Polatuzumab vedotin in combination for treating untreated diffuse large B-cell lymphoma

For public observers: ACIC redacted

Technology appraisal committee C [01 November 2022]

Chair: Stephen O'Brien

Evidence assessment group: Southampton Health Technology Assessments Centre (SHTAC)

Technical team: Albany Chandler, Linda Landells

Company: Roche

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Polatuzumab vedotin + R-CHP for DLBCL

→ **Background**

- ACM1 conclusions overview
- Clinical evidence
- Economic model
- Points to consider:
  - Outstanding issues and ACD consultation responses
  - Overall survival estimate
  - Patient weight distributions
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Abbreviations: DLBCL, diffuse large B-cell lymphoma

Background on untreated diffuse large B-cell lymphoma

DLBCL is a common form of lymphoma

Disease overview

- Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma: approx. 5,500 new cases diagnosed in UK each year

Causes

- Causes of DLBCL not well understood for vast majority of people
- Several risk factors including hereditary and acquired immune deficiencies, occupational exposures and pharmacological immunosuppression

Epidemiology

- Median age at diagnosis in UK of approximately 70 years, slightly more common in men than women

Symptoms and prognosis

- Prognosis is most commonly predicted using the IPI: 3-year overall survival for people having R-CHOP, ranges between 59% (IPI 4-5, high risk population) to 81% (IPI 2, low to intermediate risk population)
- Common symptoms include painless swellings at single or multiple sites (lymph node and non-lymph node), excessive night sweating, unexplained fever and weight loss

Abbreviations: IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Technology (Polivy®, Roche)

Table 1 Technology details

Marketing authorisation	• Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone*, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). • Type II variation granted; Orphan Drug Designation
Mechanism of action	• Polatuzumab vedotin (pola) binds to cell surface antigen CD79b which triggers internalisation of the pola molecule. The stable valine-citrulline (VC) linker within pola is cleaved by lysosomal proteases, releasing Monomethyl auristatin E (MMAE). MMAE binds to microtubules and exerts cytotoxicity by inhibiting polymerisation, disrupting cell division, and triggering apoptosis.
Administration	• Pola in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone every 21 days for 6 cycles **Pola:** 1.8 mg/kg intravenous (IV) infusion on Day 1; combination product dose varies dependent on technology
Price	• List price: £2,370 per 30mg vial; £11,060 per 140mg vial • Average course of treatment: £71,718 • Existing PAS discount (discount increased at ACD consultation if recommended for IPI score 2-5; previous PAS discount applicable if recommended for IPI score 3-5)

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; PAS, Patient Access Scheme.

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Polatuzumab vedotin is not recommended
Committee conclusions at ACM1

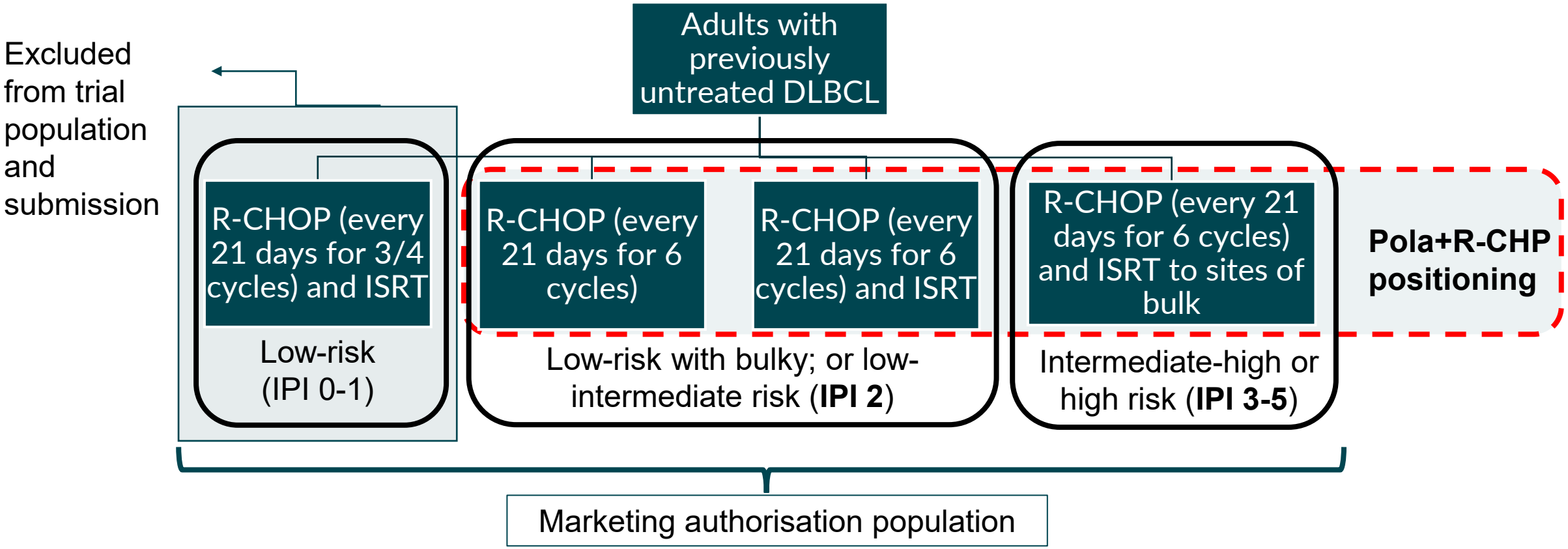
- Clinical evidence suggests progression-free survival benefit for people having polatuzumab vedotin with R-CHP compared with R-CHOP alone
- Overall survival data from the trial was immature so survival extrapolations in the model are highly uncertain
- Patient weight distributions used in the model may not be representative of NHS clinical practice
- Neither the company nor ERG base case progressed disease supportive care costs reflect NHS clinical practice
- Utility for progressed disease may not have been fully accounted for but approach in model is acceptable
- Not suitable for Cancer Drugs Fund: timeframe needed to collect useful data too long; POLARIX trial isn't collecting longer term data

Abbreviations: ACM, appraisal committee meeting; ERG, Evidence Review Group

Treatment population

Marketing authorisation includes people with IPI score 0 to 5

Figure 1 First-line treatments



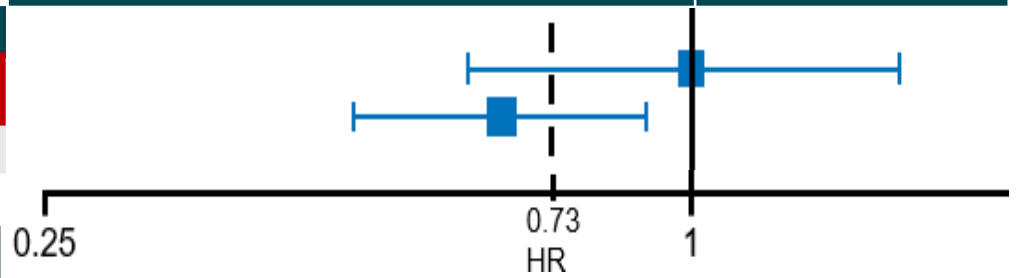
Abbreviations: BSC: best supportive care; IPI, International Prognostic Index; ISRT, involved site radiotherapy; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

POLARIX results by IPI subgroup

No difference in PFS for the IPI 2 subgroup

Table 2 Investigator-assessed progression-free survival by IPI score

Baseline risk factors	N	Pola+R-CHP (n=440)		R-CHOP (n=439)		Hazard ratio	95% Wald CI
		n	2-year rate	n	2-year rate		
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	0.6–1.6
IPI 3–5	545	273	75.2	272	65.1	0.7	0.5–0.9



Trial subgroup analyses exploratory/signal seeking, not confirmatory
POLARIX not designed or powered to compare subgroups

ACM1 conclusion:

- Exploratory subgroup suggests more benefit in higher-risk groups
- IPI 2 to 5 population should be included in the cost-effectiveness analysis

Should a higher risk subgroup of IPI score 3-5 be considered?

NICE Abbreviations: CI, confidence interval; PFS, progression-free survival; IPI, International Prognostic Index

Company and ERG base case and committee preferred assumptions at ACM1

Committee preferred assumptions at ACM1

Table 3 Conclusions on preferred model assumptions at the first committee meeting

Assumption	Company base case	ERG base case	ACM1 conclusion
PFS extrapolation	Mixture-cure model with generalised gamma parametric curve		Accepted approach
OS extrapolation	Piecewise model - KM to month 30 then generalised gamma mixture-cure model		Accepted approach - but highly uncertain
Treatment effect waning	Not included	Treatment effect waning between 30 and 60 months	Preferred company approach – no treatment waning
Utility source	GOYA trial		Accepted approach – but uncertain
Subsequent therapy costs	No CAR-T therapies		Accepted approach
	CAR-T subsequent treatment redistributed	CAR-T subsequent treatment not redistributed	Preferred company approach – subsequent treatments redistributed
End of life costs	EOL costs included PD costs	EOL costs excluded from PD costs	Preferred ERG approach – EOL costs counted once
Resource use	PFS: TA243; PD: TA306	PFS: TA243; PD: TA243	Neither approach accepted – requested updated model
Weight distribution	POLARIX trial		Approach not accepted – requested further information

CAR-T, Chimeric antigen receptor T-cell; KM, Kaplan Meier, OS, overall survival; PD, progressed disease; PFS, progression-free survival; EOL, end of life

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Clinical trial summary
POLARIX is the pivotal trial

Table 4 POLARIX clinical trial design and outcomes

	POLARIX (n=879)
Design	Phase III, double-blind, placebo-controlled study
Population	Adult patients with previously untreated DLBCL (IPI 2-5)
Intervention	Pola+R-CHP
Comparator(s)	R-CHOP
Follow up*	Median 28.2 months
Primary outcome	PFS
Key secondary outcomes	OS; Response rate
Locations	Western Europe (including UK), US, Canada, Australia and Asia
Used in model?	Baseline characteristics, PFS, OS

*Note, a further data cut was conducted in August 2022 but is not incorporated within this appraisal due to timelines

Abbreviations: G-CHOP, Obinutuzumab, cyclophosphamide, doxorubicin, vincristine and prednisone; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival

POLARIX results - PFS
Hazard ratio shows a PFS benefit for pola+R-CHP in the full population

Figure 2 Kaplan-Meier plot of time to investigator-assessed PFS (ITT population)

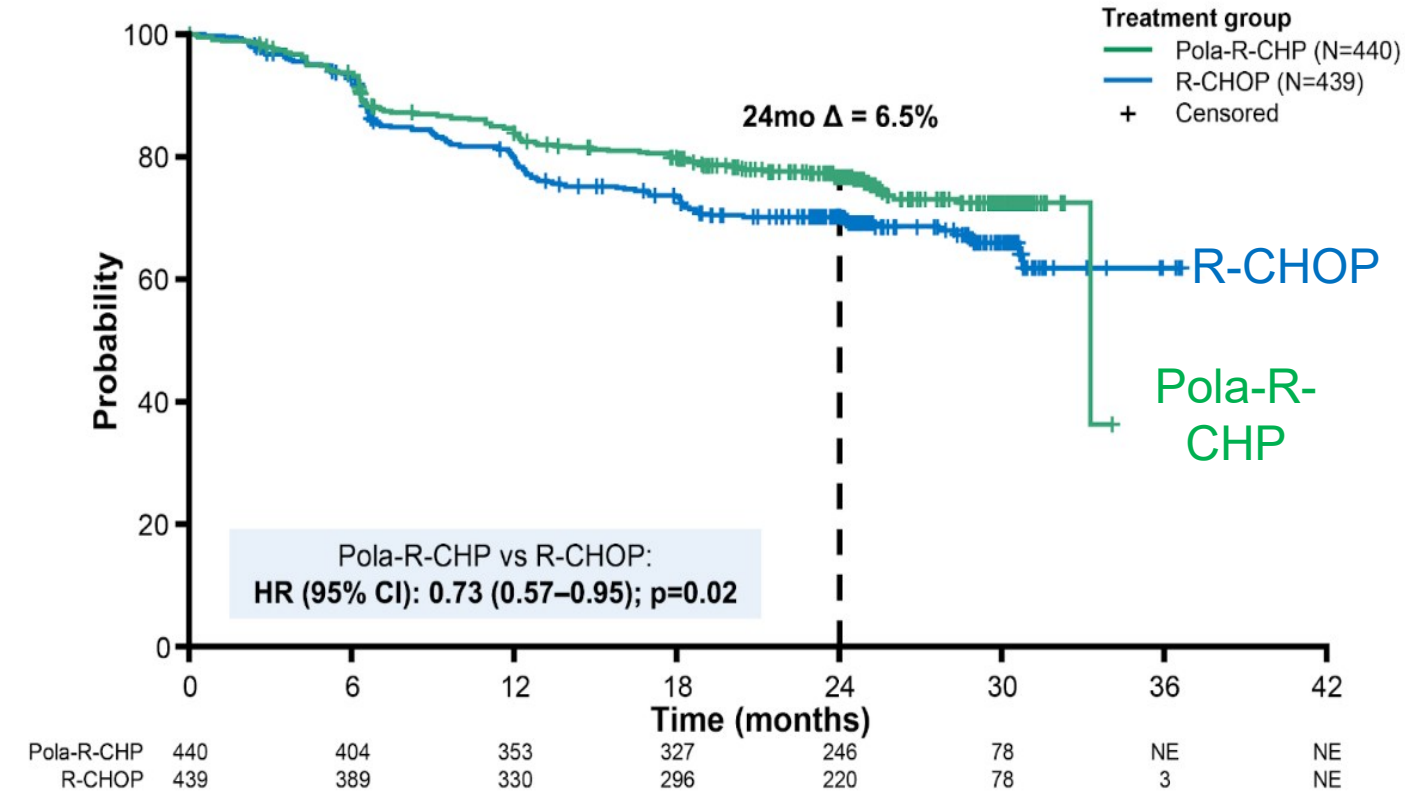

Table 5 Summary of investigator-assessed PFS (ITT population)

	Pola+R-CHP (n=440)	R-CHOP (n=439)
No. of events, n (%)	107 (24.3)	134 (30.5)
12-Month PFS probability (95% CI)	83.9 (80.4–87.4)	79.8 (75.9–83.6)
24-Month PFS probability (95% CI)	76.7 (72.7–80.8)	70.2 (65.8–74.6)

Median follow-up
Pola+R-CHP: 24.7 months (range: 0-34 months)
R-CHOP: 24.7 months (range: 0-37 months)

Abbreviations: CI, confidence interval; HR, hazard ratio, ITT, intention to treat; n, number; PFS, progression-free survival

POLARIX results - OS

Hazard ratio does not show an OS benefit for pola+R-CHP

Figure 3 Kaplan-Meier plot of time to investigator-assessed OS (ITT population)

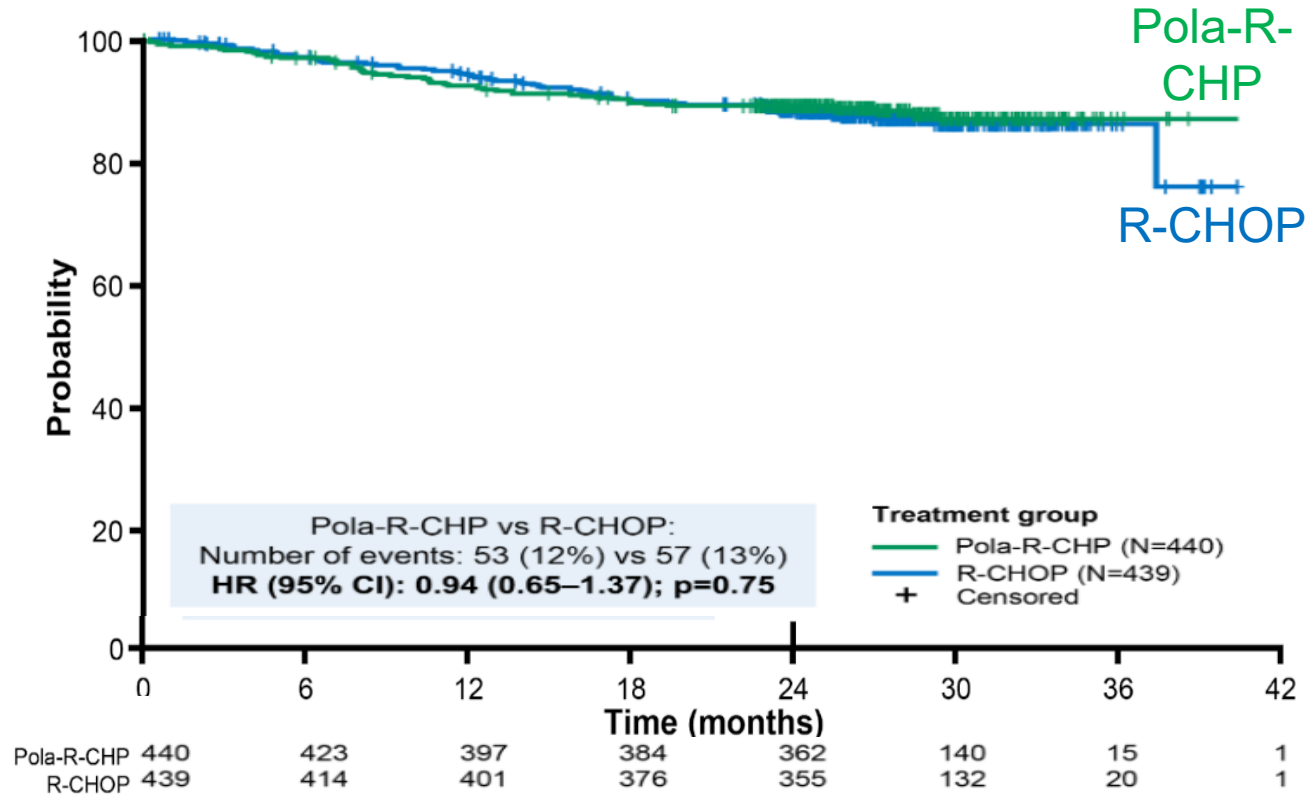

Table 6 Summary of investigator-assessed PFS (ITT population)

	Pola+R-CHP (n=440)	R-CHOP (n=439)
No. of events, n (%)	53 (12.0%)	57 (13.0%)
12-Month OS probability (95% CI)	92.2 (89.6–94.7)	94.6 (92.5–96.8)
24-Month OS probability (95% CI)	88.7 (85.7–91.7)	88.6 (85.6–91.6)

Median follow-up

Pola+R-CHP: 24.7 months (range: 0-34 months)

R-CHOP: 24.7 months (range: 0-37 months)

OS results are immature and do not meet the pre-specified threshold for statistical significance.

NICE Abbreviations: CI, confidence interval; HR, hazard ratio, ITT, intention to treat; n, number; OS, overall survival

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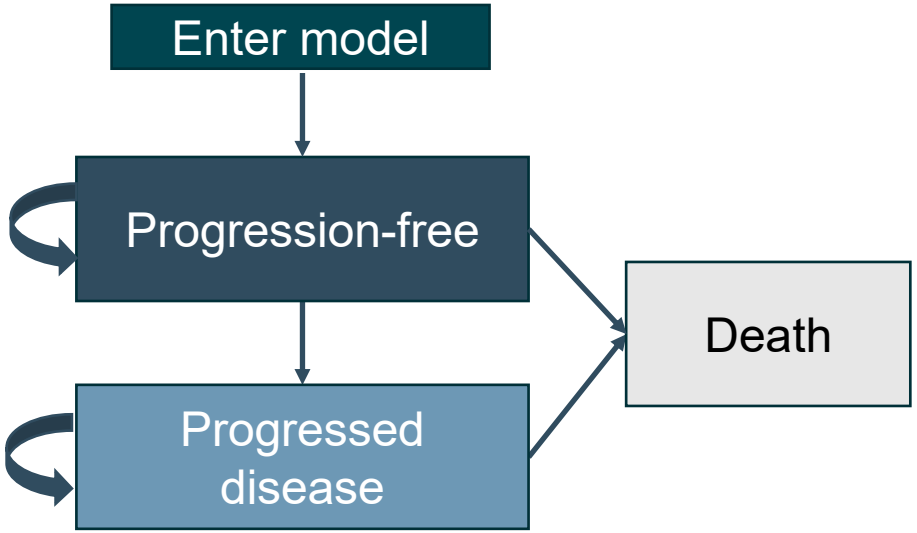
Company's model overview

Three state partitioned survival model was used

Figure 4 Model structure



- Technology affects **costs** by:
  - Increasing drug acquisition cost
  - No costs for PFS health state after 2 years in both treatment groups
- Technology affects **QALYs** by:
  - Increasing PFS and OS
  - The decrease in utility due to adverse events associated to the new technology is minor
- Assumptions with greatest ICER effect:
  - Supportive care costs
  - Exclusions of CAR-T therapies

- PFS and OS are modelled using generalised gamma mixture-cure models, with cure fractions based on the PFS model

Abbreviations: CAR-T, Chimeric antigen receptor T-cell, OS, overall survival; PFS, progression-free survival; ICER, incremental cost-effectiveness ratio

Acquisition cost of pola+R-CHP vs R-CHOP

Incremental costs in model are driven by costs other than acquisition cost

Table 7 Total acquisition cost per cycle (including pola PAS, without confidential discounts)

Treatment	pola+R-CHP	R-CHOP
Rituximab	£1,164	£1,164
Cyclophosphamide	£28	£28
Doxorubicin	£20	£20
Prednisolone	£1.64	£1.64
Vincristine	-	£10
Polatuzumab vedotin	[redacted]	-
Total	[redacted]	**£1,224**

Table 8 Costs in company base case (including pola PAS, without confidential discounts)

	Total costs	Incremental cost
Pola+R-CHP	[redacted]	[redacted]
R-CHOP	[redacted]	

Total incremental costs mostly impacted by:

- Acquisition costs (polatuzumab vedotin more costly)
- Progressed disease resource use costs (R-CHOP more costly)
- Subsequent treatment costs (R-CHOP more costly)

Table 9 Subsequent treatment costs in company model without confidential discounts

	Average number lines of treatment after 1L	Subsequent treatment costs
Pola+R-CHP	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]

Abbreviations: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Company updated model to correct PFS curve

ERG: correction produces counter-intuitive results

Company ACD response

- OS and PFS curves cross in model – curve correction required to amend implausible modelling that some people remain in progression-free survival despite dying
- Previous model included correction but had not been implemented correctly

ERG comments

- Correction doesn't address OS and PFS curves crossing, but that probability of death is higher than probability of progression
- Company's correction produces counter-intuitive results: decreasing OS produces increase in PFS
- Correction removed in ERG base case

Abbreviations: OS, overall survival, PFS, progression-free survival

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Several key issues remain after consultation

Comments on ACD received from company only

- Comments described under each point for discussion

Table 10 Key issues after ACD consultation

Issue	Resolved?	ICER impact
Uncertainty of treatment effect (subgroup analyses, overall survival extrapolations and treatment effect waning)	No – OS approach for discussion	Large
Weight distributions used in the model	No – for discussion	Large
Supportive care costs in the progressed disease health state	No – for discussion	Large
Utility values	Yes – uncertainty noted	Unknown
Exclusion of CAR-T as possible subsequent-line treatments	Yes	Large
Uncertainty about the potential use of Pola+R-CHP in low risk (IPI 0-1) untreated DLBCL	Yes	Unknown
End of life costs	Yes – company accept committee preferred assumption	Small

CAR-T therapies excluded as subsequent treatment because only recommended in CDF

Abbreviations: ACM, appraisal committee meeting; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund

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ACM1 conclusion: OS extrapolations are highly uncertain

Figure 5 Extrapolations of OS for Pola-R-CHP and R-CHOP

ERG updated base case:

- No treatment waning between 30 and 60 months
- No OS benefit with Pola+R-CHP after 60 months

More conservative approach than KM+generalised gamma without treatment waning - accounts for uncertainty and absence of evidence for OS

ACM1 conclusion

- OS extrapolations are highly uncertain
- Applying treatment waning to whole population in a mixture-cure model means there is a 'cured' population whose disease is then 'uncured' later
- No treatment waning favours polatuzumab and uncertain
- **Overall:**
  - not including treatment waning more clinically plausible so committee preferred to not include
  - company and ERG KM+generalised gamma OS extrapolation acceptable

Is the company's or the ERGs approach to OS modelling more appropriate?

NICE Abbreviations: KM, Kaplan-Meier; OS, overall survival

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Weight distributions in the model

Weight distributions may not be representative of NHS clinical practice

Issue background

- Weight distributions taken from POLARIX trial in company model
- Committee concerns this was not representative of UK population

Company ACD response

- Expect people with DLBCL to lose weight around time of diagnosis: estimate 5% lower weight than general population*
- Clinical opinion that POLARIX weight distribution is representative of NHS clinical practice
- Scenario using POLARIX Western patient population (n=598) height and weight causes 10.5% increase in ICER
- Model doesn't include vial sharing: a conservative assumption

*Based on O'Brian K et al. 2017

ERG comments

- Weight loss can be a symptom of DLBCL

Table 11 Mean patient weights

	Weight (kg)	
	Females	Males
NHS health survey	72.1	85.4
DLBCL population (with 5% weight loss)	68.5	81.1
POLARIX ITT	69.5	81.6
POLARIX Western patient population	72.9	85.9

Is the weight of participants in POLARIX ITT population generalisable to NHS clinical practice?

Abbreviations: ITT, intention to treat; kg, kilograms

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Supportive care costs for progressed disease

ACM1 conclusions

- Neither company or ERG's base case represented NHS clinical practice
- Company base case included 2 end of life costs

Company ACD response

- Updated base case with updated PD resource costs (details on next slide)

Table 12 Cost of resource by treatment for PD

Cost	Company original base case		Company updated base case		ERG base case	
	Pola+R-CHP	R-CHOP	Pola+R-CHP	R-CHOP	Pola+R-CHP	R-CHOP
One-off cost	**£385**	**£453**	**£2,228**	**£2,228**	**£2,228**	**£2,228**
Cost per week	**£398**	**£398**	**£341**	**£341**	**£172**	**£172**

ERG assumes 50% of company's PD resource cost based on estimated time spent on subsequent treatments in PD state

PD, progressed disease; CT, computed tomography; MDT, multi-disciplinary team; LDH, lactate dehydrogenase

Table 13 Average unit of resource per patient for PD per year

Resource	Company estimate
Oncologist (visit)	3.3
Haematologist (visit)	9.8
Radiologist (visit)	1.1
Specialist nurse (visit)	11.7
GP (visit)	1.8
District nurse (visit)	3.4
CT scan	1.5
Inpatient day	11.1
Full blood counts	19.1
LDH test	3.3
Liver function	17.9
Renal function	17.9
Immunoglobulin	1.5
Calcium phosphate	5.8
Day case	10.2
PET-CT	2.2
Transfusion	2.1
Dietician	4.2
MDT review	1.4
Psychology review	0.6

Added post-consultation

Supportive care costs for progressed disease continued

Company ACD response continued

- Surveyed clinicians (3 from different trusts) to understand resource use during 2L treatment
- Presented scenarios to show impact of varying progressed disease costs by 10%
- Removed end of life costs included in progressed disease costs including:
  - residential care, home care, palliative care and day care

  Note this is conservative approach as some costs (e.g. palliative care consultation) accrued before end-of-life

ERG comments

- Company update includes:
  - follow-up costs 15% lower than original; one-off costs higher due to investigations such as PET-scans
  - people assumed to incur health costs for progressed disease indefinitely - question if this reflects reality
  - time in PD state longer for R-CHOP than Pola+R-CHP – leads to higher PD costs for R-CHOP
- ERG estimates % of time spent on subsequent treatments in PD state would be [redacted] for Pola+R-CHP and [redacted] or R-CHOP – therefore base case assumes 50% reduction of company's PD costs for both arms
- Presents scenario with 25% reduction in company's PD costs

- Are the company's updated progressed disease supportive care costs reflective of NHS clinical practice?
- How long should progressed disease costs be accrued?
- Is the ERGs assumption of 50% PD costs due to time spent on subsequent treatments reasonable?

Abbreviations: PD, progressed disease; 2L, second line

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Other considerations

POLARIX is the first trial to show meaningful benefit in 20 years

Equality considerations

- There are no known equality issues relating to the use of polatuzumab vedotin in untreated diffuse large B-cell lymphoma

Innovation

- POLARIX is the first trial in over 20 years to show a meaningful improvement in the benefit-risk profile over R-CHOP in an international Phase III double-blind, randomised controlled trial

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Assumptions in company and ERG base case

Key differences in ERG and company base case

Table 14 Assumptions in company's and ERG base's case

Assumption	Company base case at ACM2	ERG base case at ACM2
PFS extrapolation	Mixture-cure model with generalised gamma parametric curve	
OS extrapolation	Piecewise model - KM to month 30 then generalised gamma mixture-cure model	
Treatment effect waning	Not included	OS assumed equal in both arms from month 60
Utility source	GOYA trial	
Subsequent therapy costs	No CAR-T	
End of life costs	End of life costs excluded from PD costs (counted once)	
Resource use	PFS: TA243; PD: clinician survey	PFS: TA243; PD: 50% of company's PD costs
Weight distribution	POLARIX	
PFS curve correction	Correction applied	Correction not applied

Company has also submitted updated PAS - included in base case

Abbreviations: PFS, progression-free survival, PD progressed disease

Cost-effectiveness results

As confidential discounts are available for comparator and subsequent treatments in the pathway, ICERs are not reported in Part 1.

ICERs including confidential discounts will be presented in Part 2.

Summary

- Company's base case (including PFS correction) is within the range of what would usually be considered cost-effective use of NHS resources
- Company's base case (not including PFS correction) is not within the range of what would usually be considered cost-effective use of NHS resources
- ERG's base case is not within the range of what would usually be considered cost-effective use of NHS resources

Impact of scenarios on company base case

Table 15 Impact on ICER of applying company or ERG scenarios compared with company base case

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
POLARIX Western patient population height and weight	↑	=	↑
IPI 3 to 5 population (+ applicable PAS discount for this population)	↑	↑↑	↓↓
Removal of PFS curve correction	↑	↑	↑↑
50% reduction in progressed disease costs	↑↑	=	↑↑
No difference in overall survival between arms after 60 months	↑	↓	↑↑
ERG preferred assumptions (ERG base case)	↑↑	↓	↑↑

↑↑ Change of more than £5,000 (before confidential prices for comparators applied)

↑ Change of less than £5000 (before confidential prices for comparators applied)

↑ Change of more than 0.3 QALYs

↑ Change of less than 0.3 QALYs

Arrow indicates direction and scale of change in costs, QALYs or ICER **compared to company base case**

Abbreviations: ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year

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Thank you.