers this to be extremely high and unlikely to be clinically plausible (as it implies that [redacted] of PFS benefit). So, treatment costs for epcoritamab are likely under-estimated
- EAG base case uses scenario from technical engagement where HR of 1.2 applied to epcoritamab PFS curve, to estimate epcoritamab TTD curve which led to a difference in mean PFS and TTD of approximately 2 years
- EAG scenario uses piecewise approach with first 24 months from KM data and then extrapolation based on lognormal curve.

Key issue: resource use in progression-free state

- Company elicited clinical feedback for resource use for epcoritamab in **'low-intensity'** phase (after complete remission)
- Output was lower than original assumptions for **'low-intensity'** phase (e.g. after treatment discontinuation for comparators)
- So, company applied revised lower resource use across **'low-intensity'** phase (e.g. for epcoritamab and comparators)
- Company follow-up note that residential care, day care, and home care were accidentally included from **PFS 'low-intensity'**; resource use in the model; the company ran scenarios with these costs excluded > small ICER impact

Table: Update to PFS 'low-intensity' resource use

Resource use	Original base case	Revised DGD base case[a]	DGD scenario
Residential care	0.75	0.75	0.00
Day care	0.28	0.28	0.00
Home care	1.17	1.17	0.00
Hospice	0.00	0.00	0.00
Oncologist	0.00	0.00	0.00
Haematologist	0.19	0.50	0.50
Radiologist	0.00	0.00	0.00
Nurse	1.00	1.00	1.00
Specialist nurse	0.17	1.00	1.00
GP	0.00	0.00	0.00
District nurse	0.38	0.38	0.38
CT scan	0.31	0.00	0.00
Full blood count	3.33	1.00	1.00
LDH	2.00	0.00	0.00
Liver function	3.33	1.00	1.00
Renal function	1.00	1.00	1.00
Immunoglobulin	0.67	0.15	0.15
Calcium phosphate	0.15	0.08	0.08

Key issue: subsequent treatments*

Company base case assumptions for subsequent treatment usage (progressed health state)

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

EAG base case assumptions for subsequent treatment usage (progressed health state)

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

NICE

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

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QALY weighting for severity*

NICE methods now include a QALY weighting system based on disease severity

Severity reflects future health lost by people living with a condition who have current standard care

Health: length and quality of life (QALYs)

QALYs people without the condition (A)

QALYs people with the condition (B)

Health lost by people with the condition: QALY shortfall

Absolute shortfall: total = A – B

Proportional shortfall: fraction = (A – B) / A

Criteria used to decide QALY weighting

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

- QALY weightings can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

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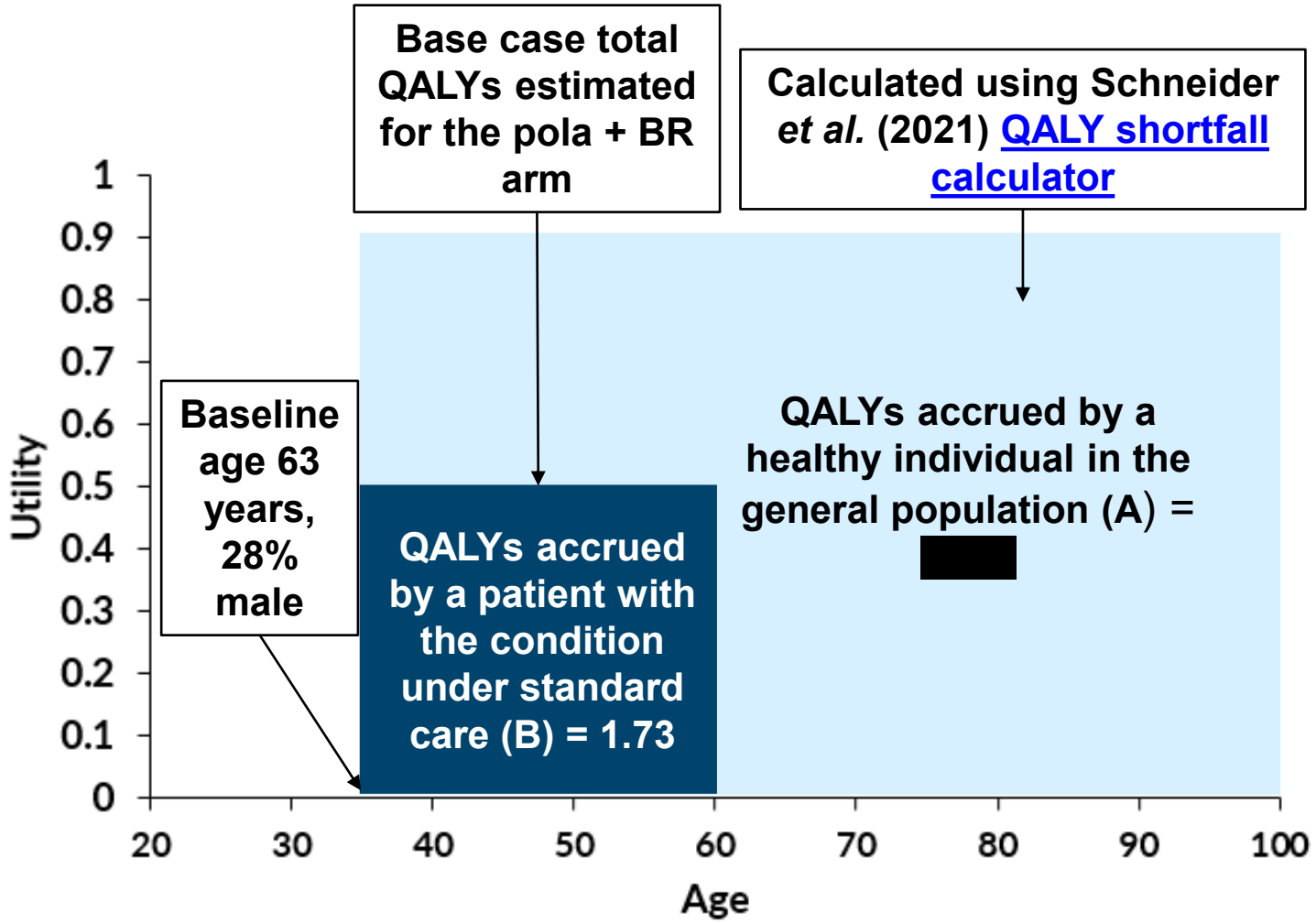
QALY weighting for severity: company model vs pola + BR *

NICE methods include a QALY weighting system based on disease severity

Example calculation: Company base case assumptions in pola + BR arm (deterministic)



Absolute shortfall = [redacted] – 1.73 = [redacted]

Proportional shortfall = ([redacted] - 1.73) / [redacted]
= 85.00%

Corresponding QALY weights:

- **Absolute shortfall** = 1
- **Proportional shortfall** = 1.2

The higher weight of 1.2 was applied by the company

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QALY weighting for severity*

Key for applying severity modifier

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

QALY shortfall analysis*

Treatment	Expected total QALYs without disease	Total QALYs with condition, under current treatment	Absolute shortfall	Proportional shortfall	QALY weight
Company base-case assumptions (deterministic)					
R-based CIT	[redacted]	0.88	[redacted]	94%	1.2
Pola + BR	[redacted]	1.73	[redacted]	85%	1.2
Axi-cel	[redacted]	5.86	[redacted]	59%	1
EAG base-case assumptions					
R-based CIT	[redacted]	1.27	[redacted]	91.13%	1.2
Pola + BR	[redacted]	1.75	[redacted]	83.4%	1
Axi-cel	[redacted]	5.58	[redacted]	61.03%	1
Glofitamab company base case assumptions (cure at 3 years)					
BR	11.62	1.20	10.42	89.67%	1.2
Pola+BR	11.62	2.63	8.99	77.36%	1
Axi-cel	11.62	4.98	6.64	57.14%	1
Loncastuximab tesirine company base case assumptions					
Chemotherapy	11.66	0.92	10.74	92%	1.2
Pola+BR	11.66	1.82	9.84	84%	1

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

- Company have not submitted a detailed proposal but have noted the ongoing phase 3 randomised trial, EPCORE™ DLBCL-1, in the same population comparing epcoritamab with investigator's choice chemotherapy; primary study completion December 2024
- Committee concluded that the trial only includes 1 of the 3 relevant comparators so it was unlikely to resolve the main uncertainties such as the efficacy of epcoritamab compared with pola + BR and axi-cel.

Key clinical trial: EPCORE™ NHL-1

Cohort from single arm trial presented in company submission

Clinical trial design and outcomes

	EPCORE™ NHL-1
Design	Single-arm, phase 1 / 2, open-label, multicentre
Population	Adults with relapsed, progressive, or refractory B-cell lymphoma: 1 of 3 cohorts in trial expansion (using recommended dose regimen) included aggressive B-cell non-Hodgkin lymphoma / large B-cell lymphoma
Intervention	Epcoritamab
Comparator(s)	None
Duration	Ongoing; estimated completion April 2029
Primary outcome	Overall response rate (Lugano criteria assessed by IRC)
Key secondary outcomes	Response rates (i.e. complete response), PFS, OS, AEs, FACT-Lym and EQ-5D-3L, time to next treatment
Locations	Australia, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Singapore, South Korea, Spain, Sweden, UK ([redacted] over [redacted] sites), US
Used in model?	Yes; OS, PFS, TTD, adverse events, HRQoL

Indirect comparisons: EPCORE™ NHL-1 is single arm-study so company conducted unanchored MAICs using individual patient data from EPCORE™ NHL-1 weighted to match each comparator trial

Summary of company and EAG preferences (ACM1)*

Assumption	Company base case	EAG exploratory analyses
MAIC adjustment for comparison vs R-based CIT	Partially adjusted (7 variables)	Adjusted for 9/10 reported variables (*company scenario A.4*)
EPCORE™ NHL-1 population matched to ZUMA-1	DLBCL, no prior CAR-T, CAR-T eligible	LBCL, no prior CAR-T, CAR-T eligible (to provide comparable groups) (*company scenario B.1*)
LTR assumption	Removed for all comparators	Re-introduced for all comparators at 2 years after end of treatment with no further follow-up costs but notes substantial limitations of these scenarios
OS, PFS, TTD extrapolation curves	As per slides	Alternative curves for most arms of each comparisons For pop B, applied HR of 1.2 to epcoritamab PFS curve, to estimate epcoritamab TTD curve
PFS curves for axi-cel	Curves for epcoritamab and axi-cel [redacted]	Conduct 2 scenarios: 1) assume epcoritamab and axi-cel curves are same after crossing; 2) allow epcoritamab curve to cross axi-cel [redacted]
Epcoritamab follow-up costs	People with epcoritamab assumed to incur less resource use after [redacted] months	PFS on-treatment cost when patients progression-free on treatment
Axi-cel costs in addition to £41,101*	Added monitoring costs to cover bed costs related to adverse events Added bridging costs	Remove company's additional monitoring costs Alternative bridging costs
Subsequent treatment	Included rituximab costs for CIT Added QALY adjustment for subsequent axi-cel	Removed rituximab from R-based CIT Removed company QALY adjustment for subsequent axi-cel

*See summary of differences at ACM2