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

Part 1
For screen – confidential information redacted

Technology appraisal committee C [9 December 2025]

Chair: Richard Nicholas

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Company: AbbVie

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

- ✓ **Recap**
- ❑ Responses to consultation

NICE National Institute for Health and Care Excellence

Draft guidance recommendation – September 2025

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

Why the committee made this recommendation:

- Uncertain clinical effectiveness due to differences in the design and populations of trials in the indirect comparison
- Uncertainties in the economic model – assumptions used to model usual treatment

Consultation comments received from:

- AbbVie (company) – additional analyses
- K Linton (clinical expert)
- A Brown (patient expert)
- Lymphoma Action (stakeholder)
- Member of the public (web comment)

Epcoritamab (Tepkinly, AbbVie)

Marketing authorisation	• Indicated as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy • Granted on 23 June 2025
Mechanism of action	• Epcoritamab is an IgG1-bispecific antibody engineered to bind to CD3 on the surface of T-cells and CD20 on malignant B-cells to promote T-cell mediated cell death • Depends on simultaneous engagement of CD20 cancer cells and CD3 T-cells
Administration	• Subcutaneous injection • Dosing regimen varies for the first 10 28-day cycles with a full dose being 48 mg
Price	• List price of £547.33 for pack of 1 4mg/0.8ml concentrate for solution for injection vials • List price of £6,568 for pack of 1 48mg/0.8ml solution for injection vials • 12 months of treatment at list prices: £166,076 in year 1 and £85,618 in year 2+ • A patient access scheme is applicable
Stopping rule	• Marketing authorisation: use epcoritamab 'until disease progression or unacceptable toxicity' • Company base case stops treatment after 3 years when complete response achieved

Abbreviations: IgG1, immunoglobulin G1.

Key issues

Key issues for discussion	ICER impact
Treatment positioning of epcoritamab	Small
Uncertainty with EPCORE NHL-1	Unknown
Adjusting survival data for COVID-19	Large
Suitability of comparator data	Unknown
Feasibility of treatment comparison **New for ACM2**	Unknown
Modelling of comparator efficacy	Moderate
CAR-T subsequent treatment and PET scan costs	Moderate
Severity weighting	Moderate

Resolved issues (small ICER impact)

- **Utilities for comparator PFS state:** not treatment specific
- **Haematological consultation costs:** weekly for 1st month then monthly
- **AE costs:** treatment-specific AE rates and costs used

Abbreviations: ICER, incremental cost effectiveness ratio; CAR-T, chimeric antigen receptor T-cell; PET, positron electron tomography; PFS, progression free survival; AE, adverse event.

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

- ❑ Recap
- ✓ **Responses to consultation**

NICE National Institute for Health and Care Excellence

Consultation responses 1/2

Clinical expert

- Welcomed any access to epcoritamab (regardless of treatment line)
- Recommendation not suitable because sources of UK-only comparator data have not been considered:
  - Third-line comparator data from HMRN dataset
  - Foundation UK registry (available in Q4 2025)
- Suggested following supporting sources for company's COVID-19 mortality adjustment:
  - Optimisation cohort of EPCORE NHL-1 which largely recruited post-pandemic
  - UNCOVER blood cancer health data research programme which has
    - over 17,500 FL patients in the NCRAS dataset from 2014-2021
    - reported a 14% increase in mortality for FL patients diagnosed after 2020
- Assertion that HMRN dataset was not specific to relapsed or refractory FL is not true
- UK lacks access to CAR-T, and other treatments which accounts for worse FL outcomes in the UK HMRN data compared to other countries – as shown by LEO CReWE data.

Member of the public

- Many people are left with no treatment options besides palliative care for this terminal disease
- Committee discussion did not explain the limited treatment options for many high-risk FL patients clearly
  - Noted that treatment options are similar across lines, meaning they may be exhausted after 3L
  - Retreatment is likely to be resisted – as patient expert from committee meeting had experienced
- Welcomed an effective treatment option, like epcoritamab, at later stages

Abbreviations: HMRN, Haematological Malignancy Research Network; FL, follicular lymphoma; NCRAS, National Cancer Registration and Analysis Service; CAR-T, chimeric antigen receptor T-cell; LEO, Lymphoma Epidemiology of Outcomes; CReWE, Consortium for Real World Evidence; 3L, third line.

Consultation responses 2/2

Patient expert

- Epcoritamab is urgently needed for FL patients, especially for the 20% with difficult-to-treat disease
- Concerned that comparing epcoritamab at distinct lines of treatment doesn't capture how relapsed or refractory FL is treated in practice
  - Given that treatments regularly fail to be effective and relapses occur, epcoritamab would be a beneficial option compared to weeks more in hospital with increasingly desperate treatment efforts
- Worried that, short of new studies, evidence won't be available to demonstrate cost effectiveness at 3L/4L
- Hoped that others could benefit from epcoritamab as the patient expert did through trial participation

Lymphoma Action

- Acknowledged the present limitations of clinical and cost effectiveness evidence, but hoped that these could be resolved and that patient experience could be taken into account
- Patient experts note that epcoritamab is more accessible and better-tolerated compared to other therapies
- Recommendation has not properly considered the mental strain from the fear of having no suitable treatments available for people with FL
- No new FL treatments have been recommended by NICE since 2020 despite indisputable unmet need

Abbreviations: FL, follicular lymphoma; 3L/4L, third-/fourth-line.

Updated company base case for 4L+

Company base case adopted committee's following preferred approaches

Assumption	Original company approach	Updated company approach
Utility values	Treatment-specific, complete-response-derived progression-free HSUVs	No treatment-specific HSUVs
Application of HRs	Derived from MAIC and applied to baseline epcoritamab survival data for comparator (4L+ current care)	Derived from MAIC and applied to reweighted epcoritamab survival data for comparator (4L+ current care)
Resource use	Haematologist consultations once monthly	Haematologist consultations weekly for the first month, then once monthly after that
AE costs	• AE rates for R-CHOP used to determine AE costs for all treatments in the comparator basket • CRS costs excluded	• AE costs based on weighted AE rates for respective treatments in the comparator basket • CRS costs remain excluded per committee preference

Abbreviations: 4L, fourth line; HSUV, health state utility values; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; AE, adverse event; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; CRS, cytokine-release syndrome.

Committee requested analyses

Requested analyses	DG section	Company updated analysis
Updated analysis including people having 3L treatment	3.3	Yes – limits base case to the 4L+ population, but has exploratory analyses in the 3L+ population
Full justification and clear definition of treatments at 4L+ if 3L cannot be modelled	3.3	N/A – 3L+ is modelled
Longer follow-up data for EPCORE NHL-1 dose-optimisation cohort	3.4	Yes – data provided but not in base case
Full exploration of alternative comparator data, updated ITC, and assessment of generalisability to the UK	3.5 and 3.7	Partially – explored comparator data sources and assessed generalisability, but no updated ITC
More complex methods to adjust for COVID-19 deaths in EPCORE NHL-1 data	3.6	Yes – further analysis provided; but retains full censoring in base case
Stronger justifications for company's approach to modelling comparator survival	3.9	Partially – scenario with standard care as the reference curve
Scenario analyses that exclude people who had CAR-T therapy from efficacy estimates	3.11	Yes

Abbreviations: DG, draft guidance; 3L/4L, third-/fourth-line; ITC, indirect treatment comparison; CAR-T, chimeric antigen receptor T-cell.

Key issues: Treatment positioning of epcoritamab

Company base case 4L+; EAG base case 3L+

Background

- For ACM1, company restricted population to 4L+ and did not provide analysis for full MA including 3L+
- Now company has provided 3L+ scenario analysis and chooses to restrict base case to 4L+
- EAG notes unmet need at 4L+ but says 3L+ should be base case as greater clinical need begins there

Company

- Notes 4L+ remains base case as it has greatest unmet need and ongoing appraisal (ID6586) looks at 2L+
- New 3L+ scenario compared epcoritamab against HMRN data for 3L+ basket based on market share

Treatment in comparator arm	4L+ share	3L+ share
R-chemotherapy (rituximab + bendamustine)	[redacted]	[redacted]
Chemotherapy (chlorambucil)	[redacted]	[redacted]
R^2 (rituximab + lenalidomide)	[redacted]	[redacted]
Other immuno-chemotherapies (bendamustine + obinutuzumab)	[redacted]	[redacted]

EAG comments

- Clinical experts advised that greater clinical need starts at 3L+ and clinicians would prefer to use epcoritamab at this earlier line
- Chlorambucil rarely used, so [redacted] share in 3L+ comparator too high – 15% at most with R-chemo share increased

Should epcoritamab be considered in 3L+ or 4L+ population?

Abbreviations: 2L/3L/4L, second-/third/fourth-line; EAG, external assessment group; ACM, appraisal committee meeting; MA, marketing authorisation; HMRN, Haematological Malignancy Research Network (database).

HMRN Sankey diagram in appendix

Key issues: Uncertainty with EPCORE NHL-1

Company and EAG base case use COVID-adjusted dose expansion data

Background

- At ACM1, dose expansion FL cohort of ongoing EPCORE NHL-1 trial used for treatment comparison, but company advised that longer follow-up for dose optimisation cohort was available

Company

- Dose optimisation cohort has [redacted] months median follow-up on epcoritamab and recruited after peak-pandemic with no COVID-related deaths observed
- Retained COVID-modified dose expansion base case, noting that dose optimisation gives increased benefit

	Period of follow-up	Follow-up (Median)	OS at 18 Months	COVID-related mortality?	Grade 3-4 COVID-related TEAEs
Dose Expansion	[redacted]	[redacted] months (n=81)	[redacted]%*	Yes	[redacted]%
Dose Optimisation	[redacted]	[redacted] months (n=41)	[redacted]%	No	0%

EAG comments

- Generalisability of EPCORE NHL-1 findings to UK remains uncertain
- Dose optimisation cohort - small with short follow up

Which data source should be used for epcoritamab?

Abbreviations: EAG, external assessment group; ACM, appraisal committee meeting; FL, follicular lymphoma; OS, overall survival; TEAE, treatment emergent adverse event.

Key issues: Adjusting survival data for COVID-19 1/3

Company censors all COVID deaths; EAG censors those in omicron wave

Background

- Committee agreed with company that COVID-19 excess deaths should be accounted for, but it preferred more sophisticated approach (e.g. causal inference) as opposed to censoring individuals
- In ACM1, clinical experts highlighted that the latest DCO for dose optimisation cohort of EPCORE NHL-1 was recruited after the peak pandemic and could validate COVID-adjusted outcomes

Company

- Modelled survival of dose optimisation cohort (post COVID) and found it predicted better survival than the original COVID-censored dose expansion analysis
- Provided the following analysis at 3L+ and 4L+ :

1. COVID-adjusted dose expansion data; censors all COVID deaths. Retained for base case
2. Omicron-adjusted dose expansion data; censors COVID deaths occurring during Omicron wave
3. IPCW – weighting to account for bias associated with informative censoring; but limited by low number of events (n=[redacted])

4L+ epcoritamab OS data

[redacted]

Abbreviations: EAG, external assessment group; ACM, appraisal committee meeting; DCO, data cut-off; 3L/4L, third-/fourth-line; IPCW, inverse probability of censoring weighting; OS, overall survival.

Key issues: Adjusting survival data for COVID-19 2/3

Adjusted 3L+ epcoritamab OS data – IPCW v. COVID-adjusted

Adjusted 3L+ epcoritamab PFS data – IPCW v. COVID-adjusted

Adjusted 4L+ epcoritamab OS data – IPCW v. COVID-adjusted

Adjusted 4L+ epcoritamab PFS data – IPCW v. COVID-adjusted

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Abbreviations: 3L/4L, third-/fourth-line; OS, overall survival; IPCW, inverse probability of censoring weight; PFS, progression-free survival.

Key issues: Adjusting survival data for COVID-19 3/3

EAG comments

- Agrees that dose optimisation cohort validates plausibility of company's original COVID-modified base case but residual uncertainty persists for longer-term outcomes beyond the follow-up period
- Agrees with company that IPCW similar results to COVID adjusted analysis, analysis had some limitations and missing reporting. EAG provide scenario using this data in model.
- Uses omicron-adjusted analysis in base case as middle ground based on expert input

MAIC-adjusted HRs, EPCORE v. HMRN (95% CI)

Approach	3L+ OS	3L+ PFS	4L+ OS	4L+ PFS
Dose expansion Apr 2024 DCO				
COVID-unmodified	[redacted]	[redacted]	[redacted]	[redacted]
COVID-modified	[redacted]	[redacted]	[redacted]	[redacted]
Omicron-modified	[redacted]	[redacted]	[redacted]	[redacted]

EAG base case

Company base case

What is the preferred approach for adjusting for COVID-19 deaths?

Abbreviations: EAG, external assessment group; IPCW, inverse probability of censoring weights; MAIC, matching-adjusted indirect comparison; HR, hazard ratio; HMRN, Haematological Malignancy Research Network (database); CI, confidence interval; 3L/4L, third-/fourth-line; OS, overall survival; PFS, progression-free survival.

Key issues: Source of comparator data 1/3

Company use HMRN 4L+ data in base case (derived from MAIC); EAG use HMRN 3L+ data directly in base case

Background

- Committee wanted further exploration of alternative, generalisable data sources for comparators
- Company says HMRN data most relevant for 3L+/4L+ but explored scenarios with other sources to validate
- EAG uses HMRN data in base case but considers other sources potentially useful, e.g. Wasterlid (2024)

Company

- Reviewed sources from SLR and suggested sources, but considered them inappropriate for ITC in 3L+/4L+
- HMRN data remains the most relevant to UK population – patient profile, treatment pathway and study conduct differences in international datasets account for improved outcomes compared to UK
  - Specialist academic centres offer better treatments such as bispecific antibodies and CAR-T therapies for 3L+/4L+ that don't represent UK and may include fitter patients who live close to medical services
  - HMRN data reflects UK patients, while SCHOLAR-5, ReCORD-FL and US Flatiron datasets have been used to represent comparators for CAR-T eligible patients who tend to tolerate aggressive treatment and have favourable disease characteristics for long-term survival
- Clinical experts say that combination of above differences, and unknown confounding, explain differences in survival outcomes between UK and international datasets

Abbreviations: HMRN, Haematological Malignancy Research Network; 3L/4L, third-/fourth-line; MAIC, matching-adjusted indirect comparison; 3L/4L, third-/fourth-line; EAG, external assessment group; SLR, systematic literature review; ITC, indirect treatment comparison; CAR-T, chimeric antigen receptor T-cell.

Key issues: Source of comparator data 2/3

Source	Company view	EAG view
Wasterlid (2024)	Swedish register reports on 3L+ and 4L+ FL with similar treatment pathway to UK but only reports 1L baseline characteristics so inappropriate	**Most relevant**, company could have asked authors for data but agree with company that baselines are not at 3L+ or 4L+
LEO CReWE	Inappropriate as exclusively US, 6% were 4L+, treatments were heterogenous, cohort from elite/specialist academic centres and 98 received experimental treatment	Other 94% is at 3L, heterogenous treatments in HMRN too, 22% 'experimental treatments' no reason to exclude full study but agrees US-based generalisability limitations
ReCORD-FL	Not generalisable as healthier population than UK practice, excludes ECOG score > 1 and undertaken in international academic centres	80% at 3L, includes European patients, EFS available in absence of PFS, and only small % with ECOG > 1 in EPCORE NHL-1

EAG comments

- Considers 3 sources appropriate alternatives for comparators: LEO CReWE, ReCORD-FL & Wasterlid (2024)
- HMRN data is representative for 3L+ comparator care in NHS but Swedish Wasterlid (2024) also relevant due to common treatment pathway, data available by treatment line and long follow-up
- EAG scenario with naive comparison - EPCORE v. Wasterlid.

Abbreviations: EAG, external assessment group; 1L/3L/4L, first-/third-/fourth-line; LEO, Lymphoma Epidemiology of Outcomes; CReWE, Consortium for Real World Evidence; HMRN, Haematological Malignancy Research Network; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; PFS, progression-free survival.

Key issues: Source of comparator data 3/3

Note: curves were digitised from respective sources by the NICE technical team

Summary

- Company and EAG disagreed on limitations of sources
- Company preferred HMRN
- EAG used HMRN but said Wasterlid (2024) was most relevant to UK NHS context
- Heterogeneity across comparator data sources highlights importance of population definition and uncertainty
- Uncertainty is compounded further by different reference curves chosen by company and EAG for application of MAIC HR

Which source should be used for comparator data?

Abbreviations: EAG, external assessment group; HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; HR, hazard ratio.

Key issues: Feasibility of treatment comparison

Company and EAG use MAIC (4L+ and 3L+ respectively) for relative effect

Background

- Committee requested a simulated treatment comparison, if feasible, to validate the MAIC

Company

- Timing limited feasibility of simulated treatment comparison, so prioritised other requested analyses
- MAIC preferred over STC due to MAIC precedent in prior NICE TAs, sufficient overlap in population characteristics, balance between matching variables/preserving sample, limited observed events for STC
- STC good practice requires 10 events per covariate for stable, unbiased estimates but only [redacted] OS and [redacted] PFS events in 4L+ analysis (allowing for only 2-3 covariates to be adjusted for)
- 3L+ MAIC provided plus sensitivity analysis around refractory status (in 3L+ and 4L+ population)

EAG comments

- Company lacked quantitative feasibility assessment of STC or exploration of semi-parametric or reduced covariate approaches – also, reference to previous appraisals is not a substitute for assessing feasibility
- MAIC, with its ESS reduction, does not have 'high' covariate overlap as company argued, so 4L+ STC would have been useful, for validation
- 3L+ MAIC similar limits as 4L+: confounding, covariates based on availability not prognostic importance
- Analysis around refractory status suggests choice of variables doesn't introduce bias, but ESS small

Is the MAIC suitable for decision making?

Abbreviations: EAG, external assessment group; MAIC, matching-adjusted indirect comparison; 3L/4L, third-/fourth-line; STC, simulated treatment comparison; TA, technology appraisal; OS, overall survival; PFS, progression-free survival; ESS, effective sample size.

Key issues: Feasibility of treatment comparison

Variable	EPCORE 3L+	HMRN 3L+	EPCORE 4L+	HMRN 4L+
Age ≥60	64.8%	[redacted]	69.1%	[redacted]
Sex (male)	61.7%	[redacted]	65.4%	[redacted]
Disease stage III - IV*	85.2%	[redacted]	85.2%	[redacted]
Prior ASCT	18.8%	[redacted]	18.5%	[redacted]
Prior CAR-T	4.7%	[redacted]	7.4%	[redacted]
Prior lines of therapy**	63.3%	[redacted]	49.4%	[redacted]
POD24 after first line CIT	42.2%	[redacted]	37.0%	[redacted]
Refractory to both anti-CD20 and alkylator therapy	70.3%	[redacted]	74.1%	[redacted]
Refractory to most recent anti-lymphoma therapy	68.8%	[redacted]	76.5%	[redacted]
Prior treatment with R²	21.1%	[redacted]	30.9%	[redacted]

* At baseline for EPCORE but at diagnosis for HMRN ** Prior lines >3 for 3L+, >4 for 4L+

- At ACM1, committee wanted to understand if the data suggests that EPCORE or HMRN populations would have better prognoses than the other
- Ubieto (2023), a review of key prognostic factors in r/r FL, suggests that prognosis most impacted by:
  - POD24
  - resistance to CIT
  - being refractory to previous line of therapy
  - numbers of prior lines of therapy

Clinical experts, which are the key prognostic variables? How much healthier is one population compared to the other? Which population has the better prognosis?

Abbreviations: HMRN, Haematological Malignancy Research Network; 3L/4L, third-/fourth-line; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; POD24, progression of disease within 24 months; CIT, chemoimmunotherapy; R², rituximab + lenalidomide; ACM, appraisal committee meeting; r/r, relapsed or refractory; FL, follicular lymphoma.

Key issues: Modelling of comparator efficacy 1/2

Company uses epcoritamab as reference curve; EAG uses HMRN comparator and differs in chosen parametric models

Background

- In ACM1, company selected expert-predicted fitted curves to adjusted EPCORE NHL-1 data and then generated 4L+ comparator outcomes from the MAIC (which used unadjusted EPCORE NHL-1 data)
- Committee requested different approach to modelling efficacy which used extrapolated comparator data as the reference curve with the MAIC's hazard ratios applied to generate epcoritamab long-term efficacy
- Committee requested further justification, including investigation into underlying hazards and statistical fit

Company

- Explored scenarios with epcoritamab efficacy generated by inverse hazard ratio from MAIC applied to HMRN data comparator arm (at 3L+ and 4L+)
- Prefers original approach but notes that using committee-preferred inverse HRs to generate epcoritamab outcomes leads to a greater OS benefit for epcoritamab compared to comparators at 4L+
- Based on low AIC/BIC, hazards fit, and clinical opinion parametric curves were selected for each scenario:
- **4L+ base case (epcoritamab HR reference) extrapolation:** log-normal chosen for OS, PFS and TTD
- **4L+ scenario (comparator HMRN HR reference) extrapolation:** log-normal chosen for OS and PFS, and exponential for TTD

Abbreviations: EAG, external assessment group; HMRN, Haematological Malignancy Research Network; ACM, appraisal committee meeting; 3L/4L, third-/fourth-line; MAIC, matching-adjusted indirect comparison; HR, hazard ratio; OS, overall survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; HR, hazard ratio; PFS, progression-free survival; TTD, time to treatment discontinuation.

Key issues: Modelling of comparator efficacy 2/2

EAG comments

- Applied inverse HR from MAIC to HMRN reference curve
- 3L+: Preferred alternative parametric models based on statistical fit and fit with company's expert opinion (see table). OS and PFS HMRN curves options are shown on the next slide
- 4L+ used same parametric models as company (log-normal) and applied a 15-year cap to OS

3L+ survival model choices with EAG justification

Study	Outcome	Company	EAG	
			Base case	Justification
HMRN reference curve	OS	Log-normal	Log-normal	Best-fitting model
	PFS	Weibull	Generalised gamma	Statistically best-fitting model
EPCORE NHL-1 reference curve	OS	Log-normal	Log-logistic	All models similar fit but log-logistic most in line with company's experts
	PFS	Log-normal	Generalised gamma	Generalised Gamma best fit and most in line with company's experts but log-normal also good fit

Should the comparator be used as the reference curve?
What is the preferred extrapolation approach?

Company 3L approach

EAG base case

Abbreviations: 3L/4L, third-/fourth-line; EAG, external assessment group; OS, overall survival; PFS, progression-free survival; HMRN, Haematological Malignancy Research Network; HR, hazard ratio; MAIC, matching-adjusted indirect comparison.

HMRN 3L+ OS extrapolations

[redacted]

— Company approach with HR applied to fitted EPCORE data

[redacted]

— EAG approach with inverse HR applied to fitted HMRN data

Abbreviations: HMRN, Haematological Malignancy Research Network; 3L, third line; OS, overall survival; HR, hazard ratio; EAG, external assessment group.

HMRN 3L+ OS extrapolations

Abbreviations: HMRN, Haematological Malignancy Research Network; 3L, third line; OS, overall survival; KM, Kaplan-Meier; EAG, external assessment group.

Key issues: CAR-T subsequent treatment and PET scan costs

Background

- People received CAR-T therapy in EPCORE NHL-1, but wouldn't in NHS. Committee requested adjusting for subsequent CAR-T therapy use benefits/costs
- Committee wanted scenarios with and without 12 monthly PET scans

Company

- Explored the impact of excluding patients at baseline that go on to receive CAR-T therapy and censoring at time of CAR-T therapy – small impact on OS and ICERs for 3L+/4L+ due to small CAR-T numbers

EAG comments

- **CAR-T:** agreed original and CAR-T-censored KM curves were similar so subsequent CAR-T may not impact OS
- Noted possible informative censoring excluded systematically different patients – some uncertainty remains
- Provided a scenario where people receiving CAR-T were censored. Scenario increased base case ICER but has limitations and should be interpreted with caution
- **PET scans**: provided a scenario with PET scans applied once per year (base case assumes none)

How should people receiving CAR-T be adjusted for?
Should annual PET scans be modelled?

See appendix for impact of CAR-T censoring

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Abbreviations: CAR-T, chimeric antigen receptor T-cell; PET, positron emission tomography; OS, overall survival; ICER, incremental cost effectiveness ratio; 3L/4L, third-/fourth-line; EAG, external assessment group; KM, Kaplan-Meier.

Key issues: Severity weighting

3L+: severity doesn't apply in company or EAG analysis

4L+: severity applies in company and (tentative) EAG base case

Background

- **4L+:** age at baseline 64.8 years, female 34.6% = 1.2x

Base case	QALYs of people without condition	QALYs with the condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
4L+					
Company	10.91	1.285	9.625	88.22%	1.2
EAG (tentative)	10.91	1.281	9.629	88.26%	1.2

In company scenario using HRMN data 4L+ as reference curve, modifier does not apply.
EAG 15-year OS cap means the modifier is applied in EAG base case.

Should HMRN data be used as the reference curves? Should an OS cap be applied?

Abbreviations: 3L/4L, third-/fourth-line; HMRN, haematological malignancy research network; QALY, quality-adjusted life year; EAG, external assessment group.

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG tentative base case
Epcoritamab positioning	4L+	3L+
Epcoritamab survival	COVID **adjusted** OS and PFS data from EPCORE NHL-1 (log-normal distribution)	Inverse HR from omicron-adjusted MAIC applied to OS and PFS extrapolated data for HMRN 3L+
Current care survival	HRs from MAIC applied to OS and PFS extrapolated data for epcoritamab	Use of OS and PFS data direct from HMRN data (log-normal distribution)
Utilities for PFS and PD	Sourced from EPCORE NHL-1 EQ-5D data, PD estimated using Wild et al	
Haem. consultations	Weekly for first month, monthly thereafter for epcoritamab	
AE incidence	Reweighted value for each AE for each treatment in the basket	
Inclusion of CRS events	CRS events not included	

EAG tentative base case at 4L+ matches company, except an OS cap at 15 years for comparator is applied

Abbreviations: EAG, external assessment group; 3L/4L, third-/fourth-line; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; PD, progressed disease; EQ-5D, EuroQol five dimension (questionnaire); Haem, haematological; AE, adverse event; CRS, cytokine release syndrome.

Cost-effectiveness results

Decision-making ICERs are shown in Part 2 due to confidential prices

Company base case ICERs are below £30,000 per QALY

EAG base case ICERs are below £30,000 per QALY

Scenario analyses on the EAG base case vary. Most are below £30,000 per QALY.

Key issues

Key issue	ICER impact	Slide
Treatment positioning of epcoritamab	Small	11
Uncertainty with EPCORE NHL-1	Unknown	12
Adjusting survival data for COVID-19	Large	13
Source of comparator data	Unknown	16
Feasibility of treatment comparison	Unknown	19
Modelling of comparator efficacy	Moderate	21
CAR-T subsequent treatment and PET scan costs	Moderate	25
Severity weighting	Moderate	26

Abbreviations: ICER, incremental cost effectiveness ratio; CAR-T, chimeric antigen receptor T-cell; PET, positron electron tomography.

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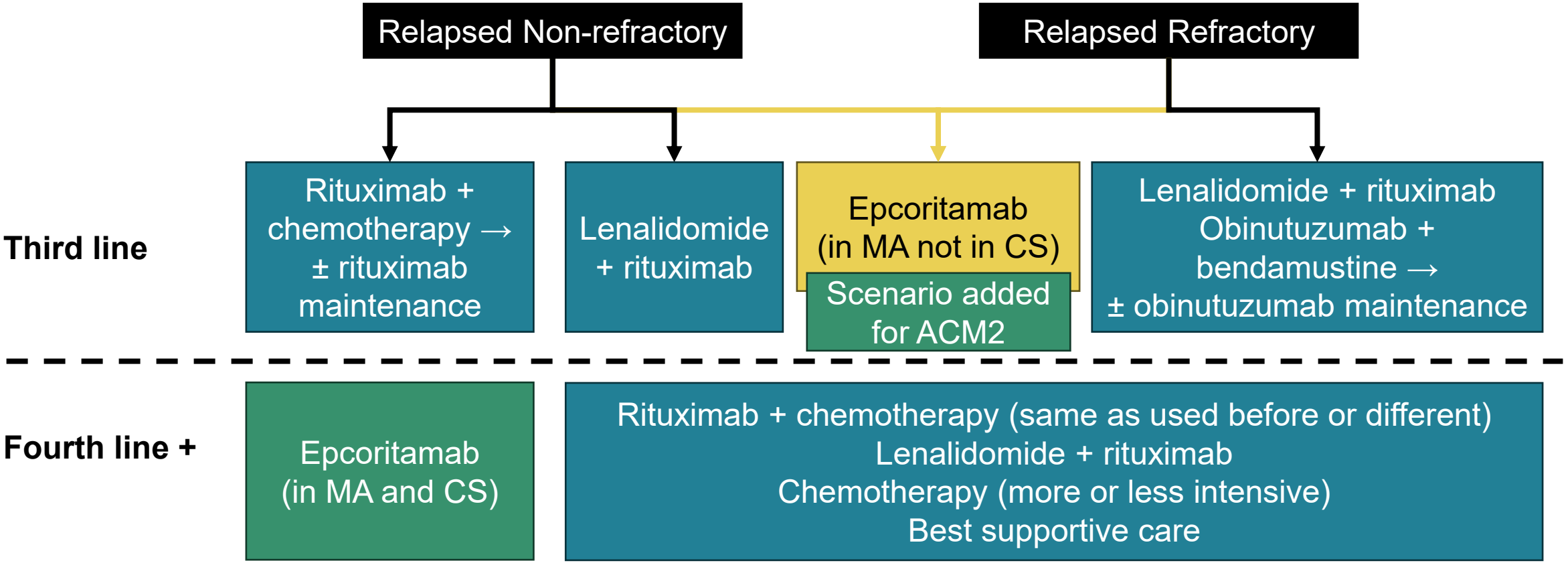
Supplementary appendix

NICE National Institute for Health and Care Excellence

Treatment pathway – relapsed/refractory FL



Does the treatment pathway seem reasonable?

What proportion of patients would be expected to reach 3L and 4L?

What is the average age at diagnosis and at 3L and 4L in NHS clinical practice?

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Abbreviations: CS, company submission; FL, follicular lymphoma; MA, marketing authorisation

Treatment by line in HMRN data

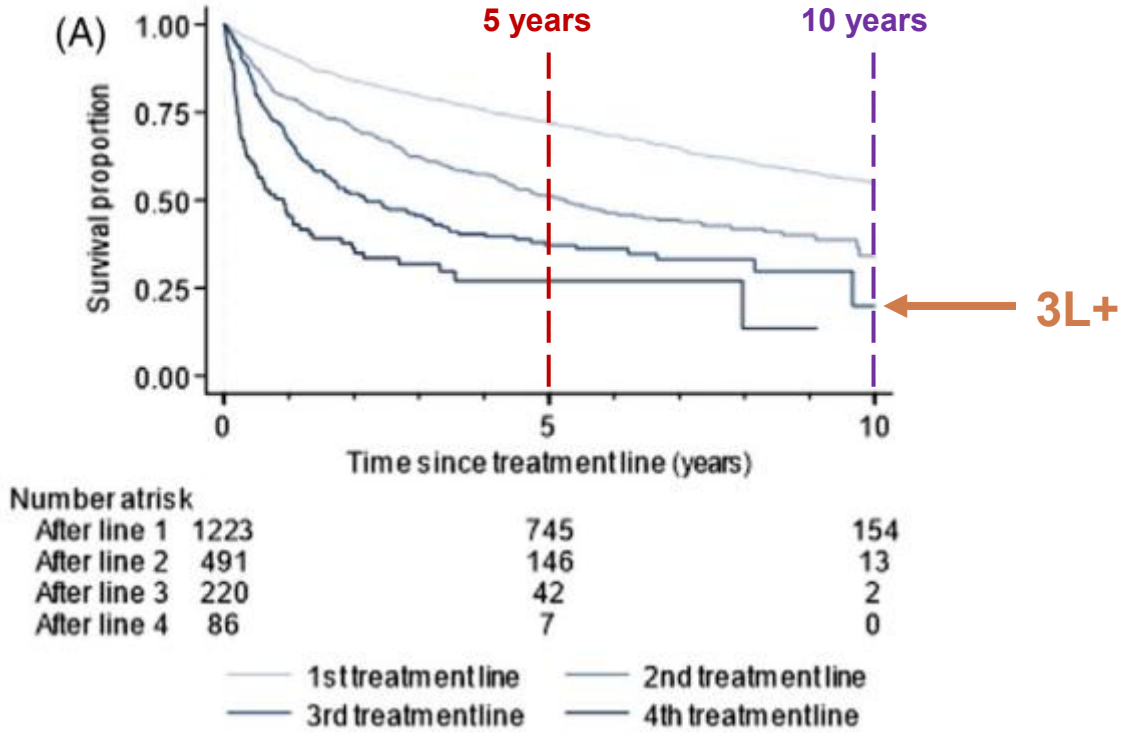
3L+ HMRN data and Wasterlid (2024) OS

HMRN OS from start of 3L+, months

[redacted]

From company submission

Wasterlid (2024) OS, years



Abbreviations: 3L, third line; HMRN, Haematological Malignancy Research Network; OS, overall survival.

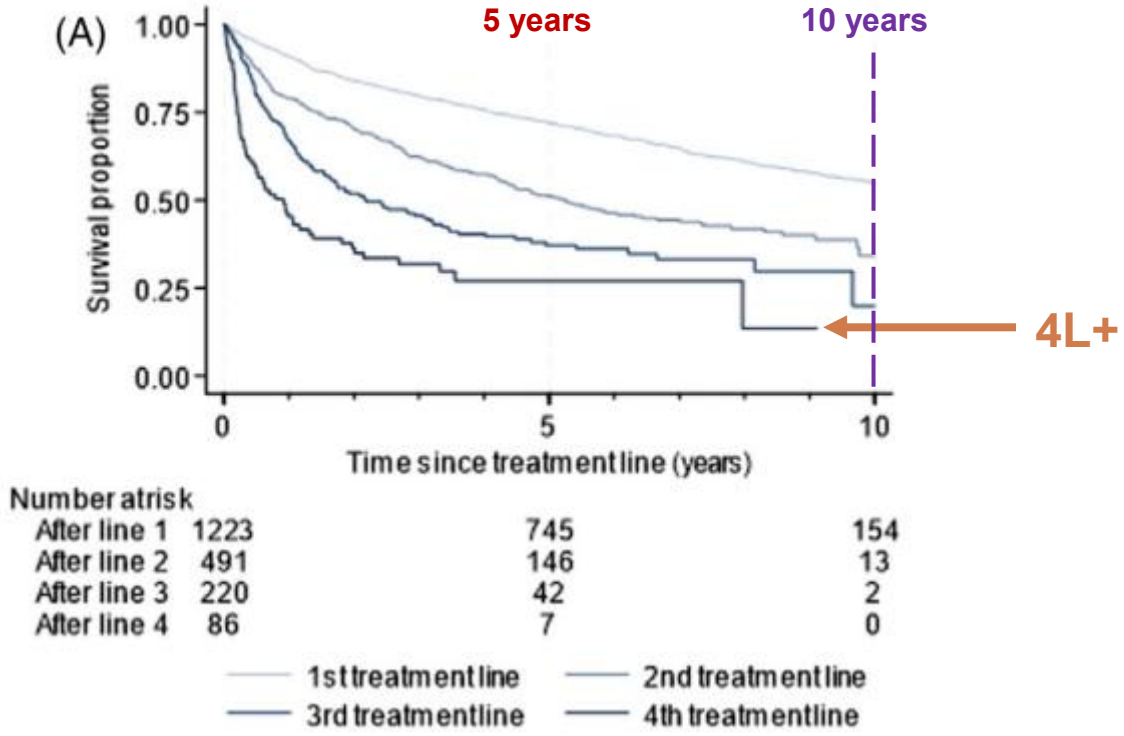
4L+ HMRN data and Wasterlid (2024) OS

HMRN OS from start of 4L+, months

[redacted]

From company submission

Wasterlid (2024) OS, years



Abbreviations: 4L, fourth line; HMRN, Haematological Malignancy Research Network; OS, overall survival.

Approximate OS landmarks by source

Source	HMRN	Wasterlid 2024	LEO CReWE Casulo 2022	ReCORD-FL Salles 2022	Chihara 2025
Location	Yorkshire & Humber	Sweden	US	7 countries including Europe	US
Dates	[redacted]	2007-2014	2002 - 2018	1998 - 2019	2000 - 2017
EAG critique	UK registry, small study, limited reporting of baseline characteristics	Large study, generalisable to NHS but no baseline characteristics	US based, heterogeneous treatments (inc. experimental); 94% at 3L	No PFS data (but EFS as proxy); 80% at 3L; excluded ECOG >1	-
3L+ OS: 2 years	[redacted]	52%	90% approx.	85% approx.	59%
3L+ OS: 5 years	[redacted]	37%	75%	68% approx.	33%
3L+ OS: 10 years	[redacted]	NR	63% approx.	52% approx.	15% approx.
4L+ OS: 2 years	[redacted]	36%	N/A	75% approx.	52%
4L+ OS: 5 years	[redacted]	27%	N/A	55% approx.	26%
4L+ OS: 10 years	[redacted]	NR	N/A	40% approx.	12% approx.

Abbreviations: OS, overall survival; HMRN, Haematological Malignancy Research Network; LEO, Lymphoma Epidemiology Outcomes; CReWE, Consortium for Real World Evidence; EAG, external assessment group; PFS, progression-free survival; EFS, event-free survival; ECOG, Eastern Cooperative Oncology Group; 3L/4L, third-/fourth-line; NR, not reported.

MAIC methodology (3L+)

EPCORE NHL-1 data is adjusted to match HMRN data

EPCORE NHL-1 3L+
COVID modified
MAIC **unadjusted** IPD data
N = 128

Reweighted to match characteristics of HMRN data for relevant treatment effect modifiers and prognostic variables

Prognostic variable	Share in adjusted cohort
Age (≥ 60)	[redacted]
Male	[redacted]
Disease stage III – IV	[redacted]
Prior ASCT	[redacted]
Prior CAR-T	[redacted]
POD24 after first line CIT	[redacted]
Refractory to most recent anti lymphoma therapy	[redacted]
Refractory to both anti-CD20 and alkylator therapy	[redacted]
Prior lines of therapy ≥ 3	[redacted]
Prior treatment with R^2	[redacted]

EPCORE NHL-1 3L+ COVID modified MAIC **adjusted** IPD data
N = 79

+

HMRN 3L+ summary data (re-created IPD data)
N = [redacted]

=

- Progression-free survival
- Overall survival
- Objective response rate
- Complete response

Abbreviations: ASCT, Autologous Stem Cell Transplant; CIT, Chemoimmunotherapy; HMRN, Haematological Malignancy Research Network; IPD, individual patient data; MAIC, matching adjusted indirect comparison; POD24, disease progression within 24 months; R^2, rituximab + lenalidomide

Key MAIC results (3L+)

MAIC adjusted outcomes for epcoritamab were better than unadjusted outcomes

Table: Results of the 3L+ MAIC-adjusted analyses

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

Table: COVID adjustment in 3L+ population

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

"All refractory variables" sensitivity analysis reduces ESS from 128 to 63 and [redacted] HRs in [redacted] of epcoritamab

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; HMRN, Haematological Malignancy Research Network; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression free survival

MAIC methodology (4L+)

EPCORE NHL-1 data is adjusted to match HMRN data

EPCORE NHL-1 4L+
COVID modified
MAIC **unadjusted** IPD data
N = 81

Reweighted to match characteristics of HMRN data for relevant treatment effect modifiers and prognostic variables

Prognostic variable	Share in adjusted cohort
Age (≥ 60)	[redacted]
Male	[redacted]
Disease stage III – IV	[redacted]
Prior ASCT	[redacted]
Prior CAR-T	[redacted]
POD24 after first line CIT	[redacted]
Refractory to most recent anti lymphoma therapy	[redacted]
Refractory to both anti-CD20 and alkylator therapy	[redacted]
Prior lines of therapy ≥ 4	[redacted]
Prior treatment with R^2	[redacted]

EPCORE NHL-1 4L+ COVID modified MAIC **adjusted** IPD data
N = 40

+

HMRN 4L+ summary data (re-created IPD data)
N = [redacted]

=

- Progression-free survival
- Overall survival
- Objective response rate
- Complete response

Abbreviations: ASCT, Autologous Stem Cell Transplant; CIT, Chemoimmunotherapy; HMRN, Haematological Malignancy Research Network; IPD, individual patient data; MAIC, matching adjusted indirect comparison; POD24, disease progression within 24 months; R^2, rituximab + lenalidomide

Key MAIC results (3L+)

MAIC adjusted outcomes for epcoritamab were better than unadjusted outcomes

Table: Results of the 4L+ MAIC-adjusted analyses

Epcoritamab vs current-care in 4L+ setting	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]

Adding in COVID deaths increases unadjusted OS HR from [redacted] to [redacted], adjusted OS HR from [redacted] to [redacted] and unadjusted PFS HR from [redacted] and adjusted PFS HR from [redacted] to [redacted]

Inclusion of primary refractory, and refractory to any prior anti-CD20 therapy reduces ESS from 81 to 31 and [redacted] HRs in [redacted] of epcoritamab

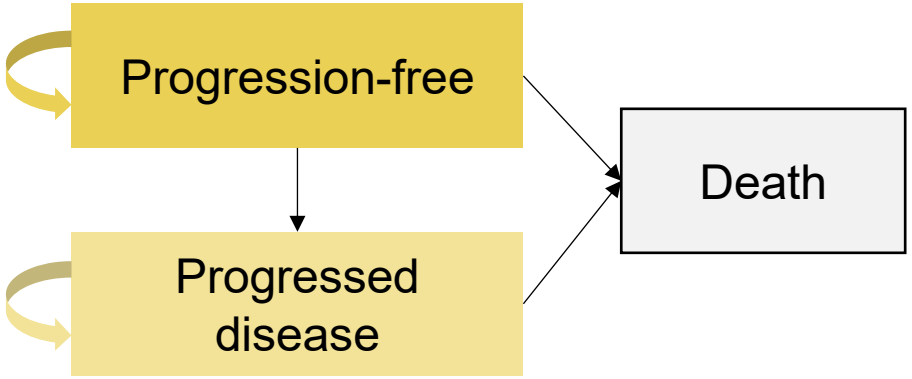
"All refractory variables" sensitivity analysis reduces ESS from 81 to 26 and [redacted] HRs in [redacted] of epcoritamab

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; HMRN, Haematological Malignancy Research Network; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression free survival

Company's model overview

Partitioned survival model with weekly cycle length and 35.2-year time horizon



- Background mortality included
- Treatment duration limited to 3 years for people with CR on epcoritamab
- Treatment waning not included
- BSC not included in comparator
- AE disutility not included

- Technology affects **costs** by:
  - treatment duration and health state occupancy, which are informed by PFS, OS, and TTD
  - frequency of adverse events
- Technology affects **QALYs** by:
  - Utility values assigned to the different health states
  - Source of data and method of informing relative efficacy
- Assumptions with greatest ICER effect:
  - estimating PFS and OS outcomes for comparator directly from HMRN data
  - informing relative efficacy via a naïve comparison

Abbreviations: AE, adverse event; BSC, best supportive care; CR, complete response; HMRN, Haematological Malignancy Research Network; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

Impact of CAR-T therapy censoring on survival

At 3L+ and 4L+, censoring CAR-T therapy at a subsequent line had limited impact on overall or progression-free survival

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

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

Other scenarios, including censoring from baseline those who would subsequently have CAR-T, had limited impact on survival. See Appendix 7 of company DG response.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; 3L/4L, third-/fourth-line; OS, overall survival; KM, Kaplan-Meier; DG, draft guidance.