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

For committee – contains ACIC information

Technology appraisal committee C [10 October 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

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Patient and clinical perspectives*

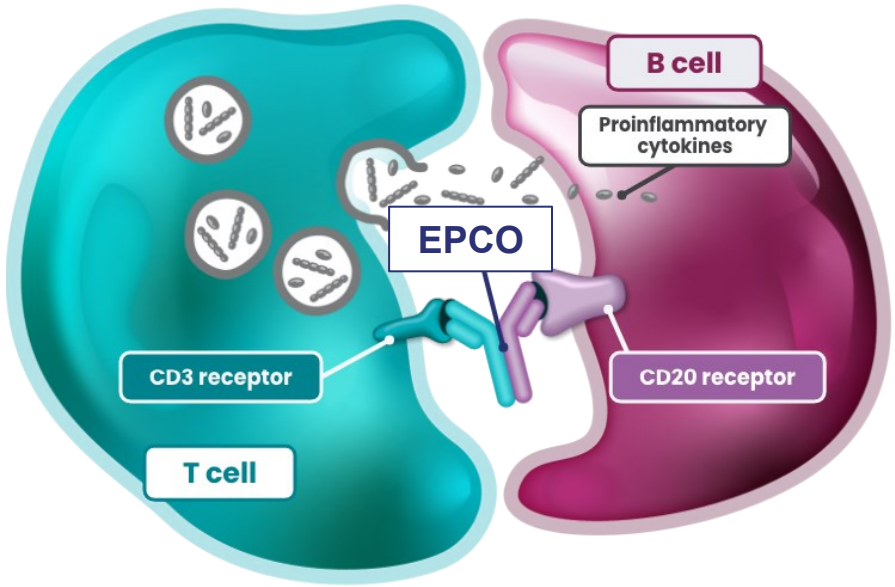
Epcoritamab

- Only subcutaneous treatment option → could improve access compared with CAR-T
- Option if ineligible for or refractory to CAR-T
- High tolerability (possibly fewer side effects than CAR-T)
- Concerns it needs to be led by specialist haematology centres; training needed to manage side effects in non-CAR-T centres

Bispecifics are important new drugs for DLBCL treatment

- Epcoritamab and glofitamab have similar mechanisms of action

Figure: Mechanism of action of epcoritamab

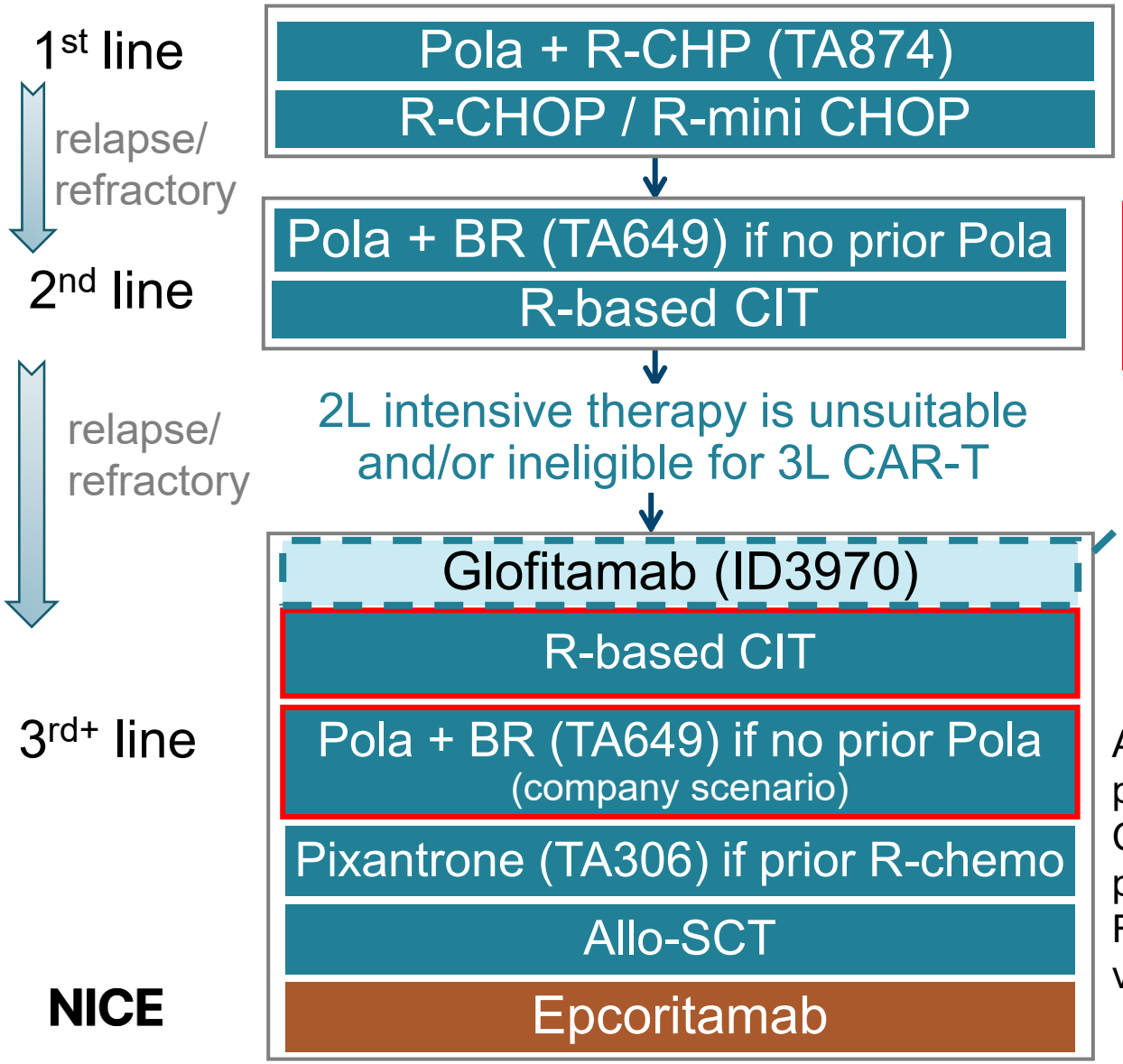


	Mode of administration	Treatment duration
Epcoritamab	Subcutaneous	Continues until progression
Glofitamab	Intravenous	Max 12 cycles

Abbreviations: EPCO, epcoritamab

*See appendix for background

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



Included in company submission as relevant comparators

FDG available for appeal.
Final publication anticipated: October 2023

Are pola + BR and R-based CIT the appropriate comparators?

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

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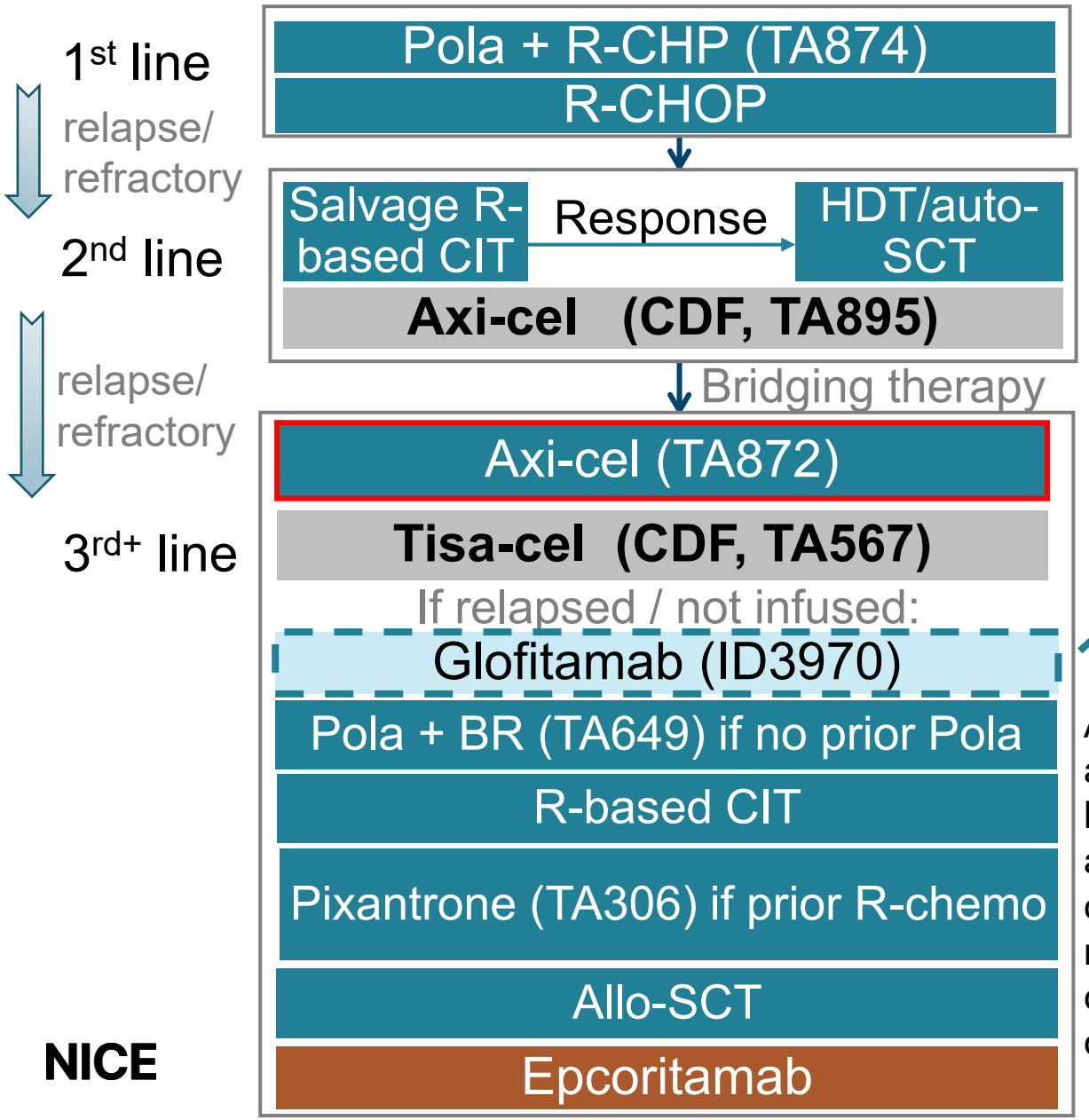
Treatment pathway for DLBCL – intensive Rx suitable (population B)



Included in company submission as relevant comparator

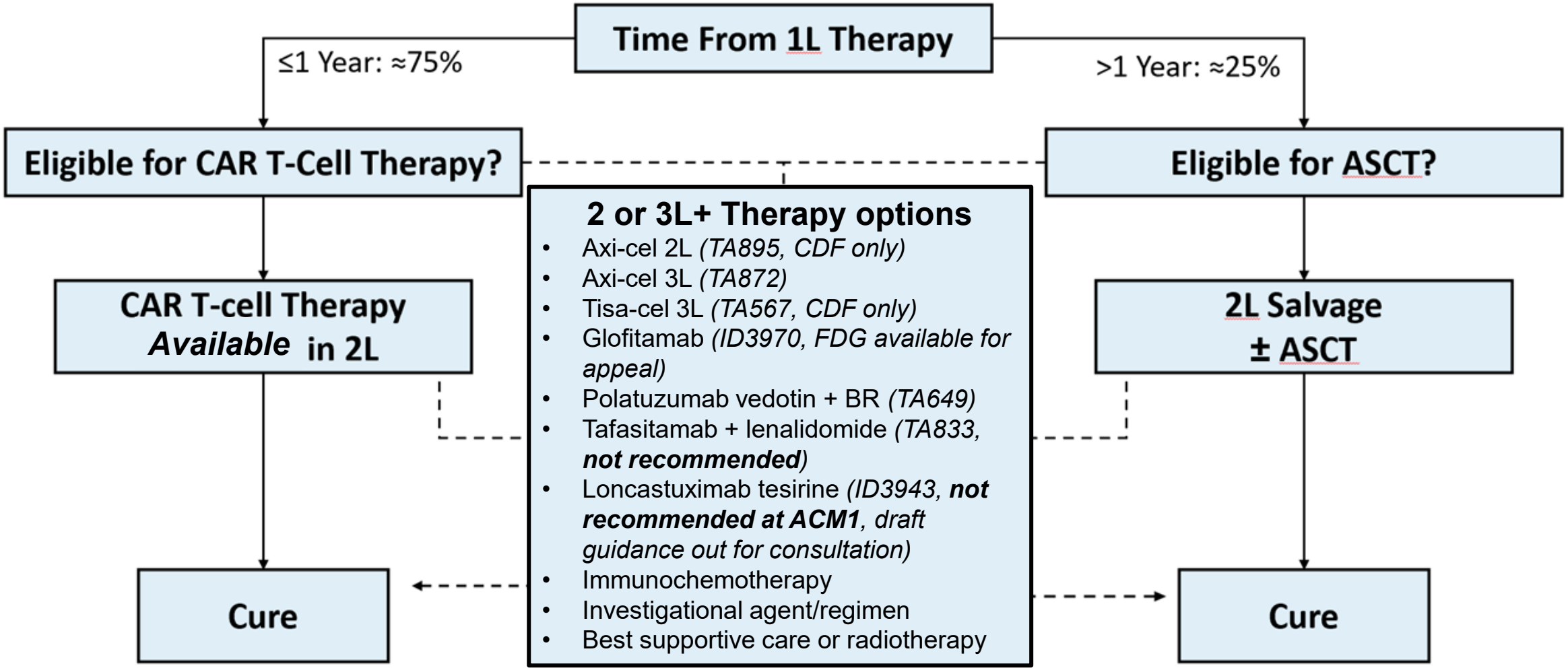
CDF drugs not considered in appraisal

FDG available for appeal.
Final publication anticipated: October 2023

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

Pathway evolving: time to relapse more important?

Pola + R-CHP (TA874)



Abbreviations: ASCT, autologous stem cell transplant; Pola + R-CHP, polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisolone

With thanks to Wendy Osborne. Adapted from Westin and Sehn; Blood 2022;139:2737-2749

Epcoritamab (Tepkinly®, AbbVie)

Marketing authorisation	• Expected marketing authorisation wording: [redacted]
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[a]
Administration	Subcutaneous injection

Price	• List price: [redacted]
	• Confidential simple patient access scheme in place
	• Average cost of a course of treatment[b]:
	  • Between [redacted] and [redacted] for people not eligible for, or choose not to have, intensive treatments (population A)
	  • [redacted] for people eligible for intensive treatments (population B)

[a] Similar mechanism of action to glofitamab (seen by committee C in August)
[b] provided by company and based on modelled time to treatment discontinuation within the company's analyses

Key issues*

Key issues	Resolved?	ICER impact
1. Concerns with MAIC(s)	No, to discuss	Unknown
2. Long-term outcomes		
- remission	No, to discuss	Moderate
- OS & PFS	No, to discuss	Large
- TTD	No, to discuss	Large
3. Longer term treatment with epcoritamab		
- subsequent treatment and associated costs	No, to discuss	Large
- follow up costs	No, to discuss	Large
4. Comparators in a changing pathway	No analysis	Unknown

*See appendix for other issues and MAIC critique

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

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Key clinical trial: EPCORE™ NHL-1 (n=139)*

Company present cohort from expansion part of ongoing single-arm phase 1/2 trial

Clinical trial treatment

Cycle 1, week 1-3: step-up doses once weekly → **Cycle 1, week 4 to cycle 3:** full dose once weekly → **Cycles 4-9:** full dose every other week → **Cycles 10+:** full dose every 4 weeks

Primary outcome	Overall response rate*
Key secondary outcomes	Response rates (i.e. complete response), **PFS, OS, AEs,** FACT-Lym and **EQ-5D-3L**, time to next treatment

Note: 28-day cycles; treatment taken until progression or unacceptable toxicity (no stopping rule)

Efficacy results of EPCORE™ NHL-1 ([redacted] data cut; median follow-up [redacted])

Outcome	DLBCL population (N=139)
ORR rate (95% CI)*	[redacted]
CR (95% CI)*	[redacted]
DOR, median months (95% CI)*	[redacted]
Median PFS (95% CI)*	[redacted]
Median OS (95% CI)	[redacted]
Any grade ≥3 adverse event, % (n)	[redacted]
Adverse event leading to discontinuation, % (n)	[redacted]

*Lugano criteria assessed by IRC

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*See more trial details in appendix

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Key issue: adjustment in MAICs

EAG: factors imbalanced – additional adjustment needed; Company: fully adjusted MAICs over-adjusted

Background

- Some reported baseline characteristics in EPCORE™ NHL-1 and comparator studies not adjusted for

Company (TE)

- Uses partially adjusted MAICs in base case. Conducted scenarios with fully adjusted MAICs for all 3 comparators. Results have high degree of uncertainty and issues with over-adjustment as UK clinical experts confirm some variables correlated (i.e. disease stage and IPI score)
- For axi-cel and R-based CIT, results of fully adjusted MAICs overall consistent but fully adjusted results introduce bias, producing clinically implausible results

EAG comments

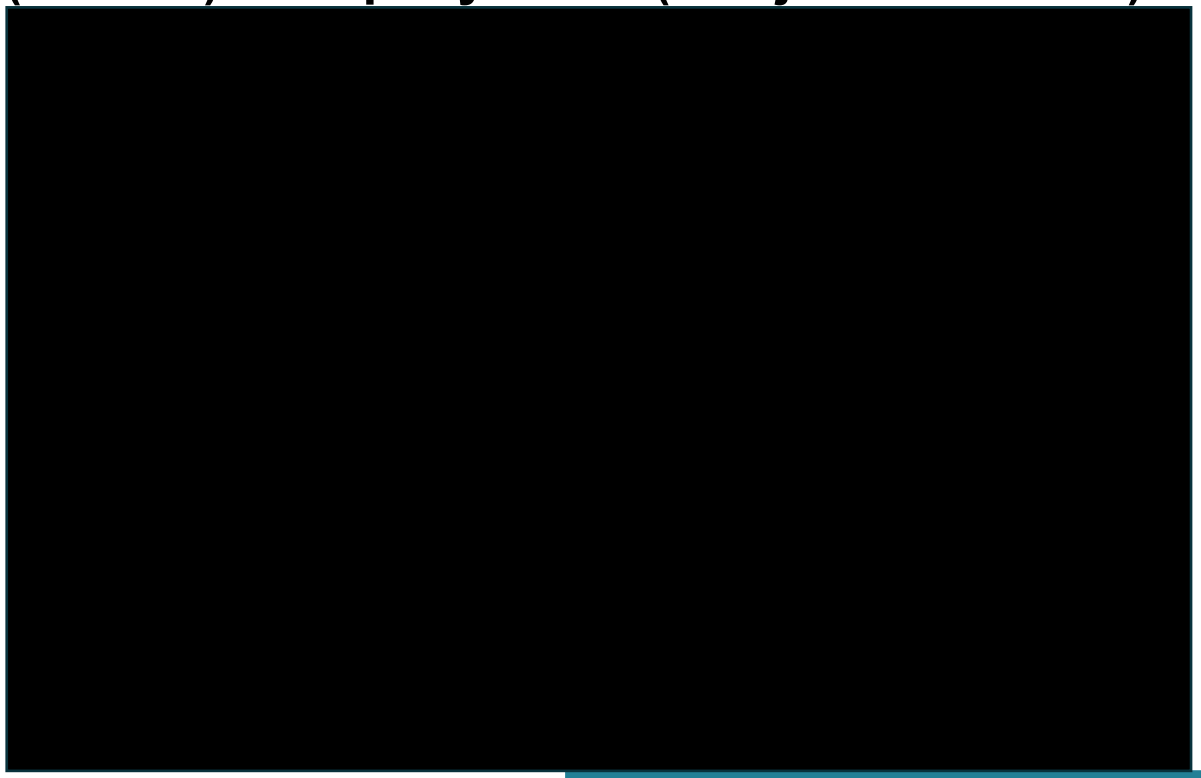
- Prefers results from fully adjusted MAICs for pola + BR and axi-cel, partially adjusted MAIC (9/10 reported variables) for R-based CIT
- Adjustment for factors in unanchored comparisons important (NICE DSU TSD18)
- While number of patients in the analyses (precision) reduces with further adjustment, 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 – concerns about robustness of MAICs remain

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

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)
- Company not used EAG-preferred data source for R-based CIT (Crump et al)
- 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 and no option to use fully adjusted MAICs in the model
- Lack of overlap between trials in MAIC (small sample sizes and factors remain imbalanced). Difference between trials may be too large for robust conclusions

*See appendix for PFS curves; ** value amended after committee

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 (7 adjusted factors)

[redacted]

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

[redacted]

EAG comments:

- Company base case does not use fully adjusted MAICs and no option to use fully adjusted MAICs in the model
- 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

*See appendix for PFS curves

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

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*See appendix for other issues and MAIC critique

Key issue: Long-term remission in model*

Company have removed long-term remission from model post-TE

Background

- Original company model: all patients in progression-free state enter long-term remission (LTR) 2 years after start of model
- Update at TE: mature data from EPCORE™ NHL-1 and axi-cel so LTR assumption not needed as patients entering LTR now captured in modelled survival curves; removed for all comparators

EAG comments

- Inappropriate removal of LTR for all comparators; assumes patients progression-free after 2 years: could have further progression, have same healthcare resource as PFS-off treatment (not discharged from follow-up), and have mortality rate associated with being in PFS state
- No justification of change – impacts follow-up costs as well as survival
- Not clinically plausible – clinical expert noted patients who have not progressed 2 years after the end of their treatment would be considered to be in LTR (i.e., further disease progression unlikely)
- EAG have conducted scenario reintroducing LTR, but note substantial limitations of these scenarios

Clinical experts (at TE)

- Reasonable to assume LTR if progression-free 2 years after completion of treatment

Should long-term remission be included in the model?

*See more on LTR in appendix

Company and EAG-preferred OS, PFS and TTD extrapolations*

Company and EAG preferred OS and PFS extrapolations with EAG-preferred MAIC

*See links to appendix in table

Population	Preferred MAIC		Treatment	OS extrapolation [a]		PFS extrapolation [a]		TTD extrapolation [a]	
	Company	EAG		Company	EAG	Company	EAG	Company	EAG
Population A Epcoritamab vs R-based CIT (link)	Company base case (7 adjusted)	Scenario A4 (9/10 adjusted)[b]	Epcoritamab	Lognormal	Exponential	Gompertz	Gen. gamma	Exponential	Lognormal
			R-based CIT	Lognormal	Gen. gamma	NA[c]	NA[c]	NA[d]	NA[d]
Population A Epcoritamab vs Pola + BR (link)	Company base case	Company base case [e]	Epcoritamab	Gen. gamma	Lognormal	Gen. gamma	Lognormal	Exponential	Lognormal
			Pola+BR	Log-logistic	Lognormal	Gamma	Gen. gamma	NA[d]	NA[d]
Population B (link)	Company base case (7 adjusted)	Scenario B1 (LBCL) [e]	Epcoritamab	Gompertz	Lognormal	Gompertz	Lognormal	Exponential	Lognormal
			Axi-cel	Gompertz	Gompertz	Gompertz	Gen. gamma	NA[f]	NA[f]

[a] Company-preferred extrapolations when using the EAG-preferred MAIC. [b] Scenario with results from adjusted 9/10 reported variables MAIC. [c] Modelled based on OS HR. [d] Company assumed that TTD would be the same as PFS based on expert opinion and lack of data. [e] EAG preferred to use fully adjusted MAICs but these were not provided. [f] Axi-cel is a single-dose via IV so no TTD curve modelled.

EAG comments:

- Request curves to be fitted independently as proportional hazards did not hold for Pola + BR and axi-cel comparisons and uncertainty whether held for R-based CIT
- **OS extrapolations:** All company curves for epcoritamab overestimate survival and have clinically implausible outputs: for comparisons with R-based CIT and axi-cel, the curves predict [redacted]% of people alive at 35 years when patients are 90 years old. All company curves for comparators underestimate survival
- **PFS extrapolations:** Company chosen curves not best fitting; EAG generally preferred better fitting curves
- **TTD:** Company underestimates costs of epcoritamab and overestimates costs of R-based CIT and Pola + BR

Key issues*

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*See appendix for other issues and MAIC critique

Key issue: subsequent treatments

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

Company (at TE)

- EAG preferred assumptions for proportion receiving CAR-T are higher than in trial
- Conducted scenario with higher proportion receiving CAR-T but also applied additional QALY adjustment

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

	Company	EAG (pop A)	EAG (pop B)	EPCORE™ NHL-1
R-based CIT	52.5%	30%	30%	[redacted]
CAR-T	5%	11%	30%	[redacted]
Radiotherapy	25%	25%	25%	[redacted]
Pola	0%	0%	0%	[redacted]
Lenalidomide	0%	0%	0%	[redacted]
No treatment	13.5%	30%	12%	[redacted]
Other	0%	0%	0%	[redacted]

What subsequent treatments should be used in model?

EAG comments

- Proportion receiving CAR-T
  - For population A, EAG estimate [redacted] proportion in trial and EAG's clinical experts opinion
  - For population B, EAG estimate is higher than trial, but in trial patients received other active treatments (e.g. pola and lenalidomide) which have not been included in model
  - So EAG have removed additional QALY adjustment
- People receiving R-based CIT or pola + BR should receive subsequent palliative chemo (not rituximab-based chemo)

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Key issue: follow-up costs for epcoritamab

EAG: company's approach underestimates disease management costs for epcoritamab, without plausible clinical explanation

Company

- People having epcoritamab in model are assumed to incur less resource use (move from "PFS on-treatment" to "PFS off-treatment") after [redacted] months (median PFS for partial responders). After [redacted] months, [redacted]
- Company's clinical experts state disease in complete response requires less intense follow-up

EAG comments (after TE)

- Not appropriate for median PFS from trial to inform resource use
- EAG's clinical experts indicated they would follow epcoritamab patients in same manner as long as treatment continued
- Conducted exploratory analysis where follow-up costs (PFS on-treatment costs) incurred while patients were on treatment → large effect on ICER

What follow-up costs should be applied for epcoritamab:

- "On-treatment" follow-up costs until 4 months, followed by "off-treatment" follow-up costs?
- "On-treatment" follow-up costs for duration of treatment?

Summary of company and EAG preferences*

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 cost-effectiveness section of appendix

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Equality considerations*

- Possible inequality of access without training and support for smaller centres
- No other issues were raised by the company, EAG or stakeholders

Managed access*

- No proposal from company
- Phase 3 in progress (vs R_Gemox)
  - Unlikely to resolve uncertainty

*See more on equality considerations and managed access in appendix

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					
R-based CIT	[redacted]	0.86	[redacted]	94.00%	1.2
Pola + BR	[redacted]	1.36	[redacted]	88.27%	1.2
Axi-cel	[redacted]	5.60	[redacted]	60.90%	1
EAG exploratory assumptions (with LTR assumption included)					
R-based CIT	[redacted]	1.25	[redacted]	91.28%	1.2
Pola + BR	[redacted]	3.07	[redacted]	73.53%	1
Axi-cel	[redacted]	6.00	[redacted]	58.11%	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

In scenario with EAG exploratory assumptions **without** LTR, the QALY weight is 1.2

*See more details in appendix

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Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

- Company ICERs for comparison with R-based CIT are within the range normally considered an effective use of NHS resources; 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)
- All EAG exploratory analyses increase the ICER for comparisons with R-based CIT and pola + BR (with and without the severity modifier applied)
- In the company's base case, epcoritamab costs less than axi-cel but produces more QALYs; in the EAG's cumulative exploratory analysis, the ICER compared with axi-cel was higher than the range normally considered an effective use of NHS resources*

* Minor text amended after committee

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

Supplementary appendix

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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		

Background on diffuse-large B-cell lymphoma (DLBCL)

How many people have DLBCL?

- Around 4,850 people diagnosed with DLBCL in 2019 | accounts for ~40% of non-Hodgkin Lymphoma (NHL) cases | More common age 60 years or older and in men

Diagnosis and classification

- DLBCL is an aggressive (fast growing) form of NHL | Biopsy and testing confirms diagnosis | Staging determines treatment options and prognosis

Symptoms and prognosis

- Symptoms differ depending on which organ or tissues are affected but may present as ‘B symptoms’ or lumps in various locations
- Risk factors and indicators for poorer outcomes include high International Prognostic Index score, Eastern Cooperative Oncology Group performance status ≥2, age over 60 years

Patient perspectives

Unmet need for treatments with fewer side effects; epcoritamab easy to administer and option for people who cannot have or relapse after CAR-T

Submissions from Blood Cancer UK, Lymphoma Action

Symptoms and impact

- Lumps in neck, groin or armpit; stomach pain, night sweats, weight loss, fatigue. Symptoms progress rapidly. Psychological impact
- Time in hospital for treatment, isolated and unable to work. Financial impact

Current treatment

- Side effects can last months or years; include fatigue, peripheral neuropathy or depression/anxiety. Not curative

Epcoritamab

- Only subcutaneous treatment; with high tolerability could improve access compared with CAR-T. Option if ineligible for or refractory to CAR-T
- Long time required to reach intended dose to mitigate risk of cytokine release syndrome

"R-CHOP doesn't work for everyone…DLBCL can recur …important to have a range of second and third-line treatment options that are effective, widely available and well tolerated."

"off-the-shelf accessibility means epcoritamab would be a good treatment for patients living further away from transplant and CAR-T centres"

Clinical perspectives

Epcoritamab ‘paradigm shift’ for relapsed or refractory DLBCL, particularly in people with disease refractory to CAR-T or where CAR-T unsuitable

Submissions from NCRI-ACP-RCP-RCR

Current treatment

- Treatment aim: sustained complete remission and PFS
- No current standard of care and lack of options with durable response for disease refractory to CAR-T or for patients ineligible for CAR-T
- Pathway well-defined: palliative chemotherapy is comparator or CAR-T (if able to access)

Epcoritamab

- An option where currently no good options
- Should use in specialist haematology centres experienced in delivering lymphoma anti-cancer treatment; training needed to manage side effects* in non-CAR-T centres (which are more common with CAR-T)

“paradigm shift …offering many patients the possibility of durable remission and good quality of life in a situation that would usually be palliative and life-limiting”

“straightforward to add to current treatment pathways and…deliverable in all centres”

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* cytokine release syndrome and immune effector cell associated neurotoxicity syndrome

Back to summary slide

Decision problem

Company focus on 3 comparators (one in scenario analysis)

Population, intervention, comparators and outcomes from scope

	Final scope	Company	EAG comments
Population	Adults with relapsed or refractory LBCL who have had 2 or more systemic treatments	As scope ([redacted])	Trial limited to ineligibility for or prior failure of ASCT and ECOG 0-2
Intervention	Epcoritamab	As scope	- -
Comparators	• Rituximab-based chemotherapy • Pixantrone • Pola + BR (when SCT unsuitable) • Axi-cel • Tafasitamab with lenalidomide (when SCT unsuitable; subject to NICE appraisal)	• R-based CIT (R-GemOx) • CAR-T therapy (axi-cel) • Pola + BR (scenario)	Pola + BR important comparator Agree with other exclusions
Outcomes	OS, PFS, Response rates, AEs of treatment, HRQoL, ToT	As scope plus TTD, TTNT	-

Populations and comparators in company submission

Company focus on 3 comparators (one in scenario analysis)

Populations and comparators in company submission

	Not eligible for intensive treatments (population A)	Eligible for intensive treatments (population B)
Relevant comparators in company submission	R-based CIT Scenario: Pola + BR	Axi-cel
Expected use in clinical practice	Company: R-based CIT is primary treatment option (either R-GemOx or R-Gem) EAG clinical expert: largest population likely have R-based CIT Note: Aug committee for ID3970 (glofitamab) considered relevant comparator	Primary treatment option in routine commissioning, but current regional variation in access to CAR-T and limitations in manufacturing

EAG: clinical experts note Pola + BR useful comparison 3rd line; used if no prior Pola + R-CHP including those with PMBCL or with DLBCL and IPI score between 0 and 1

Clinical experts

- 20% receive pola + BR 3rd line or beyond but will decrease as more have Pola + R-CHP first line.
- Pola + BR option for the 30% who relapse after Pola + R-CHP beyond 1 year.

Issues - MAICs

Key issue numbering based on the EAG report

Issue	Resolved?	ICER impact
For all MAICs:		
7. Not all factors adjusted for, including some in imbalance (link)	No, to discuss	Unknown
For population A (comparisons with R-based CIT and Pola + BR):		
5. Applicability of results to people with prior CAR-T	Unresolvable	Unknown
6. Unclear if EPCORE™ NHL-1 population used specific to those ineligible for intensive treatment	Further analyses requested	Unknown
For comparison with R-based CIT:		
2. Issues with Neelapu et al paper used for SCHOLAR-1 trial	Further analyses requested	Unknown
3. Limitations of SCHOLAR-1 trial	Unresolvable	Unknown
For comparison with Pola + BR:		
4. MAIC limited to DLBCL	Yes	Likely small
9. Limitations of Sehn et al (GO29365) trial	Unresolvable	Unknown
For population B (comparison with axi-cel):		
10. Limitations of ZUMA-1 trial	Unresolvable	Unknown

Other issues

Key issue numbering based on the EAG report

Issue	Resolved?	ICER impact
1. Generalisability of EPCORE™ NHL-1 (link)	No	Likely small
8. Most recent data cut from EPCORE™ NHL-1	Yes	
Cost-effectiveness issues		
15. Utilities (link)	Further analyses requested	Unknown
16. Administration and monitoring costs of axi-cel (link)	No	Small

Key clinical trial: EPCORE™ NHL-1

Cohort from single arm trial presented in company submission

Clinical trial designs 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

EPCORE™ NHL-1 baseline characteristics

Trial population may be in slightly worse condition than in clinical practice

Baseline characteristics for patients with DLBCL (FAS)

Characteristic, % (n)	DLBCL (n=139)
International Prognostic Index (IPI) ≥3	[redacted]
Ann Arbor disease stage IV	[redacted]
Primary refractory disease	[redacted]
Double or triple hit lymphomas	[redacted]
Prior CAR-T	[redacted]
Prior ASCT	[redacted]
Median ≥4 prior lines of therapy	[redacted]

EPCORE™ NHL-1 population: worse prognostic factors and more heavily pre-treated than in UK clinical practice

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Abbreviations: FAS, full analysis set

Key issue: generalisability of EPCORE™ NHL-1

Patients in trial had ECOG 0-2 and required to have failed (or be ineligible for) prior ASCT; decision problem is more broad

Background

- EPCORE™ NHS-1 inclusion criteria: ECOG scores 0-2 and those who failed (or ineligible) prior ASCT

EAG comments

- Decision problem not restricted to above population
- Clinical expert: ECOG scores included in trial reasonable and likely population, but would not want to restrict use with higher ECOG scores i.e. where impairment is thought largely due to lymphoma rather than other patient factors

Company

- UK clinical experts at AbbVie advisory board confirmed trial generalisable to UK population in scope

Clinical experts

- Most scores ECOG 0-2; if low performance status due to lymphoma, may consider ECOG 3 (if reimbursed) (5-10% of patients). Most people at 3rd line ineligible for ASCT

Is EPCORE™ NHL-1 generalisable to NHS clinical practice?

Matching-adjusted indirect comparison (MAIC) methodology (1/3)

EAG: several unresolvable and resolvable limitations of MAICs

Background: 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

Data source for MAIC and EAG/company comments

Treatment	EAG critique	Company
Epcoritamab EPCORE™ NHL-1 (N=139 DLBCL); single-arm study	**For population A, applicability for prior CAR-T (<u>unresolvable</u>, KI5)** • People with prior CAR-T excluded to better match comparator trials, some people in clinical practice will have prior CAR-T • Limitations due to study design differences and lack of full adjustment for additional MAICs • [redacted] in those with no prior CAR-T in EPCORE™ NHL-1	• [redacted] differences in ORR based on prior CAR-T: results generalisable to all patients; updated data similar survival after [redacted] • Conducted additional MAICs – results consistent between prior CAR-T and no prior CAR-T population for EPCORE™ NHL-1
	For population A, unclear if population specific to <u>ineligible</u> for intensive treatments (KI6) • Request MAIC using no prior CAR-T, ineligible for intensive treatment subgroup of EPCORE™ NHL-1	• MAICs adjusted to comparator trials (not restricted to ineligible for intensive treatments)

MAIC methodology (2/3)

EAG: several unresolvable and resolvable limitations of MAICs

Data source for MAIC and EAG/company comments (cont.)

Treatment	EAG critique	Company

R-based CIT (population A) SCHOLAR-1 (N=340 LBCL); observational study	**Limitations of Neelapu et al. paper (KI2)**
	• Unclear if Neelapu et al reweighted to ZUMA-1 or vice versa. ZUMA-1 may not represent population A
	• Does not report censoring or % with different types of LBCL. Unclear if only 2+ prior treatments
	• Request analyses with Crump et al - may be more robust:
	  • reports proportions with LBCL types - could be adjusted for in analysis of LBCL (rather than DLBCL)
	  • reports censoring and assumption not required
	  • not specific to those with ECOG 0-1
		• ZUMA-1 matched to SCHOLAR-1 so no issue re: representing population A
		• Though not explicitly reported, Neelapu et al cited as having 3L+ prior. Crump et al: 28% only 1L prior treatment.
		• OS consistent with older studies

	Limitations of SCHOLAR-1 (<u>unresolvable</u>, KI3) • All participants refractory to at least 1 prior treatment. Refractory status is prognostic factor • Unclear how many had R-based CIT • 28% with only one prior treatment in Crump et al vs unclear in Neelapu et al	• 21% relapsed within 12 months of ASCT, comparable to EPCORE™ NHL-1 • After adjustment, baseline characteristics well balanced

MAIC methodology (3/3)

EAG: several unresolvable and resolvable limitations of MAICs

Data source for MAIC and EAG/company comments (cont.)

Treatment	EAG critique	Company
Pola + BR (population A – scenario) *GO29365 (N=131 DLBCL [n=29 in 3L+ subgroup]); randomised trial vs BR	**Limitations of GO29365 (unresolvable, KI19)** • May overestimate survival for Pola + BR outcomes vs UK population (based on Northend RWE study) • Does not report primary refractoriness - potentially important prognostic factor • Not appropriate to use Northend in base case as bias of comparing clinical trial to RWE	• Conducted MAICs using subgroup of Northend study with 2+ prior therapies
Axi-cel (population B) ZUMA-1 (N=101 LBCL); single-arm study	**Limitations of ZUMA-1 (unresolvable, KI10)** • PFS definition differ from EPCORE™ NHL-1 (IWG criteria vs Lugano) (may bias against epcoritamab but unclear) • Missing people eligible but not infused (bias against epcoritamab) • Does not report refractory to last anti-lymphoma treatment, potentially important prognostic factor	• MAIC now includes 5-year ZUMA-1 data • Agree differing PFS definitions – likely bias against epcoritamab, did not apply IWG criteria to EPCORE™ NHL-1, as requested by EAG • Agree missing those not infused

*EUnetHTA submission for baseline characteristics, Sehn et al 2019 and 2022 to estimate survival curves

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]

Adjusted after [redacted]: [redacted]

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

[redacted]

Adjusted HR: [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

Back to OS MAIC slides

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 (7 adjusted factors)

[redacted]

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

[redacted]

Back to OS MAIC slides

Summary of ITC informing company economic model

Using company MAICs: epcoritamab is [redacted] than R-based CIT, [redacted] to axi-cel and pola + BR

Comparator	Partially adjusted HR (95% CI) – company base case	EAG: factors imbalanced & not adjusted for	HR (95% CI) – EAG preference
R-based CIT SCHOLAR-1 (Neelapu et al)	Factors adjusted: 7; N_{eff}=[redacted] OS: [redacted] PFS: N/A[a]	≥3 lines of chemo and ASCT SCT any time after refractory disease	Factors adjusted: 9; N_{eff}=[redacted] OS: [redacted] PFS: N/A[a]
Pola + BR GO29365 (Sehn et al)	Factors adjusted: 6; N_{eff}=[redacted] OS[b]: [redacted] PFS[b]: [redacted]	Refractory to last anti-lymphoma treatment 2 prior lines of treatment ≥3 lines of chemo and ASCT	Factors adjusted: 10 (fully adjusted); N_{eff}=[redacted] OS: [redacted] PFS: [redacted]
Axi-cel ZUMA-1	Factors adjusted: 7;[c] N_{eff}=[redacted] OS: [redacted] PFS: [redacted]	DLBCL vs other LBCL IPI score ≥3 ≥3 prior treatment lines refractory to second line or subsequent therapy	Factors adjusted: 11 (LBCL fully adjusted); N_{eff}=[redacted] OS: [redacted] PFS: [redacted]

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[a] Not reported, modelled based on OS HR. [b] After [redacted]; separate HRs presented prior to [redacted]
[c] DLBCL only population. (Note: HRs were not used in the model; the KM curves from the MAICs were used)

Key issue: applicability of MAICs to groups with prior CAR-T

Participants with prior CAR-T not included in MAICs; unclear if generalisable

Background

- No comparator trials included participants with prior CAR-T (as studies older); participants with prior CAR-T in EPCORE™ NHL-1 were removed from the population used in MAICs and matched to comparator trials to allow better matching
- [redacted] in ORR based on prior CAR-T experience; company consider results from no prior CAR-T population generalisable to patients with prior CAR-T

EAG comments

- Survival results from EPCORE™ NHL-1 [redacted]; unclear results of MAICs without prior use applicable to results with prior use of CAR-T for base case A population
- Agree required to align studies; consider unresolvable issue

Company (at TE)

- Provided additional MAICs to cover the prior CAR-T population:
  - R-based CIT: prior CAR-T subgroup from EPCORE™ NHL-1 compared with Tomas et al (retrospective observational)
  - Pola + BR: DLBCL and no prior ASCT group from EPCORE™ NHL-1 compared with Northend et al (RWE source)
- Consider results similar to no prior CAR-T population

Key issue: applicability of MAICs to patients ineligible for intensive treatments

Unclear participants from EPCORE™ NHL-1 used in MAIC for population A is appropriate

Background

- In the MAICs for population A (those ineligible for intensive treatments), company included population 'DLBCL, no prior CAR-T' ([redacted]) from EPCORE™ NHL-1

EAG comments

- Unclear if populations from EPCORE™ NHL-1 used in MAICs for population A are ineligible for intensive treatments, or if some eligible patients also included
- May affect MAIC result and its use in economic model

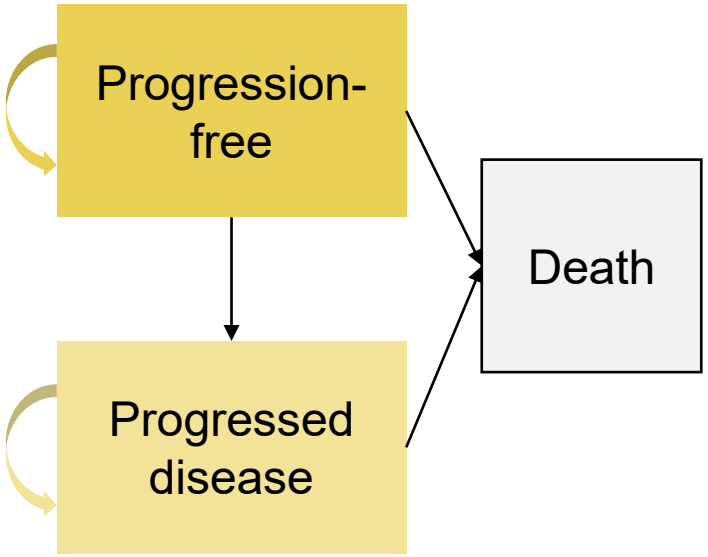
Company (TE)

- Inappropriate to adjust epcoritamab population to those ineligible for intensive therapies without doing to comparator as would introduce bias; company does not have access to individual patient data to do so
- EAG requested scenario not conducted: subgroup of patients ineligible from EPCORE™ NHL-1 matched to studies for R-based CIT and Pola + BR

Company's model overview

Company uses a partitioned survival model

Model structure



Epcoritamab affects **costs** by:

- Higher unit costs than R-based CIT and Pola + BR, but lower than axi-cel
- Lower proportion progressing so lower follow-up costs for progressed patients

Epcoritamab affects **QALYs** by:

- Increasing time in OS and PFS states → better survival and quality of life

Assumptions with greatest ICER effect:

- using EAG-preferred MAIC and survival distributions
- removal of assumption that epcoritamab patients stop incurring follow-up costs in the NHS at [redacted] when paired with the EAG's preferred survival curves
- subsequent treatments used in model
- re-introduction of long-term remission assumption for comparisons with pola + BR and axi-cel (but EAG notes substantial limitations of these scenarios)

- OS, PFS and ToT estimated from EPCORE™ NHL-1 IPD for epcoritamab
- Parametric curves fitted independently for each treatment

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	EPCORE™ NHL-1 DLBCL population (epcoritamab), adjusted to each comparator trial
Intervention efficacy	EPCORE™ NHL-1: no prior CAR-T, n=[redacted] (base case A) or no prior CAR-T and CAR-T eligible, n=[redacted] (base case B)
Comparator efficacy	SCHOLAR-1/Neelapu (R-based CIT/base case A)* and ZUMA-1 (axi-cel/base case B) [Sehn et al (Pola +BR)]
Utilities	Epcoritamab: based on EQ-5D-3L collected in EPCORE™ NHL-1; Scenario using ZUMA-1
Costs	NHS National Reference costs, PSSRU, eMIT, BNF (2019-2020, inflated to 2022)
Resource use	R-based CIT and axi-cel: TA559 and TA872(inflated to 2022) Frequency in PFS and PD health states: NICE TA649, NICE TA559 and NICE TA306

* PFS not reported in Neelapu so PFS was modelled using the OS hazard ratio

Abbreviations: aNHL, Aggressive B-cell non-Hodgkin lymphoma (LBCL, large B-cell lymphoma); BNF: British National Formulary; eMIT: electronic market information tool; EQ-5D-3L: EuroQoL-5 dimensions-3 levels; NHS: National Health Service; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit

Key issue: Long-term remission in model

Long-term remission assumption in original company model

	Company preferred assumptions for LTR pre-TE	ID3970 – committee preferred assumptions
Timepoint at which LTR begins	2 years after starting treatment	3 years after starting treatment
Progression in LTR	No further progression events	No further progression events
Utility values in LTR	Same as PFS health state	10% decrement compared to age-matched general population
Survival in LTR	SMR of 1.41 applied to age- and sex-matched general population	SMR of 1.09 applied to age- and sex- matched general population

Comments from ID3970 FDG:

- Clinical experts advised that they would consider people cured if their cancer remained in complete remission at 2 years. But they noted that longer follow up was needed to be sure of the proportion of people treated with glofitamab that this would apply to
- EAG base case applied 41% increased risk of death in LTR. Committee: Uncertainty about exact mortality but 9% increased risk was reasonable

Population A – comparison to R-based CIT*

EAG and company differ on preferred extrapolations for OS, PFS and TTD

	Company [a]	EAG
OS	**Epcoritamab:** Lognormal **R-based CIT:** Lognormal	**Epcoritamab:** Exponential *(best-fitting)* **R-based CIT:** Gen. gamma *(2nd best-fitting)*
PFS	**Epcoritamab:** Gompertz **R-based CIT:** N/A (based on OS HR)	**Epcoritamab:** Gen. gamma *(best-fitting)* **R-based CIT:** N/A (based on OS HR)
TTD	**Epcoritamab:** Exponential **R-based CIT:** Assumed same as PFS	**Epcoritamab:** Lognormal *(best-fitting)* **R-based CIT:** Assumed same as PFS

[a] Company-preferred extrapolations when using EAG-preferred MAIC (adjusted for 9/10 reported variables; company scenario A4)

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:

- Concerned by assumption that OS gain for epcoritamab is proportionally same as PFS gain
- R-based CIT curve underpredicts long-term OS compared to SCHOLAR-1 KM data (and therefore also underpredicts PFS)
- Epcoritamab curve overpredicts OS (in model, [redacted] of patients alive at 90 years old)
- TTD curve underestimates treatment costs for epcoritamab and overestimates costs for R-based CIT
- EAG preference for best fitting curves which are more clinically plausible, but noted still uncertainty which may favour epcoritamab

NICE  Which extrapolations should be used in the model?

*Back to overall summary slide

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

EAG: curves not flexible enough but company's choice overpredict survival for epcoritamab and underpredict for R-based CIT; prefer alternative

Company-preferred curves using EAG-preferred MAIC [a]

EAG base-case extrapolations (using EAG-preferred MAIC [a])

[a] EAG-preferred MAIC: adjusted for 9/10 reported variables (company scenario A4)

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

EAG: curves not flexible enough but company's choice overpredict survival for epcoritamab and underpredict for R-based CIT; prefer alternative

EAG

- Company curves overestimate survival in epcoritamab and underestimate survival in R-based CIT:
  - Underpredicts survival in R-based CIT compared with Neelapu at 24 months and Crump at 5 years
- More flexible models needed to capture underlying change in hazards for both arms
- Best fitting curves for R-based CIT (exponential, generalised gamma) have more plausible long-term survival, but still underestimate survival compared with KM. Exponential also underestimates epcoritamab survival at 5 years ([redacted] compared with 15% in Crump). No ideal curve

Which extrapolation should be used in the model?

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

PFS determined by applying HR from MAIC for OS to the PFS epcoritamab curve; EAG requested company use HR between epcoritamab OS and PFS curves to explore uncertainty - not provided by company

Company-preferred curves using EAG-preferred MAIC [a]

EAG base-case extrapolations (using EAG-preferred MAIC [a])

[a] EAG-preferred MAIC: adjusted for 9/10 reported variables (company scenario A4)

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

PFS determined by applying HR from MAIC for OS to the PFS epcoritamab curve; EAG requested company use HR between epcoritamab OS and PFS curves to explore uncertainty - not provided by company

EAG

- Concerns:
  - proportional hazards assumption between trials for both OS and PFS
  - underestimation of OS curve for R-based CIT (see earlier slide)
  - assumption that OS gain is proportionate to PFS gain
- Prefer to use HR between OS and PFS KM curves for epcoritamab (unadjusted, DLBCL, no prior CAR-T population) and apply to extrapolated OS curve for R-based CIT; company did not do - considered inappropriate to assume relationship between OS and PFS for epcoritamab same as R-based CIT, given epcoritamab more effective than R-based CIT. EAG approach more conservative
- Unlikely a lot of patients treated with R-based CIT would be progression-free at 2 years but likely more than company assumption ([redacted])

Which extrapolation should be used in the model?

PFS and TTD extrapolations: epcoritamab vs R-based CIT

EAG: company and EAG exploratory analyses have large difference between mean PFS and TTD for epcoritamab, which underestimates costs for epcoritamab

Company-preferred curves (for epcoritamab) using EAG-preferred MAIC [a]

EAG base-case epcoritamab extrapolations (using EAG-preferred MAIC [a])

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

TTD extrapolations: epcoritamab vs R-based CIT

EAG: company and EAG exploratory analyses have large difference between mean PFS and TTD for epcoritamab, which underestimates costs for epcoritamab

EAG comments

- Discrepancy between clinical expert opinion in original submission vs after TE
  - Original submission: TTD curve would be similar shape but repressed compared to PFS, as people likely to remain on treatment until progression. Epcoritamab is well tolerated
  - After TE: people are unlikely to remain on treatment after 5 years
- [redacted] of DLBCL patients discontinued due to toxicity in trial
- In company base case, there is a difference of [redacted] years between mean PFS and mean TTD in model
- When using best-fitting curve for TTD for epcoritamab (EAG exploratory analyses), there is a difference of [redacted] years between mean PFS and mean TTD. Given that epcoritamab is well tolerated, this difference is highly likely to underestimate treatment costs for epcoritamab
- Not appropriate to assume that people on R-based CIT do not discontinue treatment for reasons other than progression. Cazelles et al. suggests that 10% of patients discontinue R-based CIT due to toxicity. Likely overestimates cost of R-based CIT

Company

- Assumption that TTD is the same as PFS for R-based CIT based on feedback from UK clinical experts and lack of any suitable data on the proportion and timing of patients discontinuing treatment with R-based CITdue to reasons other than progression

Population A – comparison to Pola + BR*

EAG and company differ on preferred extrapolations for OS, PFS and TTD

	Company	EAG
OS	**Epcoritamab:** Gen. gamma **Pola + BR:** Log-logistic	**Epcoritamab:** Lognormal *(best-fit)* **Pola + BR:** Lognormal (*best-fit)*
PFS	**Epcoritamab:** Gen. gamma **Pola + BR:** Gamma	**Epcoritamab:** Lognormal *(best-fit)* **Pola + BR:** Gen. gamma *(best-fit)*
TTD	**Epcoritamab:** Exponential **Pola + BR:** N/A	**Epcoritamab:** Lognormal *(best-fit)* **Pola + BR:** N/A

Company rationale for preferred extrapolations:

- Clinical experts state gen. gamma, loglogistic and lognormal are plausible for epcoritamab OS curve and gen. gamma is most plausible for epcoritamab PFS. For TTD, very few patients expected on treatment after 5 years, so exponential selected

EAG comments:

- In fully adjusted MAIC, epcoritamab and Pola + BR OS curves converge at ~15 months (no convergence in company base case) and PFS curves cross at [redacted] in company base case). So all company's and EAG's estimates over-estimate benefit of epcoritamab vs fully adjusted MAIC
- OS: log-normal is best-fitting and clinically plausible. Company and EAG approach underpredicts vs Sehn et al. for Pola + BR
- TTD: Company approach underestimates costs of epcoritamab and over-estimates costs of Pola + BR

NICE Which extrapolations should be used in the model?

*Back to overall summary slide

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

EAG: company curves overestimate epcoritamab and underestimate pola + BR survival; no curves replicate plateau from Sehn et al

EAG base-case extrapolation [a]

EAG

- Company curves overestimate survival with epcoritamab and underestimate survival with pola + BR in Sehn et al.
- No curves replicate possible plateau from Sehn et all between 18 to 27 months – EAG-preferred likely still underestimated survival after 18 months
- Fully adjusted MAIC (EAG preference) shows convergence between epcoritamab and pola + BR at 15 months but company's choice never converges

[a] EAG preferred to use fully adjusted MAICs but these were not provided

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

EAG: company curves poorly fitted; no curves fit well but prefer better fitting curves with clinically plausible results

Company-preferred extrapolations

EAG base-case extrapolations [a]

[a] EAG preferred to use fully adjusted MAICs but these were not provided

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

EAG: company curves poorly fitted; no curves fit well but prefer better fitting curves with clinically plausible results

EAG

- Fully adjusted epcoritamab KM PFS curve [redacted] whereas company KM partially adjusted curve [redacted], overestimating PFS benefit
- Extrapolated curves chosen by company poor fit to partially adjusted KM data
- More flexible modelling approach more appropriate to capture change in hazard for epcoritamab
- Company preferred gamma curve overestimates PFS for initial period, then underestimates PFS at 24 months vs Sehn et al ([redacted]% vs 30%) – also do not capture potential plateau for last 12 months, and do not capture [redacted]
- Available curves not flexible enough but prefer best fitting curves that have clinically plausible results

PFS and TTD extrapolations: epcoritamab vs Pola + BR (1/2)

EAG: company base case has [redacted] year difference between mean PFS and TTD for epcoritamab, which underestimates costs for epcoritamab

Company base-case epcoritamab extrapolations

EAG base-case epcoritamab extrapolations [a]

[a] EAG preferred to use fully adjusted MAICs but these were not provided

TTD extrapolations: epcoritamab vs Pola + BR

EAG: company base case has [redacted] year difference between mean PFS and TTD for epcoritamab, which underestimates costs for epcoritamab

EAG

- In company base case, there is a difference of [redacted] years between mean PFS and mean TTD in model
- When using best-fitting curve for TTD for epcoritamab (EAG's exploratory analysis), there is a difference of [redacted] months between mean PFS and mean TTD. EAG considers this to be more realistic than estimate for epcoritamab vs R-based CIT
- Not appropriate to assume that people on Pola + BR do not discontinue treatment for reasons other than progression – likely overestimates cost of Pola + BR.

Company

- Assumption that TTD is the same as PFS for Pola + BR based on:
  - Feedback from UK clinical experts
  - Lack of any suitable data on the proportion and timing of patients discontinuing treatment with Pola + BR due to reasons other than progression

Population B – comparison to axi-cel*

EAG and company differ on most preferred extrapolations for OS, PFS and TTD

	Company [a]	EAG
OS	**Epcoritamab:** Gompertz **Axi-cel:** Gompertz	**Epcoritamab:** Lognormal *(2nd best fit)* **Axi-cel:** Gompertz *(best fit)*
PFS	**Epcoritamab:** Gompertz **Axi-cel:** Gompertz	**Epcoritamab:** Lognormal *(best fit)* **Axi-cel:** Gen. gamma *(2nd best fit)*
TTD	**Epcoritamab:** Exponential **Axi-cel:** N/A	**Epcoritamab:** Lognormal *(best fit)* **Axi-cel:** N/A

[a] Company-preferred extrapolations when using EAG-preferred MAIC (LBCL population; company scenario B1)

Company rationale for preferred extrapolations:

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

EAG comments:

- Company OS curves do not [redacted], and axi-cel and epcoritamab curves converge at [redacted] compared with [redacted] in KM curves
- Company PFS curves do not reflect KM data for epcoritamab MAIC-adjusted and the ZUMA-1 unadjusted PFS curves
- Both company base case and EAG exploratory analyses have a difference [redacted] years between mean PFS and mean TTD – unlikely to be clinically plausible and underestimates costs for epcoritamab

NICE Which extrapolations should be used in the model?

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

EAG: company and EAG curves do not [redacted]; company-preferred curves converge later than KM curves suggest

EAG base-case extrapolation [a]

[a] Using EAG-preferred MAIC: LBCL population; company scenario B1

EAG

- Fully adjusted and partially adjusted KM curves are similar
- Prefer base case with LBCL population from EPCORE™ NHL-1 compared with DLBCL used by company
- [redacted] not captured in company or EAG curves
- Company curves converge at [redacted] but the [redacted]
- EAG scenario: maximum between curves taken from point of curves crossing → implying epcoritamab converge with OS curve (instead of becoming worse)
- No curves flexible enough to accurately predict EPCORE™ NHL-1KM data; epcoritamab survival benefit overestimated in both company and EAG exploratory analyses

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

EAG: prefer curves that fit the data better than company-preferred curves

Company-preferred extrapolations for results from EAG-preferred MAIC [a]

EAG base-case extrapolation (using EAG-preferred MAIC [a])

[a] EAG-preferred MAIC: LBCL population; company scenario B1

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

EAG: prefer curves that fit the data better than company-preferred curves

EAG

- Gompertz curve for epcoritamab (company base case) likely provides implausible [redacted] not in trial; whereas, lognormal (EAG exploratory) has plausible long-term prediction in line with company's experts: 20–30% progression-free at 5 years
- For axi-cel, best fit (generalised gamma) and second-best (Gompertz – company choice) similar including divergence at 60 months
  - KM PFS curves [redacted], but company extrapolations [redacted]
  - EAG-preferred curves [redacted]
  - KM curves suggest epcoritamab has higher progression than axi-cel, but limited data after 2 years for epcoritamab to judge this

PFS and TTD extrapolations: epcoritamab vs axi-cel

EAG: company and EAG exploratory analyses have large difference between mean PFS and TTD for epcoritamab, which underestimates costs for epcoritamab

Company-preferred extrapolations for results from EAG-preferred MAIC [a]

EAG base-case epcoritamab extrapolations (using EAG-preferred MAIC [a])

[a] EAG-preferred MAIC: LBCL population; company scenario B1

TTD extrapolations: epcoritamab vs axi-cel

EAG: company and EAG exploratory analyses have large difference between mean PFS and TTD for epcoritamab, which underestimates costs for epcoritamab

EAG

- In company base case, there is a difference of just over [redacted] years between mean PFS and mean TTD in model
- When using best-fitting curve for TTD for epcoritamab (EAG's exploratory analysis), there is a difference of [redacted] years between mean PFS and mean TTD. 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
- Conducted a scenario where applied an HR of 1.2 to epcoritamab PFS curve, to estimate epcoritamab TTD curve which led to a difference in mean PFS and TTD of approximately 2 years – this was conducted to demonstrate the impact that the underestimation of the epcoritamab curve versus the axi-cel curve has on the results

Key issue: utilities

EAG: further scenarios would be helpful to explore uncertainty

Company after TE

- For population A, confirmed that population for utility is aligned with population for efficacy estimates (DLBCL, no prior CAR-T population). Considered it inappropriate to conduct scenario restricted to people ineligible to receive CAR-T (for both efficacy and utility estimates)

EAG comments (after TE)

- For population A, requested a scenario which matches definition of population A in company submission (e.g. people ineligible to receive CAR-T)
- For population B, requested a scenario using LBCL population (rather than DLBCL population) to match the population in ZUMA-1

Are the populations the company has used to derive utility values appropriate?

Key issue: administration and monitoring costs of axi-cel

Company add axi-cel bridging costs; EAG/NHSE lead: reasonable

Background

- TA872: "NHSE have accepted [£41,101] as a total cost for the first 100 days and recommend NICE consider this in all ongoing CAR-T appraisals"; this includes all CAR T-cell therapy delivery costs
- Company also include monitoring cost (to account for excess bed days from adverse effects) and 'one-off' bridging costs

Company and EAG preferred assumptions for proportions receiving bridging therapy

	Company	EAG
% require bridging	**85%**	**92%**
Pola + BR	60%	40%
Radiotherapy	18%	30%
Steroids	8%	5%
Chemotherapy	0%	17%
Total cost	**£24,368**	**£23,850**

EAG comments

- Disagree with company's addition of monitoring costs but company scenario removes this → minimal impact on ICER
- Bridging costs not included in administration cost recommended by NICE (stated in TA872)
- Applied weighted bridging costs based on advice from NICE and NHSE (see table) → total costs are similar and impact on ICER is small

Should bridging costs be included in the model and what proportions are appropriate?

Abbreviations: NHSE, NHS England

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)

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:
  "Ongoing phase 3 randomised trial, EPCORE™ DLBCL-1, in the same population [redacted] "
- [redacted]

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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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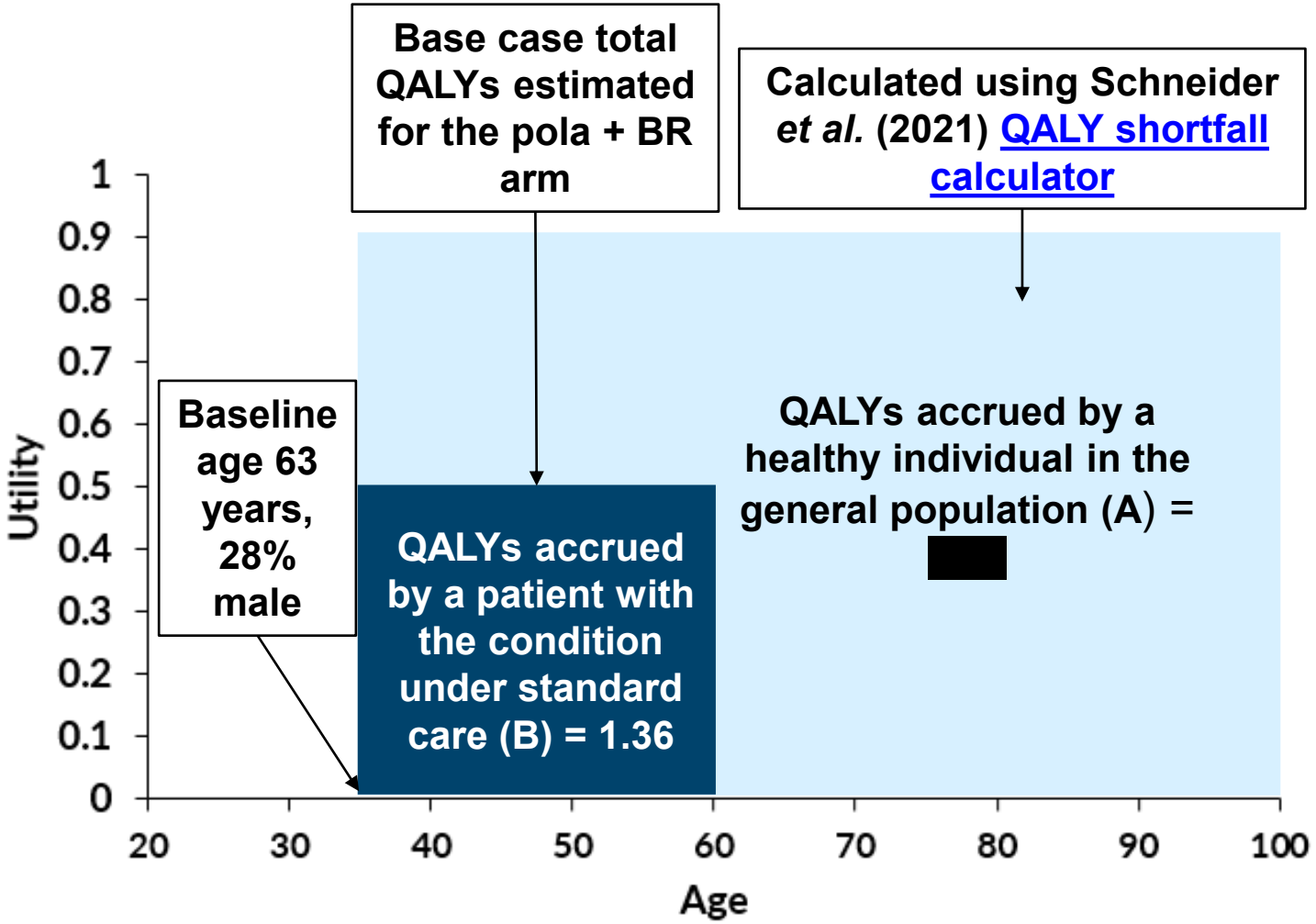
QALY weighting for severity: company model vs pola + BR

NICE methods include a QALY weighting system based on disease severity

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



Absolute shortfall = [redacted] – 1.36 = [redacted]

Proportional shortfall = ([redacted] - 1.36) / [redacted] = 88.27%

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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