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

For public – confidential information redacted [redacted]

Technology appraisal committee C [9 September 2025]

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

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

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Background on relapsed or refractory follicular lymphoma

Common, slow growing lymphoma with high risk of relapse or refractory disease

Causes

- Lymphomas are cancers of the lymphatic system, part of the immune system
- Follicular lymphoma (FL) is a slow growing, low-grade lymphoma affecting B-lymphocytes

Epidemiology

- In England in 2022 there were 2,404 new diagnoses of FL (1,217 female and 1,187 male)
- FL is the second most commonly diagnosed lymphoma, and mainly affects people aged over 60
- FL has a high risk of relapse or refractory disease (cancer returns or stops responding to treatment)

Diagnosis and classification

- FLs are commonly staged from I (best prognosis) to IV (worse prognosis)
- Staging depends on size, number and location of nodes affected, and whether other organs are affected

Symptoms and prognosis

- FL typically presents as painless lumps in neck, armpit or groin; might also include night sweats and fevers
- Some people do not have symptoms so the disease may have advanced by the time it is diagnosed
- The 5-year survival rate for those diagnosed with follicular lymphoma is around 90%
- By the 4L+ stage, R/R FL is not considered slow growing

Abbreviations: 4L+, fourth treatment line plus; FL, follicular lymphoma; R/R, relapsed or refractory

Technology (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 • Application via the international recognition procedure (reference regulator: EMA) • 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 • This mechanism differs from conventional CD20 targeting monoclonal antibodies that introduce cytotoxicity through Fc-mediated effector functions
Administration	• Subcutaneous injection • Administered by a healthcare professional qualified in the use of anti-cancer therapies • 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: EMA, European Medicines Agency; FL, follicular lymphoma; IgG1, immunoglobulin G 1

Patient perspectives (1)

Patients and carers live with constant fear and feel isolated

Submissions from Follicular Lymphoma Foundation, Lymphoma Action, and one patient expert

- FL is not curable, so treatment aims to extend remission as long as possible
- FL can have a profound emotional impact, it is a very anxious time when adjusting to the diagnosis and waiting for treatment, hoping it will work
- Constant uncertainty with most common fear that FL will return or transform into a more aggressive form, or running out of treatment options
- FL is low grade and often viewed as less serious, this leaves people feeling isolated and forgets the emotional burden that having an incurable cancer is
- Significant impact on carers due to anxiety, helplessness and daily support
- Current treatments are very limited, with some people having active surveillance or "worry and wait" in early disease stages
- Chemoimmunotherapy is typical active treatment and can be very intense and carry lots of side effects

"Every scan is terrifying with the constant fear is of another relapse and then the sickening blow when it comes back"

"It's hard to…look ahead more than a couple of months…It's a slow torture really"

"My partner feels the same emotional impact of living with the uncertainty of an incurable cancer as I do"

"The need for repeated courses of chemotherapy can lead to cumulative toxicity"

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Abbreviations: FL, follicular lymphoma

Patient perspectives (2)

Patients favour the administration of epcoritamab

Submissions from Follicular Lymphoma Foundation, Lymphoma Action and one patient expert

- Clear unmet need around access to newer, better tolerated treatments, with the potential for longer remission and ultimately cure
- Urgent need for more accessible, well-tolerated treatments, better patient education, and a more individualised, long-term approach to care
- Epcoritamab has clear advantage of being given subcutaneously, a much simpler method of administration than some of the current treatments
- Patients also feel that epcoritamab can offer a treatment option with fewer side effects which is better tolerated, though there is some uncertainty on this
- The possibility of using epcoritamab more than once is a real advantage
- However, patients recognised the need for more clinical trial data to build confidence as uncertainty remains high due to limited understanding

Perspectives from 2 clinical experts are added to key issue slides where relevant

"The most important thing of all for FL patients is that there are as many treatments as possible, because many of us are going to need them all"

"Use of s/c administration could be a significant factor in tolerability of regimes in this group [due to age]"

"[Epcoritamab] has been very straightforward for me, a bit like having a flu jab every week, not difficult at all and I've been able to work throughout"

"The ease of [epcoritamab] treatment is a big advantage but of course the effectiveness is what really counts"

Abbreviations: FL, follicular lymphoma

Key issues

Key issues for discussion	ICER impact
Population restricted to fourth line (4L) +	Unknown
Uncertainty with EPCORE NHL-1	Unknown
Suitability of comparator data	Unknown
Adjusting survival data for COVID-19	Large
Modelling of comparator efficacy	Large
Severity weighting	Large

Other key issues in appendix	ICER impact
Utilities for comparator PFS state	Small
Subsequent treatment, resource use and adverse event costs	Small

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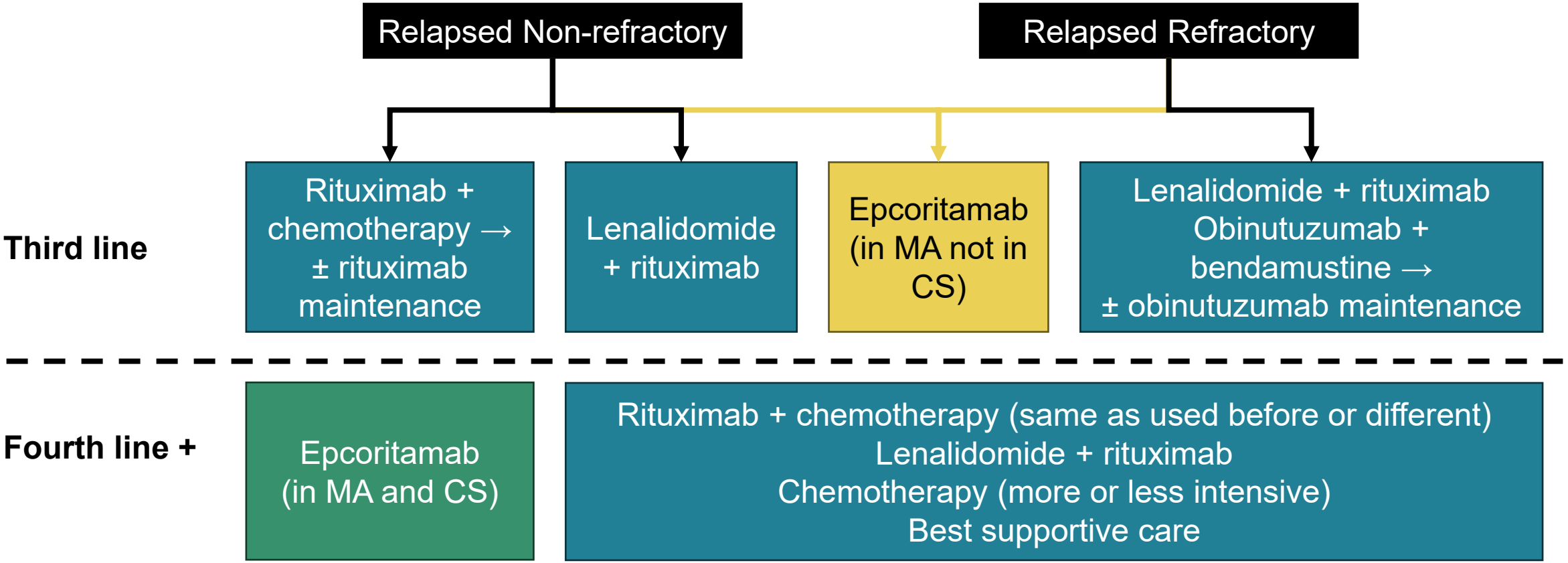
Abbreviations: PFS, progression free survival

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

Key issue: Population restricted to fourth line (4L) +

Company restricted full population to 4L+, EAG questions if this is appropriate

Company

- Submission provides results for a population restricted to 4L+ (excluding people at 3L in MA and scope)
- Explain this is to address the population with the greatest unmet need due to facing a short life expectancy
- There are no treatments approved specifically for the treatment of 4L+ patients

EAG comments

- EAG clinical experts consider greatest unmet need for optimised treatment options is at 3L+
- Company also shared clinical evidence for 3L+ and EAG has reported this evidence alongside the 4L+
- Generalisability of 3L+ data to UK is difficult to assess but EAG experts did not have any major concerns

Clinical experts

- Strong unmet need at 3L as well as 4L+, epcoritamab has demonstrated effectiveness in 3L
- Epcoritamab is more effective in earlier lines (although still retains high CR rates ~50% in 5L+ therapy)
- Main challenge is demonstrating comparative effectiveness at 3L against available therapies
- Comparisons against rituximab + lenalidomide are flawed due to low-risk 2L population in AUGMENT trial and the inability to adjust for lines of therapy in comparative analyses

Abbreviations: CR, complete response; MA, marketing authorisation

Should the modelled population be 3L+ or 4L+?

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Key clinical trials – EPCORE NHL-1 and HMRN data

	EPCORE NHL-1	HMRN dataset
Design	Open label single arm phase 1/2 study	Retrospective, observational dataset
Population	Dose expansion cohort, FL, 4L+ (used in company submission)* N = 81 ([redacted] in UK)	Adults with R/R FL initiating treatment 4L+ N = [redacted]
Intervention	Epcoritamab 48 mg once weekly	Varied including rituximab and chemotherapy
Comparator	N/A	N/A
Start / end date	June 2020 to ongoing (data cut [redacted])	[redacted]
Duration	Median follow-up: [redacted] months	Median follow-up: [redacted] months
Primary outcome	ORR	OS, PFS, TTD, ORR, CR, PR
Key secondary outcomes	CRR, OS, PFS, safety, QoL measures including EQ-5D-3L	N/A
Locations	Multinational including UK	Yorkshire and Humber & Yorkshire Coast
Used in model?	Yes – main evidence for epcoritamab	Yes – main evidence for comparator

*Data with [redacted] months follow up for the dose optimisation cohort was shared but not used in the company analysis, new data with [redacted] months follow up is now available but was not shared in time for use in analysis

Abbreviations: CR, complete response; CRR, complete response rate; FL, follicular lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response; QoL, quality of life; R/R, relapsed or refractory

Is HMRN data generalisable to current NHS practice?

Key issue: Uncertainty with EPCORE NHL-1

EAG have concerns with generalisability, subgroups and COVID-19 adjustment

Company

- UK experts stated baseline characteristics in EPCORE NHL-1 are aligned with UK clinical practice
- Some noted that the overall fitness of patients in the EPCORE trial population is reduced compared with standard trial populations, presenting with high-risk features that are typical in real world populations
- Experts anticipate that the results observed will closely reflect the responses expected in clinical practice

EAG comments

- EPCORE NHL-1 data are from subgroups relating to number of prior lines of treatment and some data from the latest data cuts could not be validated, not all data shared by the company has been validated by EAG
- EAG consider there are uncertainties with the COVID-19 adjustment (see separate key issue)
- Concerns with generalisability as only [redacted] out of [redacted] people in the 4L+ expansion cohort were from the UK, and were younger (mean age [redacted] years), [redacted] of white family background and mostly male ([redacted]%)
- EAG unsure about the generalisability of the findings to the population in clinical practice, but note that company and EAG clinical experts consider the baseline characteristics generalisable to UK

Is data from EPCORE NHL-1 suitable for decision-making?

Key issue: Suitability of comparator data

EAG have concerns with differences in EPCORE NHL-1 and HMRN data

Company

- Company assessed feasibility of STC but decided to do a MAIC due to low number of events, a single comparator, and a preference for MAICs in previous NICE STAs
- No studies identified via SLR were appropriate for use in an ITC, either due to inclusion of a non-UK generalisable population or the inclusion of treatment options not available in the UK
- So, company engaged with HMRN to identify the most appropriate data to inform the MAIC
- The HMRN dataset was the only identified data source considered suitable for inclusion in the MAIC

EAG comments

- Important differences between EPCORE-1 and HMRN that raises concerns with MAIC validity:
  - study design (phase 2, open-label clinical trial versus retrospective, observational dataset)
  - years of conduct (since June 2020 versus [redacted] to [redacted])
  - sample size (81 versus [redacted]) and follow-up (median follow up of [redacted] months versus [redacted] months)
  - inclusion criteria (4L+ and R/R disease in EPCORE versus patients with 4L+ in HMRN dataset)
  - baseline characteristics, including treatment effect modifiers such as prior treatments, and lack of reporting in HMRN (race, ethnicity, BMI, renal and hepatic function were not reported)
- EAG searches did not find alternative comparator data for 4L+, but suitable data may be available for 3L+

Abbreviations: BMI, body mass index; HMRN, Haematological Malignancy Research Network; MAIC, matching adjusted indirect comparison; SLR, systematic literature review

Is the comparator HMRN dataset suitable for decision-making?

Key issue: Adjusting survival data for COVID-19

EAG prefers to use COVID-unmodified survival data

Company

- EPCORE NHL-1 took place during COVID-19 pandemic and excess mortality was observed in trial
- Clinical review identified [redacted] COVID-19 attributable deaths, [redacted] of which had achieved complete response so were unlikely to progress, so COVID-19 deaths are censored in survival outcomes and MAIC
- No COVID-19 deaths were reported in HMRN dataset, so censoring EPCORE NHL-1 data is consistent

EAG comments

- Prefer to use COVID-unmodified data from EPCORE NHL-1 for PFS and OS due to following concerns:
  - EAG experts consider extrapolations from COVID adjusted data too optimistic
  - Consistent with HMRN data due to potential for COVID-19 to have affected HMRN too, plus no evidence or details have been shared to confirm claim that there were no COVID deaths in HMRN
  - Unclear whether COVID-19 is totally attributable for recorded COVID-related deaths in EPCORE

Clinical experts

- It is appropriate to adjust for COVID-19 deaths, recent data shows similar response rates but improved safety and mortality in people treated during and after the COVID-19 pandemic

How should EPCORE NHL-1 survival data be adjusted for COVID-19 deaths?

Abbreviations: HMRN, Haematological Malignancy Research Network; MAIC, matching adjusted indirect comparison

MAIC methodology

EPCORE NHL-1 data is adjusted to match HMRN data

Is this a full list of prognostic variables?

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

Is the MAIC appropriate for decision making?

Key MAIC results (1)

MAIC adjusted outcomes for epcoritamab were better than unadjusted outcomes

Table: Unadjusted and adjusted best response outcomes for epcoritamab compared with current 4L+ care

	Unadjusted Epcoritamab (N = 81)	Epcoritamab adjusted to HMRN (N = 40)
Complete response	Epcoritamab: [redacted] Current 4L+ care: [redacted]	Epcoritamab: [redacted] Current 4L+ care: [redacted]
Odds Ratio [95% CI]	[redacted]	[redacted]
Overall response	Epcoritamab: [redacted] Current 4L+ care: [redacted]	Epcoritamab: [redacted] Current 4L+ care: [redacted]
Odds Ratio [95% CI]	[redacted]	[redacted]

Table: Unadjusted and adjusted OS and PFS for epcoritamab vs current 4L+ care

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

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

Key MAIC results (2)

MAIC adjusted outcomes for epcoritamab were better than unadjusted outcomes

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

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

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Source: Figure 17, company submission, page 93

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

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Key issue: Modelling of comparator efficacy (1)

EAG prefers to use HMRN data directly to model comparator data

Company

- Applied HRs from MAIC to preferred PFS and OS extrapolations for epcoritamab
- Assume HRs are proportional as no waning effect is applied but background mortality is included
- MAIC HRs are applied to unadjusted epcoritamab survival data because adjusted data is more uncertain due to reduced sample size, also using EPCORE reference population is consistent with other inputs

EAG comments

- Agree with proportional hazards for follow up period, uncertain with assumption into the future
- Prefer to use HMRN data directly with log-normal extrapolation (naïve comparison) due to concerns with:
  - small adjusted sample size potentially biasing results (MAIC adjusted population N=[redacted])
  - strict trial criteria means MAIC unlikely to account for differences in trial and real-world populations
  - MAIC adjustment produces unexpected result [redacted] vs unadjusted analysis

Table: Comparison of modelled survival for EAG and company preferred extrapolations for the comparator

Timepoint	HMRN PFS	HMRN OS	Company PFS	Company OS	EAG PFS	EAG OS
3-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

How should comparator survival be modelled?

Key issue: Modelling of comparator efficacy (2)

EAG preferred survival for the comparator is higher than the company's modelling

Figure: Company and EAG preferred OS and PFS extrapolations for comparator

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression free survival

How should comparator survival be modelled?

Key issue: Severity weighting

Company base case meets x1.2 weight threshold, EAG base case does not

Background

- Mean age at baseline of 64.8 years and a proportion of females of 34.6% (EPCORE NHL-1, FL 4L+)
- Company base case meets severity weighting threshold of x1.2 for QALYs
- EAG base case does not meet severity weighting threshold for QALYs (weight of x1)
  - EAG note company uses appropriate value sets for calculating QALY shortfalls
  - EAG note company calculations are correct for company base case
  - Difference in severity weighting is due to EAG estimating higher QALYs with current treatment which is mostly driven by EAG preference for current 4L+ care survival to be modelled with HMRN data directly

Table: QALY shortfalls and QALY weight for severity calculated in company and EAG base cases

Base case	QALYs of people without condition	QALYs with the condition on current treatment	Absolute QALY shortfall (>12 for x1.2; >18 for x1.7)	Proportional QALY shortfall (>0.85 for x1.2; >0.95 for x1.7)	QALY weight
Company	10.91	0.985	9.93	0.91	x1.2
EAG	10.91	1.70	9.21	0.84	x1

What QALY weighting should be applied for severity?

Abbreviations: HMRN, Haematological Malignancy Research Network; QALY, quality adjusted life year

Equality considerations

No equalities issues identified

However, company submission includes:

- Patients reaching 4L+ are more likely to receive experimental treatments within clinical trials than patients in earlier lines. As access to clinical trials might be more restricted in rural or deprived areas, patients with 4L+ R/R FL are likely to benefit from access to an efficacious therapy as part of routine commissioning.

Abbreviations: FL, follicular lymphoma; R/R, relapsed or refractory

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Corrections	LDH cost not included for PFS state despite submission saying so	Corrected error by including LDH cost for PFS state as intended
Epcoritamab survival	COVID **adjusted** OS and PFS data from EPCORE NHL-1 (log-normal distribution)	COVID **unadjusted** OS and PFS data from EPCORE NHL-1 (log-normal distribution)
Current 4L+ 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	Weighted by proportion achieving CR, PD estimated using Wild et al	Sourced from EPCORE NHL-1 EQ-5D data, PD estimated using Wild et al
Haematologist consultations	Monthly visits for epcoritamab	Weekly for first month, monthly thereafter for epcoritamab
Adverse event incidence	Based on R-CHOP data	Reweighted value for each AE for each treatment in the basket
Inclusion of CRS events	CRS events not included	Grade 2 CRS events included that required treatment with tocilizumab in trial

Abbreviations: AE, adverse event; CR, complete response; CRS, cytokine release syndrome; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PD, progressed disease; PFS, progression free survival; R-CHOP, Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

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

Company scenario analyses on the company base case all have ICERs below £30,000 per QALY

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

EAG scenario analyses on the EAG base case mostly have ICERs above £30,000 per QALY

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Key issues

Key issue	Key question for committee	ICER impact	Slide
Population restricted to fourth line (4L) +	Should the modelled population be 3L+ or 4L+?	Unknown	9
Uncertainty with EPCORE NHL-1	Is data from EPCORE NHL-1 suitable for decision-making?	Unknown	12
Suitability of comparator data	Is the comparator HMRN dataset suitable for decision-making?	Unknown	13
Adjusting survival data for COVID-19	How should EPCORE NHL-1 survival data be adjusted for COVID-19 deaths?	Large	14
Modelling of comparator efficacy	How should comparator survival be modelled?	Large	19
Severity weighting	What QALY weighting should be applied for severity?	Large	21
Utilities for comparator PFS state	How should PFS utility be modelled?	Small	30
Subsequent treatment, resource use and adverse event costs	What costs should be modelled for subsequent treatments, resource use and adverse events?	Small	31

Abbreviations: PFS, progression free survival; QALY, quality adjusted life year

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Supplementary appendix

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Key clinical trials – EPCORE NHL-1 and HMRN data

Study design	EPCORE NHL-1	HMRN
Population	COVID-modified post-expansion phase 4L+ FL	4L+ FL
Sample size	81	[redacted]
Start and end date	19 June 2020 to ongoing	[redacted]
Data cut-off	[redacted]	
Median follow-up	[redacted] months	[redacted]
Study design	Open-label trial	Observational RWE
Treatment	Epcoritamab s/c 48 mg	[redacted]
Key inclusion/ exclusion criteria	Inclusion: Histologically confirmed FL grades 1 – 3A Relapsed, progressive and/or refractory Exhausted or ineligible for standard care Received ≥4 systemic treatments (4L+) Aged ≥ 18 years Lymphocytes <5 x 10^9/L Platelet count ≥ 75 x 10^9/L Absolute neutrophil count ≥1.0 x 10^9/L	Inclusion: Follicular lymphoma diagnosis recorded via WHO ICD-O-3 code including 9579, 9690, 9695, 9698[A] Aged ≥ 18 years at diagnosis Received ≥ 3 lines of chemotherapy
Location	85 locations across Australia, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Singapore, South Korea, Spain, Sweden, UK, and USA	England (Yorkshire and the Humber & Yorkshire Coast Cancer Networks)

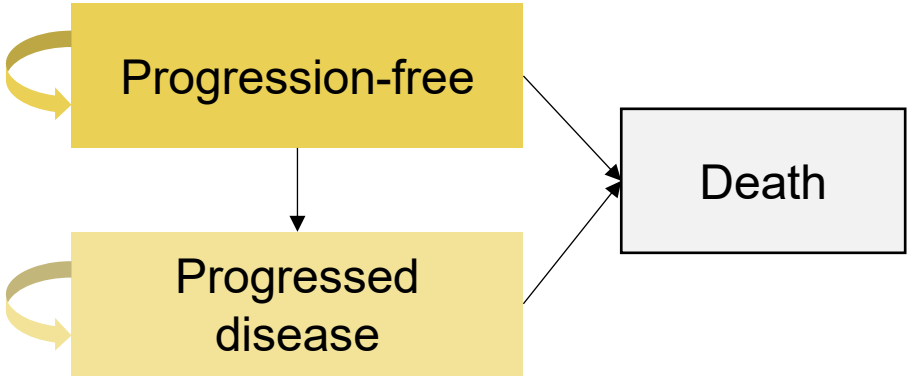
Data sources not used in company analysis

Trial Name	SCHOLAR-5	ReCORD-FL	LEO Cohort
Author, year	Ghione, 2023	Salles, 2022	Casulo, 2022
Country	US, France, UK, Spain, Portugal	US, Canada, UK, France, Germany, Spain	US
Patients from UK (%)	17%	Unknown	0%
Patients at each treatment line	3L+: 39% 4L+: 28% 5L+: 33%	3L+: 80% 4L+: 17% 5L+: 3%	3L+: 94% 4L+: 5% 5L+: 1%
Baseline characteristics accessible?	Yes	Yes	Yes
Available outcomes	ORR, CR, PFS, OS	ORR, CR, EFS, OS	ORR, CR, PFS, OS
PFS and OS KMs available?	Yes	Yes for OS and EFS, not available for PFS	Yes
Median OS	3L: 67.6 months 4L: NR 5L+: 42.8 months	3L: 133.7 months 4L: 95.8 months 5L: 46.3 months	3L+: 169 months 4L+: NR
Company reason for excluding	Generalisability concerns with treatments	PFS not reported, majority of people at earlier lines	No UK patients, only 6% of people at 4L+

Abbreviations: CR, complete response; EFS, event free survival; KM, Kapaln-Meier; NR, not reported; ORR, objective response rate; 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

Key issue: Utilities for comparator PFS state

Company models utility for comparator PFS based on response, EAG disagrees

Company

- Experts indicated that people who achieve CR are expected to have higher HRQoL than those who do not
- So a utility analysis differentiating PF utilities by 'PF with CR' and 'PF without CR' was performed
- Utility analyses were implemented into the economic model by weighting utility values according to the proportion of patients achieving CR in epcoritamab and current 4L+ care arms

EAG comments

- EAG experts agree that CR is a determinant of PF HRQoL, but they also noted the impact of AEs on HRQoL should also be considered because patients who achieve CR remain on treatment for longer
- Company approach likely to be biased, other variables and time spent with CR status should be considered
- So, EAG base case uses the same PFS utility for both arms (derived via EQ-5D in EPCORE NHL-1 trial)

Table: Utility values for PFS and PD states in company and EAG base cases

Health state	Company base case	EAG base case
PFS (epcoritamab)	[redacted]	[redacted]
PFS (current 4L+ care)	[redacted]	
PD (both arms)	[redacted]	[redacted]

Abbreviations: AE, adverse event; CR, complete response; HRQoL, health related quality of life; PD, progressed disease; PF, progression free; PFS, progression free survival

How should PFS utility be modelled?

Key issue: Cost inputs

EAG identifies treatments used in trial, but associated costs are not modelled

Subsequent treatment costs

Company: Experts state that subsequent treatment should be identical to the basket of current 4L+ care used within the comparator arm, also CAR-T usage is controlled for in MAIC so will not affect outcomes

EAG: EAG experts agree that modelled subsequent treatments are appropriate, but EAG concerned that subsequent treatment effects are modelled without associated costs as the following were received in EPCORE NHL-1: systemic anti-lymphoma therapy ([redacted]%), ASCT ([redacted]%), CAR-T ([redacted]%)

Resource use costs

Company: includes once a month haematologist consultation and no PET scans for epcoritamab

EAG: EAG experts suggest once weekly haematologist consultations for first month with monthly visits after (in EAG base case), also suggest including 12 monthly PET scans (included in EAG scenario)

Experts: Haematologist review required weekly in cycle 1, but can be stepped down to monthly from cycle 2

Adverse event costs

Company: AE data for R-CHOP used to model AEs for the basket due to limited AE data for chemotherapy

EAG: Prefers using varying proportions across therapies in basket to provide a weighted value for each AE

Abbreviations: AE, adverse event; ASCT, Autologous Stem Cell Transplant; MAIC, matching adjusted indirect comparison; PET, Positron Emission Tomography; R-CHOP, Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

What costs should be modelled for subsequent treatments, resource use and adverse events?