For screen and public observers - redacted

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: 14 November 2023

Chair: Stephen O'Brien

External assessment group: Warwick Evidence

Technical team: Kirsty Pitt, Alex Filby, Ross Dent

Company: Swedish Orphan Biovitrum

Key issues

Key issues

Issue	ICER impact
Rate of stem cell transplant after chemotherapy and long-term extrapolation of overall survival for chemotherapy - new analysis	Large 
Long-term extrapolation of overall survival for lon-tes - no new evidence	Large 
Additional benefits of lon-tes - no new evidence	Unknown 

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]

- ✓ **Recap**
- ❑ Response to consultation

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Recap - Committee's key conclusions from ACM 1
Loncastuximab tesirine is not recommended

Key conclusions

- Both pola-BR and chemotherapy are relevant comparators
- Results of the MAIC analyses were very uncertain
- Changing the rate of subsequent SCT did not have a large impact on results
- Committee would accept an ICER at the lower end of acceptable range due to uncertainty

Comparison with pola-BR

- For both OS and PFS, log-normal extrapolation was more plausible than generalised gamma
- Assumed no QALY difference between lon-tes and pola-BR

Comparison with chemotherapy

- For OS, log-normal extrapolation was most plausible
- Severity weighting of 1.2 applied

Abbreviations: ACM, appraisal committee meeting; pola-BR, polatuzumab vedotin, bendamustine and rituximab; MAIC, matching- adjusted indirected comparison; SCT, stem cell transplant; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Recap - Loncastuximab tesirine (ZYNLONTA, Swedish Orphan Biovitrum)

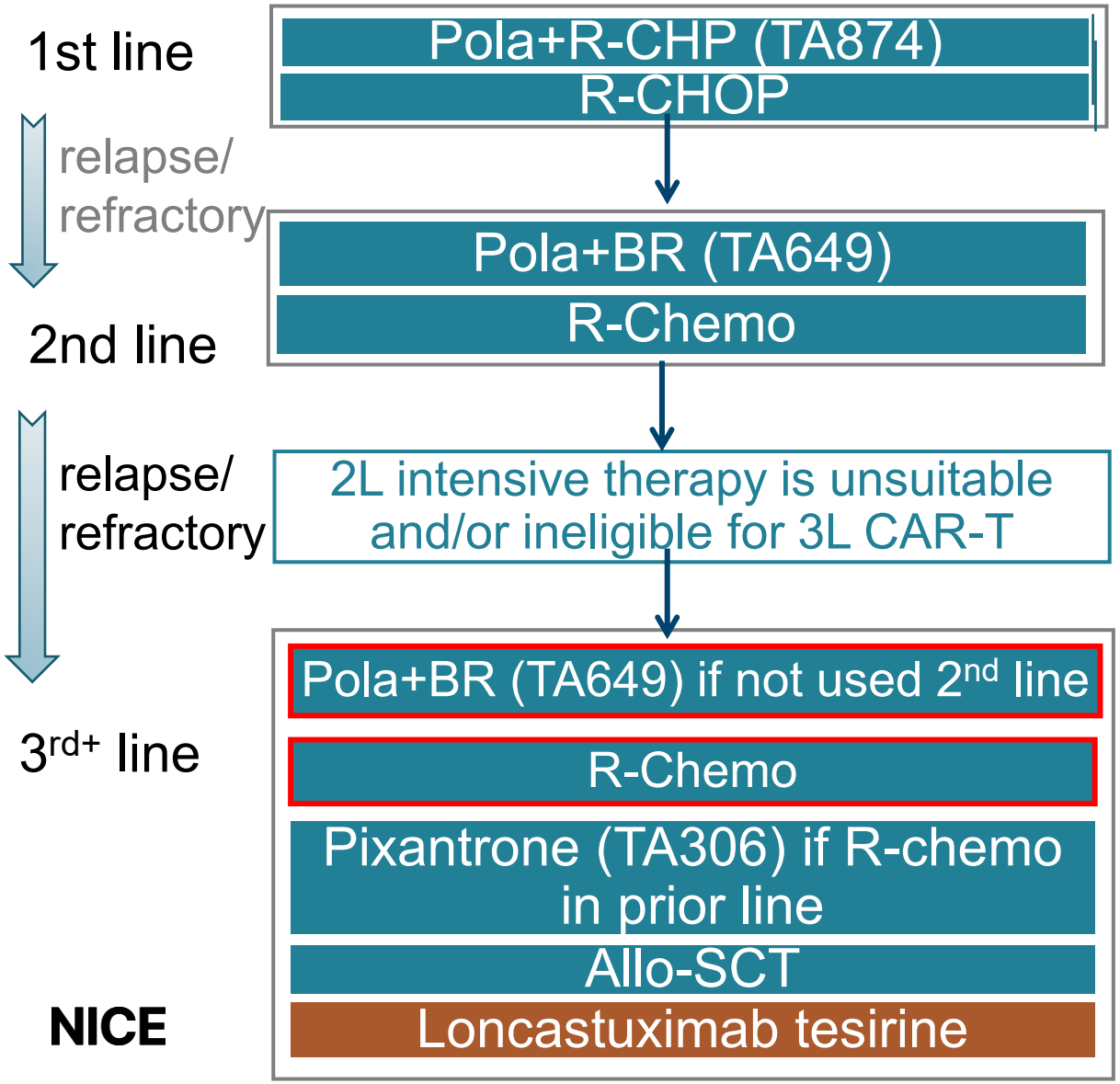
Technology details

Marketing authorisation	Adults with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy. • GB marketing authorisation February 2023
Mechanism of action	Antibody-drug conjugate targeting CD19 protein
Administration	Intravenous infusion
Price	• List price: £15,200 per vial • Average cost of a course of treatment (list price): £85,562 • Confidential simple discount patient access scheme available

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma;

Recap - Treatment pathway for DLBCL

Pathway for when intensive therapy is unsuitable for patients

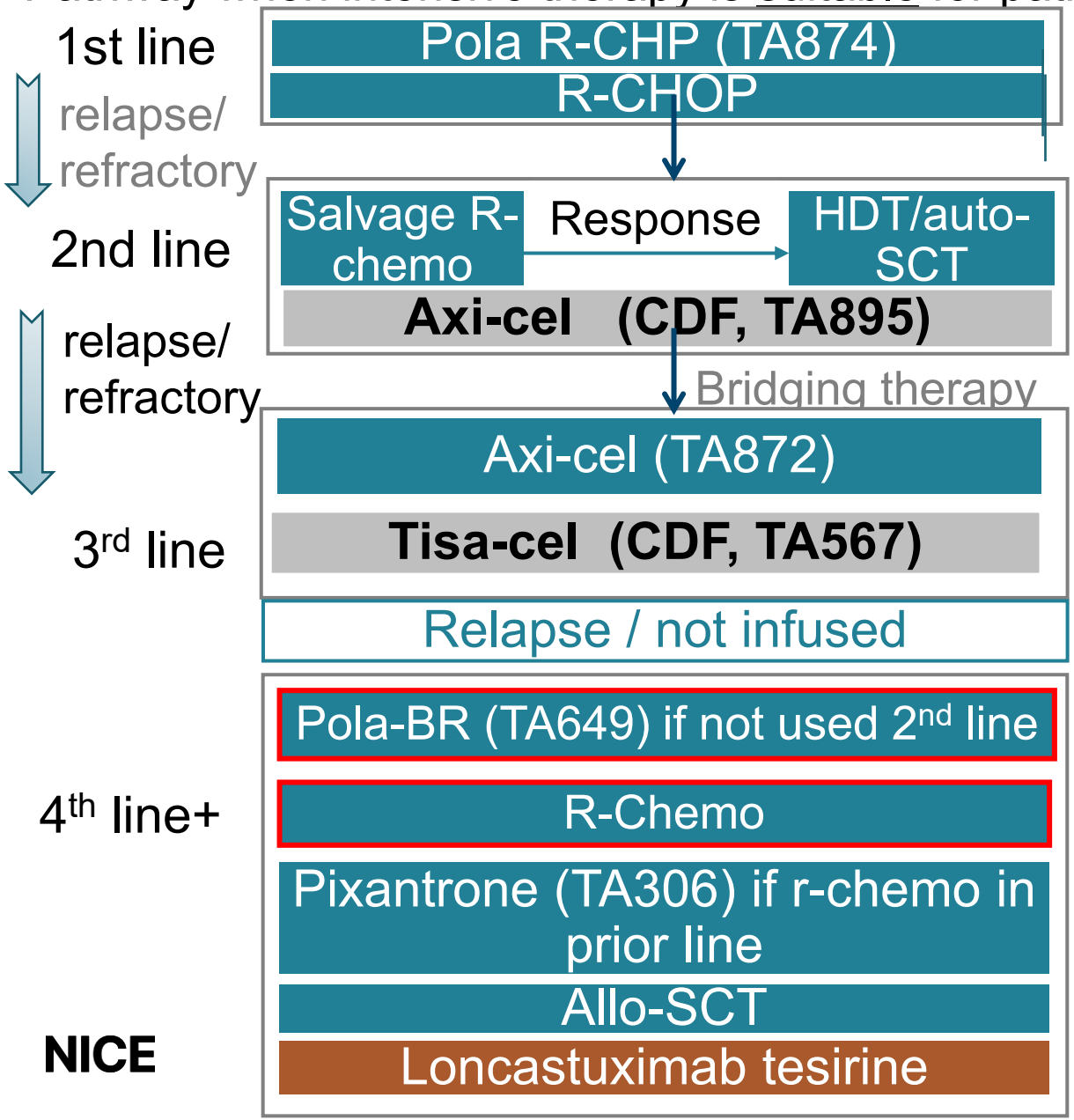


Pola+BR and R-chemo included in company submission as relevant comparators

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

Recap - Treatment pathway for DLBCL

Pathway when intensive therapy is suitable for patients



Pola+BR and R-chemo included by company as relevant comparators

CDF drugs not considered in appraisal

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

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]

- ❑ Recap
- ✓ **Response to consultation**

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Consultation responses

Summary of company's response – no other responses received

- In base case, accepts committee's preferred 3% rate of autologous stem cell transplant after chemo (previously 22%), but notes that efficacy should also be reduced, not just costs
    - Company derives an adjustment and includes in base case
- In base case, accepts committee's preferred log-normal overall survival extrapolation for lon-tes, but argues this is inconsistent with glofitamab (cure at 3 years)
    - Provides scenario with generalised gamma (original base case) and cure at 3 years (both decrease the ICER)
- Highlights additional benefits not captured in the QALY
- Accepts committee's preferred assumptions for pola-BR comparison in base case
- Increased PAS

Abbreviations: QALY, quality-adjusted life year; PAS, patient access scheme; ICER, incremental cost-effectiveness ratio

Rate of autologous stem cell transplant after chemotherapy [1]

Company states outcomes should be adjusted if costs are

Background – original model

Rate of SCT	Company base case	EAG base case
After chemotherapy	22% (CORAL extension study)	3%
After Ion-tes	3% (LOTIS-2 trial)	3%

- Clinical experts agreed rate in CORAL was higher than expected to see in practice
- EAG provided scenario analyses with different rates – only costs adjusted

Draft guidance conclusion

- Rate is uncertain
- Changing it did not have a large impact on cost-effectiveness results

Company response

- With new PAS, relative impact of SCT rate on results is greater
- If costs are adjusted, outcomes should be as well

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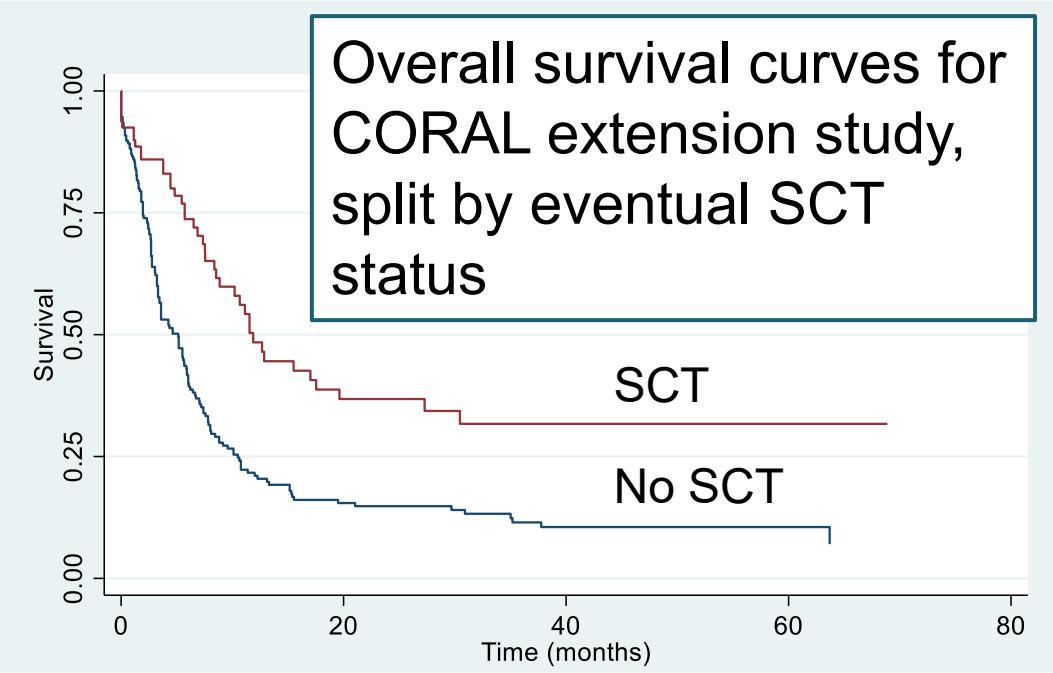
Abbreviations: SCT, stem cell transplant; EAG, external assessment group; PAS, patient access scheme

Rate of autologous stem cell transplant after chemotherapy [2]

Company new analysis to estimate effect of changing SCT rate on outcomes

- 30% of patients in CORAL extension study who received subsequent stem cell transplant (SCT) had significantly better survival outcomes than those who did not - could be due to efficacy of SCT or baseline fitness
- EAG original approach reduces costs for chemotherapy but retains better outcomes
- Company generated OS hazard ratios (HRs) for SCT/no SCT after chemotherapy
- Baseline characteristics are not reported for SCT status so same weights as for LOTIS-2 patients applied



HRs for patients with/without SCT

	HR
HR at ACM1 (from MAIC)	1.43
No SCT	1.77
SCT	0.80
Weighted average (based on 11% receiving SCT (3% autologous and 8% allogeneic) as in LOTIS-2)	1.66 – new company base case

Abbreviations: SCT, stem cell transplant; OS, overall survival; HR, hazard ratio

Rate of autologous stem cell transplant after chemotherapy [3]

EAG base case does not use HR – extrapolates OS for chemo from CORAL

EAG response

- Difference in outcomes may be explained by baseline differences
- Few variables able to be matched in original MAIC, so large amount of uncertainty remains
- Analysis could not weight LOTIS-2 data to each SCT subgroup individually as baseline characteristics not reported – further increases risk of bias
- Not clear whether HR is appropriate measure of benefit in either subgroup
- EAG method does not use HR - extrapolates OS for chemotherapy from CORAL
  - Fitted models for SCT/no SCT separately then combined using weighted average based on rate of SCT
- Company's new approach also applies to the PFS curve, EAG makes no adjustment to PFS

Background on MAICs

- Company used data from LOTIS-2 and CORAL to compare lon-tes with chemotherapy
- Matching based on 3 characteristics – International Prognostic Index, sex and prior ASCT
- Studies in MAICs had different sample sizes, and there were differences across study populations and study definitions
- MAIC results were similar to naïve comparisons

Should a HR of 1.66 be used to extrapolate OS for chemotherapy?

Abbreviations: SCT, stem cell transplant; OS, overall survival; HR, hazard ratio

Long-term overall survival extrapolations for lon-tes [1]

Company prefers generalised gamma, EAG prefers log-normal

- Company used generalised gamma to extrapolate overall survival for lon-tes in both comparisons with pola-BR and chemotherapy, EAG used log-normal
- Clinical experts advised ~5% of patients would still be alive after 10 years – log-normal predicted 10-year OS closer to 5%, than generalised gamma
- Therefore, committee considered log-normal more plausible for lon-tes

Company's response to consultation

- Using log-normal for lon-tes is inconsistent with glofitamab appraisal (TA927), where a cure point at 3 years was accepted – clinical experts suggested people could be considered cured if cancer remained in complete remission at 2 years
- Generalised gamma would better reflect the data and clinical opinions
- Clinical experts noted patients remaining progression-free after 2 years often did not need further treatment and evidence indicated plateau for lon-tes arm

Abbreviations: pola-BR, polatuzumab, bendamustine and rituximab; EAG, external assessment group; OS, overall survival

Long-term overall survival extrapolations for Ion-tes [2]

Company argue using log-normal extrapolation inconsistent with TA674

Original company base case	EAG (same after consultation)	Glofitamab (TA674)	Updated company base case
• Gen-gamma for Ion-tes OS. • Base case: no cure assumed. • Scenarios for cure point at 2, 5 and 10 years.	• Log-normal for Ion-tes OS. • No cure.	Cure at 3-years accepted, with 9% increased risk of excess mortality after 3 years.	• Log-normal for Ion-tes OS extrapolations. • No cure point. • Scenarios using generalised gamma for OS and cure point at 3 years, with SMR of 1.41 (used by company in TA649 (pola-BR) although committee didn't accept cure model).

Is log-normal still the most plausible extrapolation? Should a cure point be considered?

Abbreviations: OS, overall survival; EAG, external assessment group

Long-term extrapolation of overall survival

Comparison with chemotherapy

[redacted]

[redacted]

Overall survival		5y	10y
Comp base case	Lon-tes	[redacted]	[redacted]
	Chemo	[redacted]	[redacted]
EAG base case	Lon-tes	[redacted]	[redacted]
	Chemo	[redacted]	[redacted]

At ACM1, clinical experts advised that after 10 years it was reasonable to assume around 5% of patients would still be alive.

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Abbreviations: HR, hazard ratio; ACM, appraisal committee meeting; EAG, external assessment group

Long-term extrapolation of overall survival

Comparison with chemotherapy [2]

[redacted]

[redacted]

Overall survival		5y	10y
Comp gen gamma	Lon-tes	[redacted]	[redacted]
	Chemo	[redacted]	[redacted]
Comp cure at 3y	Lon-tes	[redacted]	[redacted]
	Chemo	[redacted]	[redacted]

At ACM1, clinical experts advised that after 10 years it was reasonable to assume around 5% of patients would still be alive.

Abbreviations: HR, hazard ratio; ACM, appraisal committee meeting; EAG, external assessment group

Long-term extrapolation of overall survival

Comparison with pola-BR

[redacted]

[redacted]

[redacted]

Overall survival		5y	10y
Comp/EAG base case	Lon-tes and pola-BR	[redacted]	[redacted]
Comp scenario – gen gamma for lon-tes	Lon-tes and pola-BR	[redacted]	[redacted]
Comp scenario – cure at 3y	Lon-tes and pola-BR	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; ACM, appraisal committee meeting; EAG, external assessment group

Additional benefits of lon-tes

Company believes lon-tes provides benefits not captured in the QALY calculation

- Lon-tes well-tolerated in LOTIS-2 trial
  - Clinicians suggest lon-tes could be beneficial for frailer patients compared with pola-BR
  - No inpatient or specialist care required to manage potential side effects e.g. neurosciences ICU required for glofitamab due to risk of cytokine release syndrome and neurological adverse effects
- Caregiver burden with alternative treatments due to frequent hospital visits and overnight stays
- Lon-tes available ready for infusion, unlike some alternative treatments available
  - EAG: benefit not quantified against the comparators so unable to validate
- Only a single 30-minute infusion required per cycle and available in outpatient setting
  - EAG: already reasonably represented in existing analyses

Are there any additional benefits of lon-tes not appropriately captured in the QALY calculation?

Abbreviations: QALY, quality-adjusted life year; pola-BR, polatuzumab, bendamustine and rituximab

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Summary of company and EAG base case assumptions

Company accepted most of EAG base case assumptions in new base case

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Rate of SCT after chemotherapy	3%	3%
Overall survival for chemotherapy	• Hazard ratio from MAIC applied to lon-tes curve. • Hazard ratio updated to 1.66 to account for changing the rate of SCT.	Fitted models to CORAL data for SCT/noSCT, combined using weighted average.
Overall survival for lon-tes (for chemo comparison)	Log-normal	Log-normal

All results presented include updated PAS for lon-tes – increased after ACM1.

EAG results use updated price for oxaliplatin.

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Abbreviations: SCT, stem cell transplant; EAG, external assessment group; ACM, appraisal committee meeting; PAS, patient access scheme; MAIC, matching-adjusted indirect comparison

Cost-effectiveness results – chemotherapy comparison

Overview of results and scenarios with confidential prices

Scenario	ICER with severity weighting x1.2 (£/QALY gained)
Company base case	Above £20,000
1. Generalised gamma distribution for lon-tes OS	Below £20,000
2. Cure at 3 years	Below £20,000
EAG base case	Above £30,000
3. Generalised gamma distribution for lon-tes OS	Below £20,000
4. Cure at 3 years	Below £20,000
5. 5% autoSCT rate	Above £30,000
6. 10% autoSCT rate	Above £30,000
7. 22% autoSCT rate	Above £30,000

Abbreviations: OS, overall survival; autoSCT, autologous stem cell transplant; ICER, incremental cost-effectiveness ratio

Cost-effectiveness results – pola-BR comparison

Overview of results and scenarios

Scenario	ICER
Company base case	Pola-BR is cost-saving
1. Generalised gamma distribution for Ion-tes OS	Pola-BR is cost-saving
2. Cure at 3 years	Pola-BR is cost-saving
EAG base case	Pola-BR is cost-saving
3. Generalise gamma distribution for Ion-tes OS	Pola-BR is cost-saving
4. Cure at 3 years	Pola-BR is cost-saving

All results for scenarios are the same due to effectiveness being set equal.

Abbreviations: OS, overall survival; autoSCT, autologous stem cell transplant; ICER, incremental cost-effectiveness ratio

Equality considerations

No equality considerations identified

No equality considerations identified in draft guidance and none raised at consultation.

Are there any equality considerations?

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Thank you.

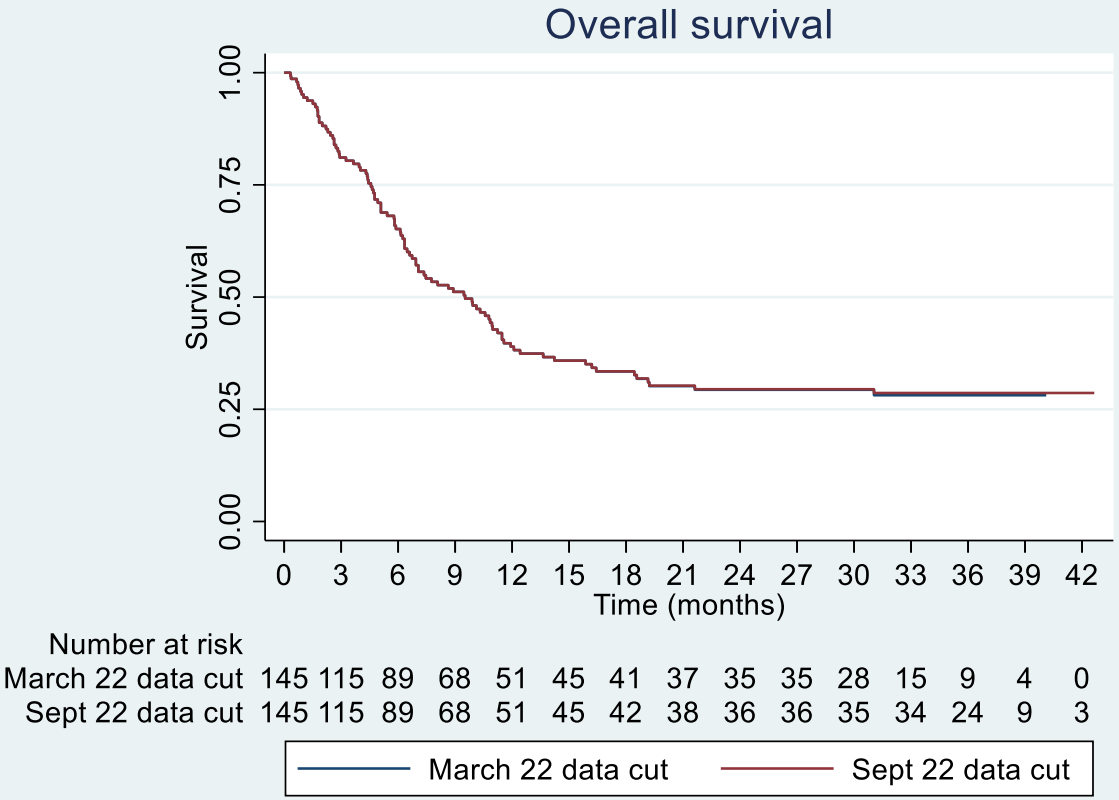
LOTIS-2 results

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

Abbreviations: CI, confidence interval; CR, complete remission; lon-tes, loncastuximab tesirine; OR, overall response; OS, overall survival; PFS, progression free survival; TE, technical engagement; TEAE, treatment emergent adverse event.

QALY weighting for severity

Slide from ACM1

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

Abbreviations: EAG, external assessment group; pola+BR, polatuzumab vedotin with rituximab and bendamustine; QALY, quality-adjusted life years.