

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

Technology appraisal committee C [12 September 2023]

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Company: Swedish Orphan Biovitrum

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic therapies [ID3943]

✓ Background

- Key issues and treatment pathway
- Clinical evidence and key clinical issues to consider
- Modelling and key cost effectiveness issues to consider
- Other considerations

Background on diffuse-large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL)

DLBCL and HGBL are aggressive (fast growing) forms of high-grade non-Hodgkin lymphoma (NHL)

How many people have DLBCL/HGBL?

- Around 4,850 people diagnosed with DLBCL in 2019
- Accounts for ~40% of non-Hodgkin Lymphoma cases
- HGBL is rarer - accounts for 1-2% of NHL cases

Symptoms and prognosis

- Symptoms differ depending on which organ or tissues are affected by the lymphoma but may present as 'B symptoms' or lumps in various locations
- Risk factors and indicators for poorer outcomes include high International Prognostic Index score, age over 60 years and ECOG performance status ≥ 2
- HGBL prognosis particularly poor | high proportion of HGBL become refractory / relapse

Patient perspectives

R/R DLBCL and HGBL can be difficult to treat, with limited and intensive treatment options

Submission from Lymphoma Action

- Lumps can appear in the neck, groin, and armpit; in some cases can appear outside lymph nodes, e.g. chest
- Symptoms include night sweats, weight loss, fatigue
- The symptoms and treatment have a severe mental and physical impact on patients and carers | This can worsen in cases of relapse or refractory disease
- No standard treatment for HGBL; often same as DLBCL
- R/R DLBCL and HGBL are aggressive and can be difficult to treat, often through intensive options; a new targeted therapy could significantly change this

“I had to spend weeks in hospital... I was very lonely and felt isolated from my family. I had fantastic care, but I was very anxious about relapse; this was more severe around the time my chemo finished and I was no longer being treated”

“...DLBCL can recur so it's important to have a range of second and third-line treatment options that are effective, widely available and well tolerated.”

Clinical perspectives

The pathway for 3rd line is not well defined and there is an unmet need for more treatment options

Submissions from NCRI-ACP-RCP-RCR

- 3rd line DLBCL is difficult to treat and there is an unmet need
- CAR-T therapy is not always an option; depends on performance status and clinically stable disease
- As an intravenous outpatient therapy, it will have less impact on hospital resource and patients compared with some current options (e.g. CAR-T)
- Lon-tes is well tolerated and will be an option where current treatment options are not tolerated

“The pathway of care beyond 2 lines of therapy is not well-defined. It depends on a number of factors, e.g. timing of relapse related to previous therapies, ability to tolerate further treatment, localisation of disease, co-morbidities, performance status, patient preference.”

“For some patients, this will be the best option as they cannot tolerate other treatments and for those patients that have relapsed after more intensive treatment, this provides a new treatment option.”

Loncastuximab tesirine (ZYNLONTA, Swedish Orphan Biovitrum)

Technology details

Marketing authorisation	Adults with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy. <ul style="list-style-type: none">• GB marketing authorisation February 2023
Mechanism of action	Antibody-drug conjugate targeting CD19 protein
Administration	Intravenous infusion
Price	<ul style="list-style-type: none">• List price: £15,200 per vial• Average cost of a course of treatment (list price): £85,562• Confidential simple discount patient access scheme available

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Background






Key issues and treatment pathway

Clinical evidence and key clinical issues to consider

Modelling and key cost effectiveness issues to consider

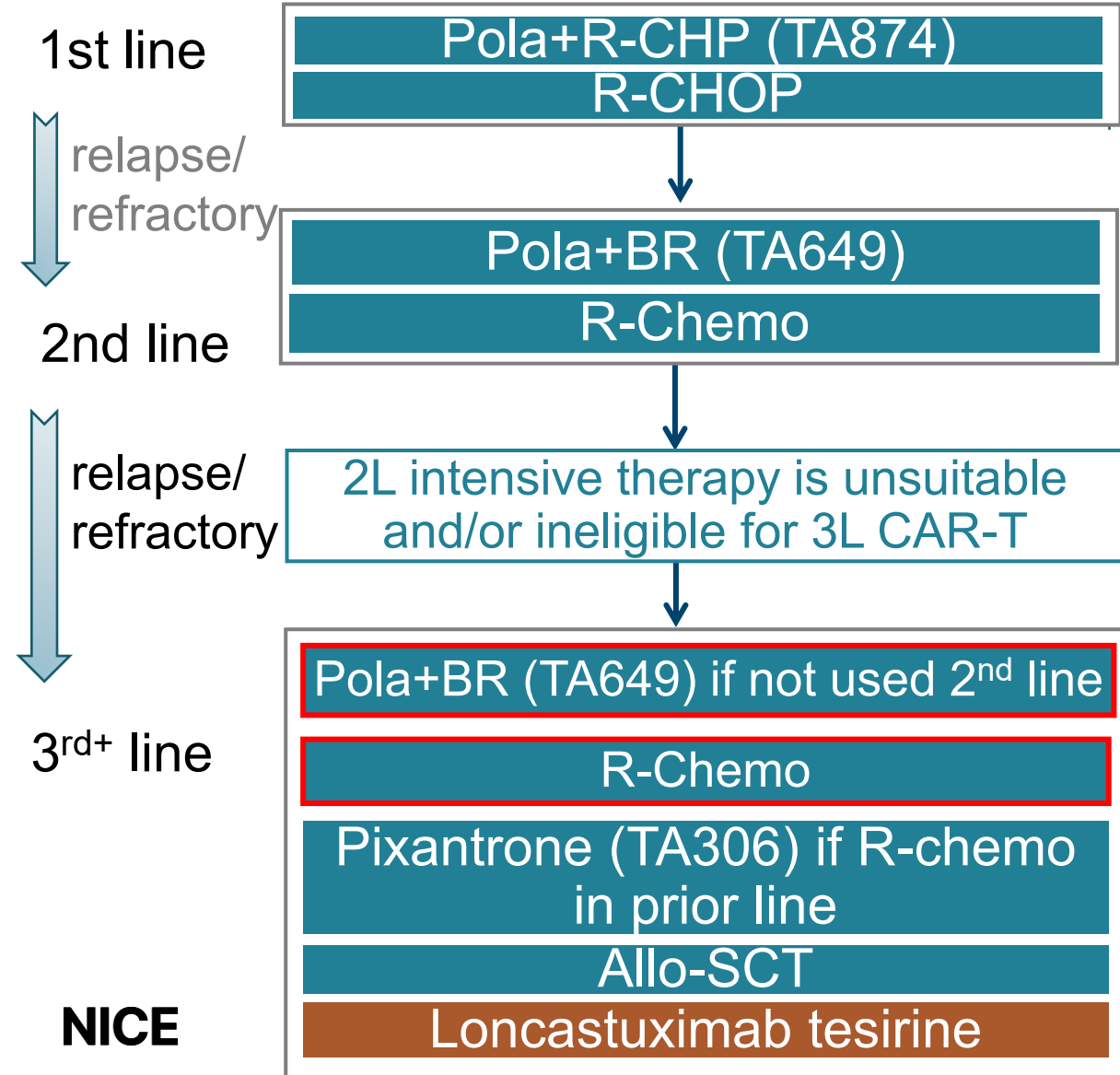
Other considerations

Key issues for discussion

Issue	ICER impact
<p>Concerns over MAIC (lon-tes versus pola+BR)</p> <p>Concerns about parameters and trial population applied in MAIC</p> <ul style="list-style-type: none"> • Are the MAIC analyses suitable for decision making? 	<p>Unknown </p>
<p>Unsupported degree of extrapolated OS benefit (lon-tes versus pola+BR)</p> <ul style="list-style-type: none"> • Is generalised gamma (company) or log-normal (EAG) the most appropriate OS extrapolation? • Should pola+BR OS be set equal to lon-tes OS? 	<p>Large </p>
<p>Unsupported degree of extrapolated PFS benefit (lon-tes versus pola+BR)</p> <ul style="list-style-type: none"> • Is generalised gamma (company) or log-normal (EAG) the most appropriate PFS extrapolation? • Should pola+BR PFS be set equal to lon-tes PFS? 	<p>Large </p>
<p>OS extrapolation (lon-tes versus chemotherapy)</p> <ul style="list-style-type: none"> • Is generalised gamma (company) or log-normal (EAG) the most appropriate OS extrapolation? 	<p>Large </p>
<p>Rate of subsequent autoSCT applied in model (chemotherapy)</p> <ul style="list-style-type: none"> • Is 22% (company – from CORAL) and 3% (EAG – same rate as lon-tes) more plausible? 	<p>Small </p>

Treatment pathway for DLBCL

Pathway for when intensive therapy is unsuitable for patients



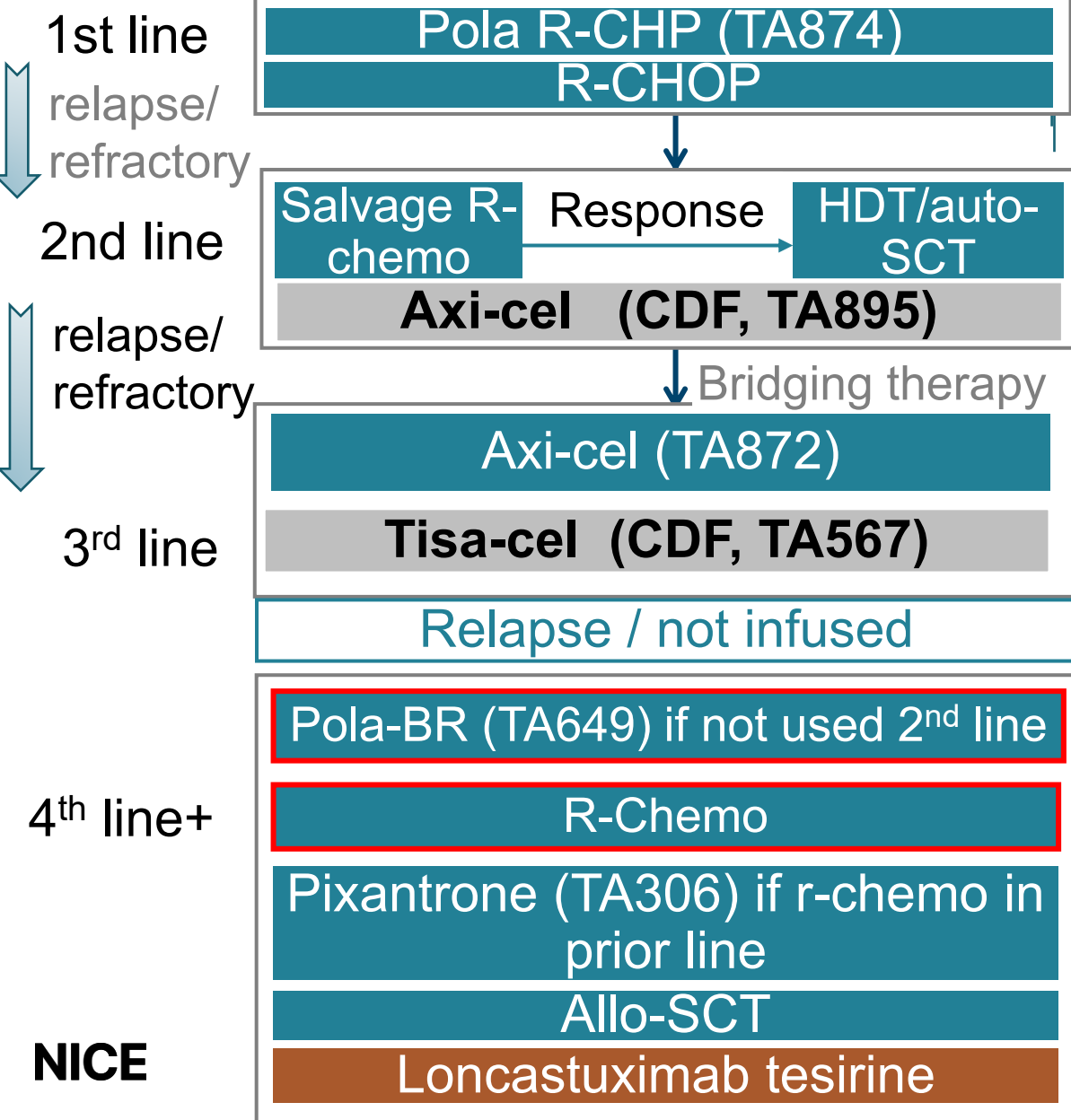
Included in company submission as relevant comparators

Abbreviations: allo-SCT, allogeneic stem cell transplant; DLBCL, diffuse large B-cell lymphoma; Pola+BR, polatuzumab vedotin with rituximab and bendamustine; Pola+R-CHP, polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisolone; R-Chemo, rituximab based chemotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Are pola+BR and R-Chemo the appropriate comparators?

Treatment pathway for DLBCL

Pathway when intensive therapy is suitable for patients



Included by company as relevant comparators

CDF drugs not considered in appraisal

Company

- CAR-T not included as comparator because lon-tes positioning is where CAR-T or SCT is unsuitable

Abbreviations: allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T cell; CDF, Cancer Drugs Fund; DLBCL, diffuse large B-cell lymphoma; HDT, high dose therapy; Pola+BR, polatuzumab vedotin with rituximab and bendamustine; Pola+R-CHP, polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisolone; R-Chemo, rituximab based chemotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; tisa-cel, tisagenlecleucel

Are pola-BR and R-Chemo the appropriate comparators?

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- Key issues and treatment pathway

- ✓ **Clinical evidence and key clinical issues to consider**

- Modelling and key cost effectiveness issues to consider

- Other considerations

Key clinical trial

Company submission uses data from 1 single-arm trial for lon-tes

Clinical trial designs and outcomes

	LOTIS-2 (NCT03589469)
Design	Phase 2, multicentre, open-label, single-arm
Population	Adults with relapsed or refractory DLBCL (including HGBL) who do not respond to or have progressive disease after salvage therapies and have a poor prognosis (n=145)
Intervention	Loncastuximab tesirine
Outcomes (relevant to scope)	ORR (primary outcome), DOR, CRR, PFS, OS, frequency and severity of AEs and SAEs, HRQoL (EQ-5D-5L and FACT-Lym)
Locations	US, Italy, Switzerland, UK

EAG comment

- Most patients based in US [REDACTED], [REDACTED] were based in UK; may raise generalisability concerns

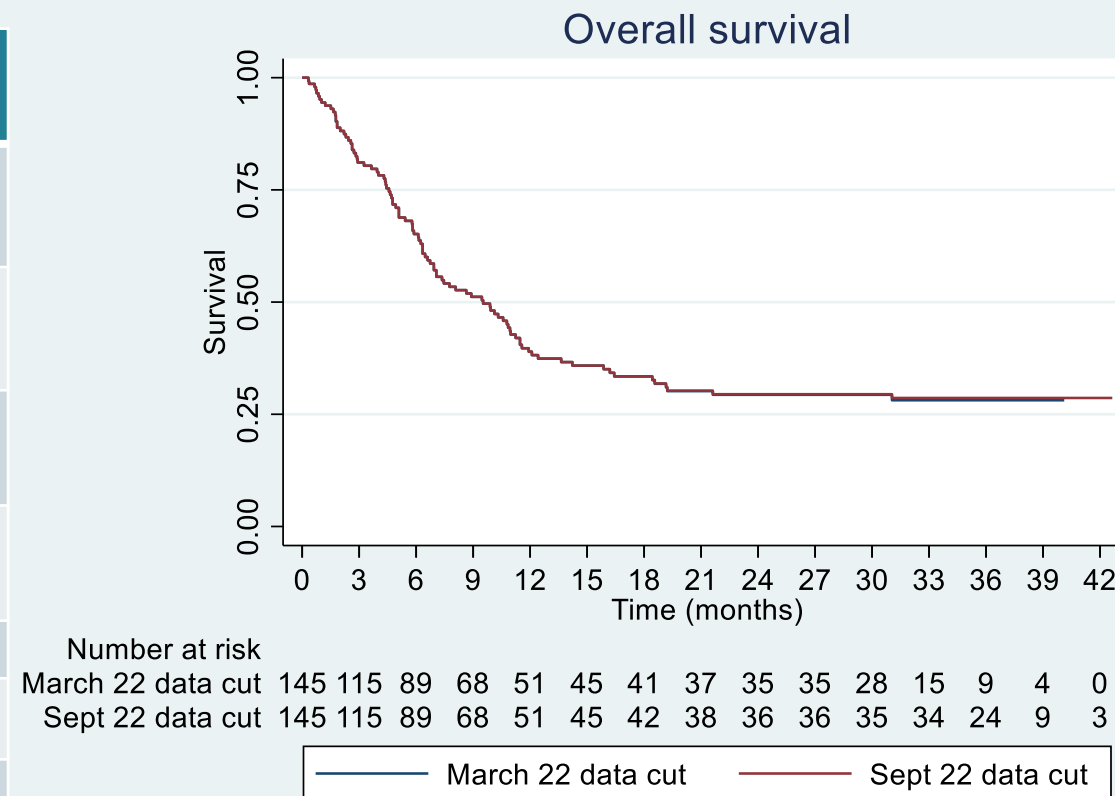
LOTIS-2 results

Findings were similar across timepoints

Efficacy results of LOTIS-2

Outcome	1 March 2022	September 2022 (updated at TE)
CR rate (95% CI)*	25 (18% to 33%)	25% (no CI reported)
OR rate (95% CI)	48% (40% to 57%)	48%
Median PFS (95% CI)	No data	4.93 months (2.89 to 8.31).
Median OS (95% CI)	No data available	9.5 months (6.7 to 11.5)
Any TEAE	98.6%	No data
Grade 3+ TEAE	73.8%	No data
TEAE leading to lon-tes withdrawal	24.8%	No data

Comparison of OS in LOTIS-2**



*Assessed by independent review committee. Investigator assessment also provided.

**No change in number at risk for PFS between March and September data cut-offs

Comparative evidence versus pola+BR (ITC1) - GO29365

Lon-tes has similar or slightly inferior efficacy compared to pola+BR

Background

- MAIC used to generate weighted populations from LOTIS-2 (lon-tes, n=145) that match available characteristics from GO29365 (n=152) matched on 7 variables. Preferred variables based on clinical input.
- Median survival times used as patient level data not available for GO29365 --> only information available
- Sensitivity analyses: 1) excludes patients who had missing data for response to primary therapy (n=14), classified as 'other'. 2) uses maximal set of variables for matching, including IPI

Outcomes from MAIC, GO29365

	Naïve comparison	Company base case, weighted	Sensitivity analysis 1: weighted	Sensitivity analysis 2: weighted
OS, HR (95% CI)			1.07 (0.75, 1.51)	1.00 (0.71, 1.40)
PFS, HR (95% CI)			1.20 (0.85, 1.70)	1.39 (0.99, 1.95)
ORR, OR (95% CI)			1.02 (0.58, 1.78)	0.91 (0.53, 1.57)
Discont. due to AEs OR			Not reported	Not reported

EAG comments

- LOTIS-2 uses different data-cuts for each comparison
- GO29365 included data for 3rd+ line, but baseline characteristics only available for whole population
- The MAIC results presented appear to use the March 2022 cut-off (rather than September 2022 cut-off)
- Analysis has not been provided that apply both sensitivity analyses simultaneously.

Comparative evidence versus pola+BR (ITC2) – COTA US

ITC2 not used in economic model

Background

- Data for pola+BR ITC2 comes from COTA US RWE database (n=43); matching based on 4 variables
- No LOTIS-2 participants excluded; 145 LOTIS-2 participants matched against 43 COTA US participants
- MAIC outcomes used patient-level data; COTA data digitally recreated

EAG comments

- MAIC results appear to use the March 2022 cut-off (rather than updated September 2022 cut-off)
- Results appear contradictory; may be explained by uncertainty around response definition in COTA US
- Minimal data available (abstract and poster, which provide different results due to different data cut-offs)

Outcomes from MAIC, COTA US

	Naïve comparison	Company base case, weighted
OS, HR (95% CI)		
PFS, HR (95% CI)		
ORR, OR (95% CI)	0.67 (0.33,1.33)	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; lon-tes, loncastuximab tesirine; MAIC, matching-adjusted indirect comparisons; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pola+BR, polatuzumab vedotin with rituximab and bendamustine.

Comparative evidence versus chemo (ITC3) – CORAL

Lon-tes superior for OS and ORR compared with chemotherapy

Background

- Data for chemotherapy from CORAL extension study (n=278); matching based on 3 variables
- 80 LOTIS-2 participants matched against 266 CORAL participants

EAG comments

- MAIC appears to use March 2022 cut-off (not updated September 2022 cut-off)

Outcomes from MAIC, CORAL

	Naïve comparison	Company base case, weighted
OS, HR (95% CI)	0.69 (0.51, 0.94)	0.67 (0.51, 0.86)
PFS, HR (95% CI)	Not available	Not available
ORR, OR (95% CI)	1.51 (0.91, 2.50)	1.53 (0.91, 2.54)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; lon-tes, loncastuximab tesirine; MAIC, matching-adjusted indirect comparisons; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pola+BR, polatuzumab vedotin with rituximab and bendamustine.



Key issue: Concerns with MAICs (1)

MAICs are uncertain and offer little improvement over naïve comparisons

Background

- MAICs based on limited number of variables and sample sizes; differences in populations and study definitions
- EAG:
 - MAIC analyses offer little improvement over naïve comparisons
 - For pola+BR, most MAIC inputs come from a wider trial population (2nd+ line not 3rd+ line)
 - At TE, requested MAIC analyses to include IPI variables and exclude participants categorised as “other” for primary refractory status.

Company (at TE)

- Analyses use robust methodology to make the best comparison possible from the available data
- Population-adjustment analysis for lon-tes versus pol+BR not suitable due to differences in study definitions (refractory to last therapy).
- Concerns around including IPI score alongside individual components of IPI score (e.g. age, ECOG status). Additional sensitivity analyses provided for both requested scenarios at TE; results similar to base-case

Abbreviations: EAG, external assessment group; ECOG, European Cooperative Oncology Group; IPI, International Prognostic Index; ITC, indirect treatment comparison; lon-tes, loncastuximab tesirine; MAIC, matching-adjusted indirect comparisons; pola+BR, polatuzumab vedotin with rituximab and bendamustine; TE, technical engagement.

Key issue: Concerns with MAICs (2)



MAICs are uncertain and offer little improvement over naïve comparisons

Clinical expert comments

Agree with concerns over suitability of MAIC analyses; variables from IPI should be included

EAG comments

- Updated analyses use the March 2022 data cut-off (not the updated September 2022 cut-off)
- Updated analyses that include both requests (exclusion of 'other' and inclusion of IPI variables) not provided.
- Kaplan-Meier plots for sensitivity analyses not provided; nor has explicit effective sample sizes
- MAIC adjustments requested by EAG have not been implemented in the model
- Concerns over analyses will remain even with requested changes due to the limited availability of matching variables; high risk of bias.



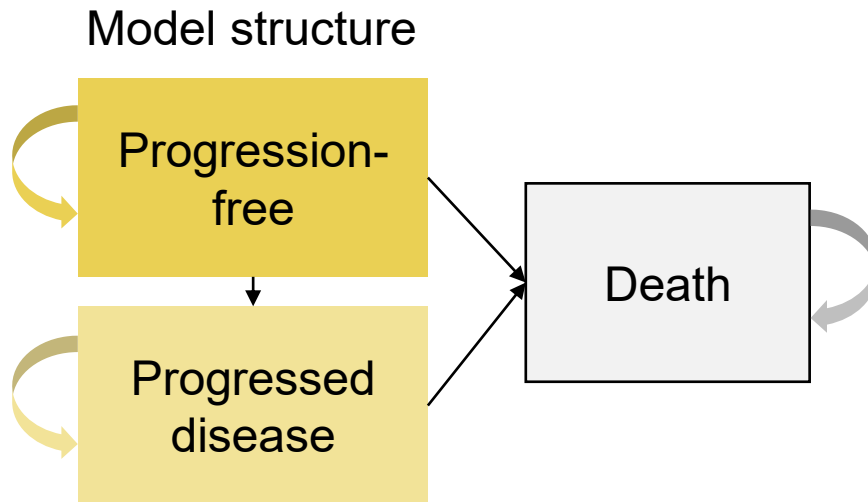
Are the MAIC analyses suitable for decision making?

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- ✓ **Modelling and key cost effectiveness issues to consider**
- Other considerations

Company's model overview

Company uses a partitioned survival model



- Technology affects **costs** by:
 - Costs of primary therapy
 - Rates of autoSCT following disease progression
- Technology affects **QALYs** by:
 - Increasing PFS and OS (company)
- Assumptions with greatest ICER effect:
 - Choice of parametric model to fit PFS and OS data
 - Assumption of survival benefit
 - Rates of autoSCT following disease progression

Key issue: Rate of subsequent autoSCT



Background

- Company model subsequent therapies, including autoSCT based on information from CORAL

EAG comments

- Clinical advice: rate of autoSCT after lon-tes and pola+BR reasonable, but after chemotherapy highly uncertain
- Suggest alternative base case (equal to lon-tes/pola-BR) and scenario analyses with different autoSCT rates.

Company

- Maintains rate of subsequent autoSCT in base case as based on best available evidence (CORAL) and more reflective of clinical practice than the alternative rate proposed by EAG
- Changing from the autoSCT rates from the CORAL study would result in significant bias

Clinical expert comments

- Rate of 22% for autoSCT after chemotherapy is too high; in practice rate of autoSCT would be very low

	Company-preferred base-case	EAG-preferred base-case
Lon-tes	3%	3%
Pola+BR	3%	3%
Chemotherapy	22%	3%



Which rate of autoSCT is more plausible?

Abbreviations: autoSCT, autologous stem cell transplantation; EAG, external assessment group; lon-tes, loncastuximab tesirine; pola+BR, polatuzumab vedotin with rituximab and bendamustine.



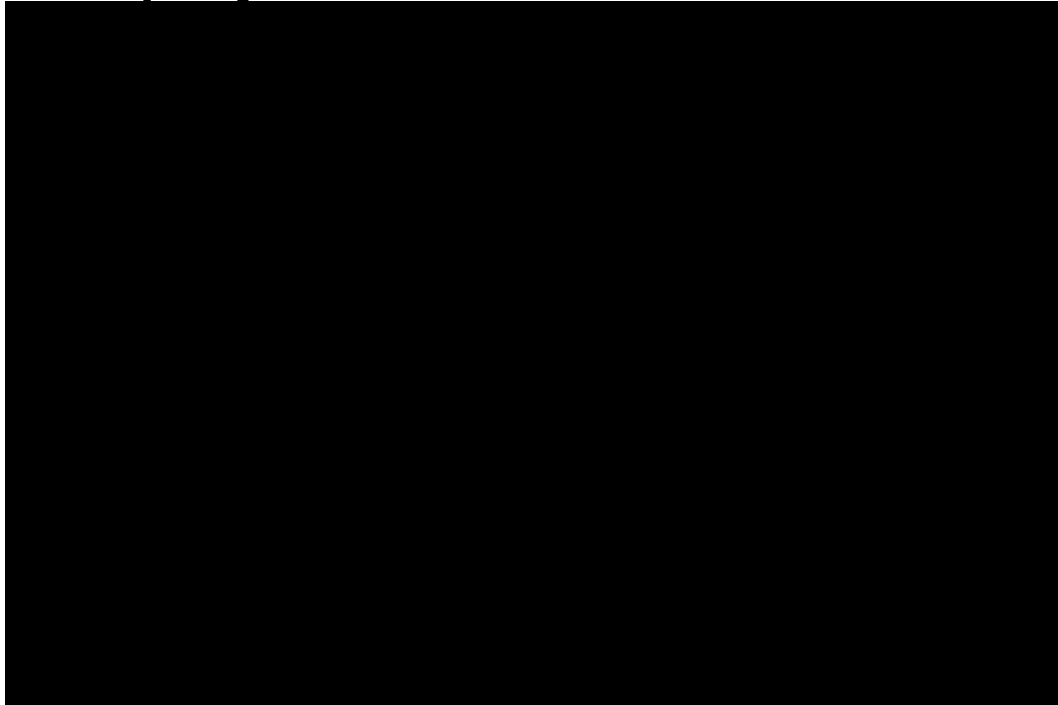
Key issue: Extrapolations of OS for lon-tes versus pola+BR

Lon-tes shows more benefit in company base case

Background

- Curves generated using MAIC of LOTIS-2 (September 2022 cut-off) and GO29365
- Company applies generalised gamma extrapolation

Company and EAG base-case OS curves



EAG

- EAG base case: prefer lognormal for lon-tes based on clinic opinion of 10-year OS (gen. gamma ■■■, log-normal ■■■)
- EAG base case: OS equal between lon-tes and pola+BR

Clinical expert comments

- Generalised gamma is too optimistic for lon-tes, OS would be similar between treatments; lognormal more appropriate



Which approach to extrapolation for lon-tes is most appropriate? (gen. gamma or log-normal)
Which assumption around pola+BR OS benefit is most appropriate?



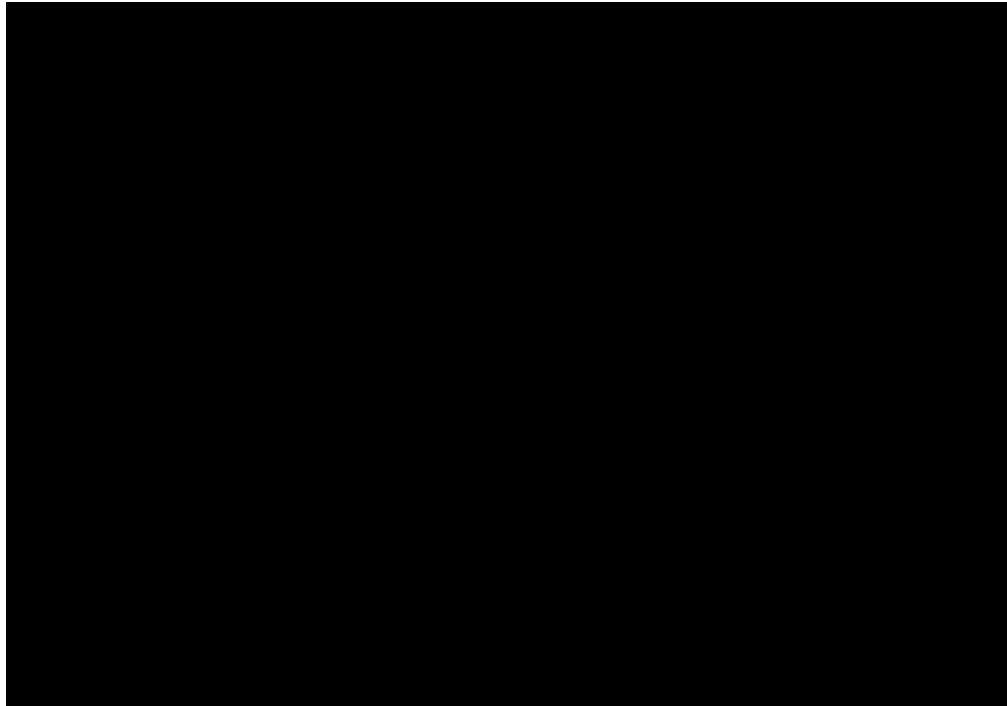
Key issue: Extrapolations of PFS for lon-tes versus pola+BR

Lon-tes shows more benefit in company base case

Background

- MAIC of LOTIS-2 (September 2022) and GO29365
- Company applies generalised gamma extrapolation

Company and EAG base-case PFS curves



Company comments

- Clinical input: Progression free at 2 yrs is 'cured'
- GO29365 biased against lon-tes due to 2L patients

Clinical expert comments

- Agree gen. gamma too optimistic for lon-tes PFS; however, log-normal may be too pessimistic - plateau around 24-30 months would be plausible.

EAG

- Clinical expert: almost all relapse, none/few 'cured'
- Company extrapolation appears consistent with apparent plateau in LOTIS-2 data, but few patients remaining at risk
- Large lon-tes benefit not supported by MAIC HRs
- EAG base case: log-normal and assume pola+BR PFS is equivalent to lon-tes, consistent with MAIC



Which approach to extrapolation for lon-tes is most appropriate? (gen. gamma or log-normal)
Which assumption around pola+BR PFS benefit is most appropriate?

Key issue: Extrapolations of OS for lon-tes versus chemotherapy



Lon-tes shows more benefit in company base case

Background

- MAIC of LOTIS-2 (September 2022) and CORAL study
- Company applies generalised gamma extrapolation

Company and EAG base-case OS curves

EAG

- Generalised gamma extrapolation could be implausibly optimistic as affected by background mortality restrictions (so as not to fall below hazard rate for age- and sex-matched population)
- Log-normal extrapolation of lon-tes preferred due to more plausible extrapolation and consistent with clinical input



Which approach to extrapolation is most appropriate? (generalised gamma or log-normal)

Abbreviations: EAG, external assessment group; lon-tes, loncastuximab tesirine; MAIC, matching-adjusted indirect comparisons; OS, overall survival; pola+BR, polatuzumab vedotin with rituximab and bendamustine.

QALY weighting for severity

Severity modifier should be applied to certain treatments

QALY shortfall analysis (company base case)

Treatment	Expected total QALYS without disease	Total QALYs with condition, under current treatment	Absolute shortfall	Proportional shortfall	QALY weight
Pola+BR	11.66	1.82	9.84	0.84	1
Chemotherapy		0.92	10.74	0.92	1.2

EAG

- Company estimates are appropriate.
- EAG base case assumptions result in the same QALY weightings for pola+BR (x1) and chemotherapy (x1.2)

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

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Model feature	Company final base case	EAG preferred assumptions	Impact
Lon-tes OS extrapolations	Generalised gamma	Log-normal	Large
Lon-tes PFS extrapolations	Generalised gamma	Log-normal	Large
Pola+BR OS	Based on GO29365	Set equal to lon-tes	Moderate
Pola+BR PFS	Based on GO29365	Set equal to lon-tes	Large
Chemotherapy OS distribution	Generalised gamma	Log-normal	Large
Subsequent autoSCT after chemotherapy	22%	3%	Moderate

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Other considerations

Equality issues

- Company, patient, professional and clinical submissions: no equality issues identified

Innovation

- Are there any benefits that are not captured in the QALY calculations?

Managed Access

- Company have not submitted a managed access proposal
 - A phase 3 study is ongoing, but for loncastuximab tesirine in combination with rituximab and earlier in pathway (1 or more previous lines of therapy)



Are there any equality issues that should be considered?

Are there any potential benefits not captured in the QALY calculation?

Cost-effectiveness results

All ICERs are reported in PART 2

because they include confidential discounts

When considering confidential prices for lon-tes and comparators:

- Compared with pola+BR, company ICERs are within the range normally considered an effective use of NHS resources. EAG assumes no QALY difference so consider cost difference only; lon-tes is more expensive than pola+BR.
- Compared with chemotherapy, ICERs are above the range normally considered as an effective use of NHS resources in company and EAG base case.

Thank you.