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

For public, redacted

Technology appraisal committee C [06 September 2022]

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NICE National Institute for Health and Care Excellence

Pola+R-CHP for DLBCL

→ **Background**

- Key issues and decision problem
- Clinical evidence
- Cost effectiveness evidence
- OS extrapolations
- Costing in the model
- Utility
- Summary

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Abbreviations: DLBCL, diffuse large B-cell lymphoma

Background on untreated diffuse large B-cell lymphoma

DLBCL is a fast-growing lymphoma

Disease overview

- Diffuse large b-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma

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

- Approx. 5,500 new cases diagnosed in UK each year
- 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

Classification of DLBCL

Prognosis is most commonly predicted using the IPI

Table 1 Independent predictors for outcomes such as overall survival (OS) and progression-free survival (PFS) used to determine International Prognostic Index (IPI)

Independent predictor	Not met	Met
Age	≤60 years	>60 years
Serum lactate dehydrogenase	Normal LDH level	Elevated LDH level
Eastern Cooperative Oncology Group (ECOG) performance status	0/1	2-4
Ann Arbor Stage	I or II	III or IV
Number of extranodal sites	0 or 1	2-4

Table 2 IPI risk group based on number of independent predictors met

Number of Independent predictor	IPI risk group
0 or 1	Low-risk
2	Low-intermediate risk
3	High-intermediate risk
4 or 5	High risk

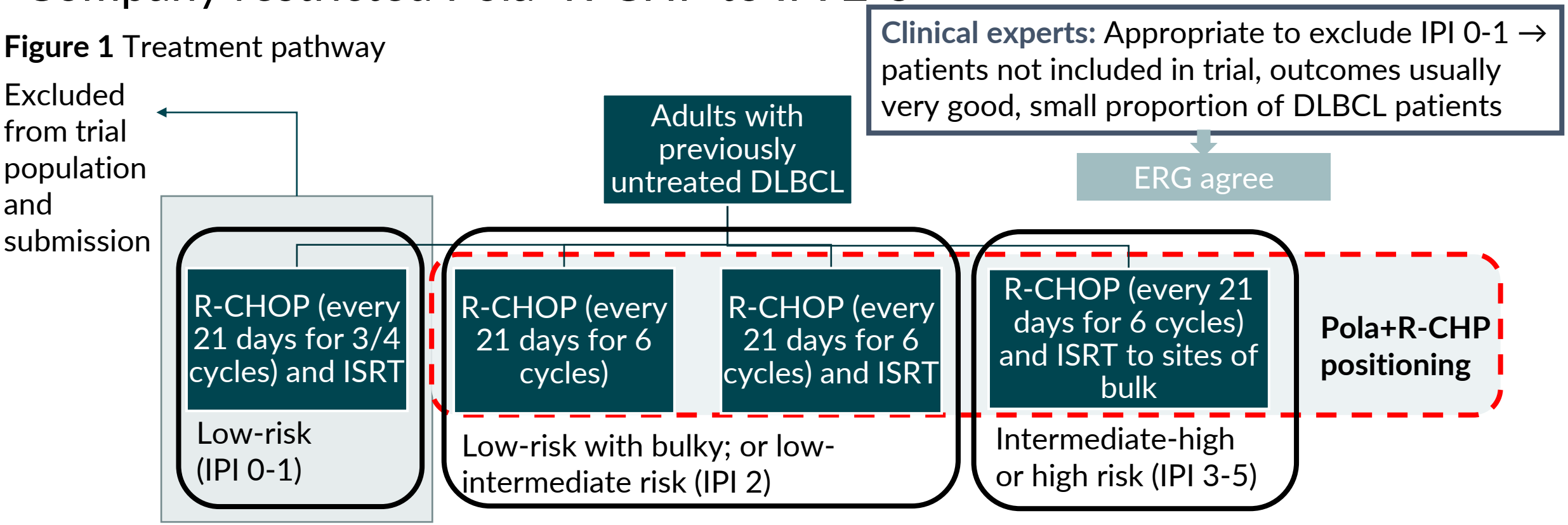
Revised versions of the IPI exist but aren't used as much in the NHS

Company target population (discussed in further detail on the next slide)

NICE Abbreviations: LDH, lactate dehydrogenase

Treatment pathway
Company restricted Pola+R-CHP to IPI 2-5

Figure 1 Treatment pathway



After first line treatment: if fit for intensive chemo - R-based salvage chemo, autologous stem cell transplant; if not fit for intensive chemoR-based chemo, polatuzumab vedotin plus bendamustine and rituximab and BSC

If the technology was recommended, the recommendation would be optimised to exclude people with IPI 0-1 (consistent with the company trial and submission) – marketing authorisation doesn't restrict according to risk

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

Patient perspectives

DLBCL is an aggressive lymphoma which is difficult to live with

Submission from Lymphoma Action

- People with DLBCL can be very ill and require a huge amount of support
- Current treatment is intensive and can take months or years to recover - this has significant impact on people's personal lives
- Unmet need for an effective, less demanding treatment with fewer side effects
- Polatuzumab combination does not include vincristine which some people felt was an advantage

"Not earning has inevitably raised some questions regarding future financial stability."

"constant fear of dying"

"I had little quality of life during [current] treatment as it dominated my life.... my husband had to take on the role of carer. We both suffered considerable stress and anxiety"

"As it [polatuzumab combination] does not contain vincristine I would consider that an advantage"

Polatuzumab combination is "Speedier treatment, more targeted. Less side effects."

Clinical perspectives

Reducing progression to relapsed disease is important to patients and the NHS

Submissions from clinical experts

- Relapse with high grade lymphoma requires intensive treatment
- PFS is very important to patients and NHS given burden/toxicity/cost of relapsed disease - 2nd line treatments have 20% less success rate requiring high-cost 3rd line treatments
- First randomised control trial in 2 decades to demonstrate PFS improvement over standard R-CHOP
- No increase toxicity and easy to deliver pola+R-CHP
- CAR-T therapy needs to be considered in evaluation given its current and future place in therapy for relapsed DLBCL*

"A relapse event in high grade lymphoma is devastating for the patient"

"[relapse] requires 3 months of high dose chemo and then a month in hospital for an autologous stem cell transplant which is associated with significant toxicity"

"I consider [pola+R-CHP] a clinically significant improvement"

Abbreviations: DLBCL, diffuse large b-cell lymphoma; PFS, progression-free survival. *CAR-T therapies are potentially subsequent treatments but are in CDF so have been excluded from model (consistent with NICE's position statement)

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Key issues

There are several key issues remaining after technical engagement

Table 3 Key issues

Issue	Resolved?	ICER impact
Uncertainty of treatment effect (subgroup analyses, overall survival extrapolations and treatment effect waning)	No – for discussion	Large
Health care resources in the progressed disease health state	No– for discussion	Large
Exclusion of chimeric antigen receptors cell therapy (CAR-T) as possible subsequent-line treatments	Partially – for discussion	Large
Utility values	No– for discussion	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	Small

NICE Abbreviations: CAR-T, chimeric antigen receptor T-cell; IPI, International Prognostic Index.

Technology (Polivy®, Roche)

Table 4 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 TE)

*prednisolone is used in the UK. Company refer to it as prednisone in context of POALRIX and use terms interchangeably in submission

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

Decision problem
Company restricted the population compared to scope

Table 5 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	Adults with untreated diffuse large B-cell lymphoma	As per final scope issued by NICE	Company restricted population to IPI score of 2 to 5 as per the POLARIX study
Intervention	Polatuzumab vedotin with R-CHP	Prednisone as well as prednisolone (within R-CHP)	None
Comparators	Chemoimmunotherapy (including R-CHOP)	As per final scope issued by NICE	Clinical guidelines - R-CHOP current UK standard care
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per NICE scope issued by NICE	Company submission reports results for all outcomes but does not provide results for all measures of health-related quality of life

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Clinical trial summary
POLARIX is the pivotal trial

Identified in literature search

Table 6 Clinical trial designs and outcomes

	POLARIX (n=879) – pivotal trial	GOYA (n=1,414)
Design	Phase III, double-blind, placebo-controlled study	Phase III, open-label study
Population	Adult patients with previously untreated DLBCL (IPI 2-5)	Adult patients with previously untreated CD20-Positive DLBCL (IPI 2-5)
Intervention	Pola+R-CHP	G-CHOP
Comparator(s)	R-CHOP	R-CHOP
Follow up*	Median 28.2 months	Median 47.7 months
Primary outcome	PFS	PFS
Key secondary outcomes	OS; Response rate	OS; Response rate
Locations	Western Europe (including UK), US, Canada, Australia and Asia	Western Europe (including UK), US, Canada, Australia and Asia
Used in model?	Baseline characteristics, PFS, OS	Utilities

*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)

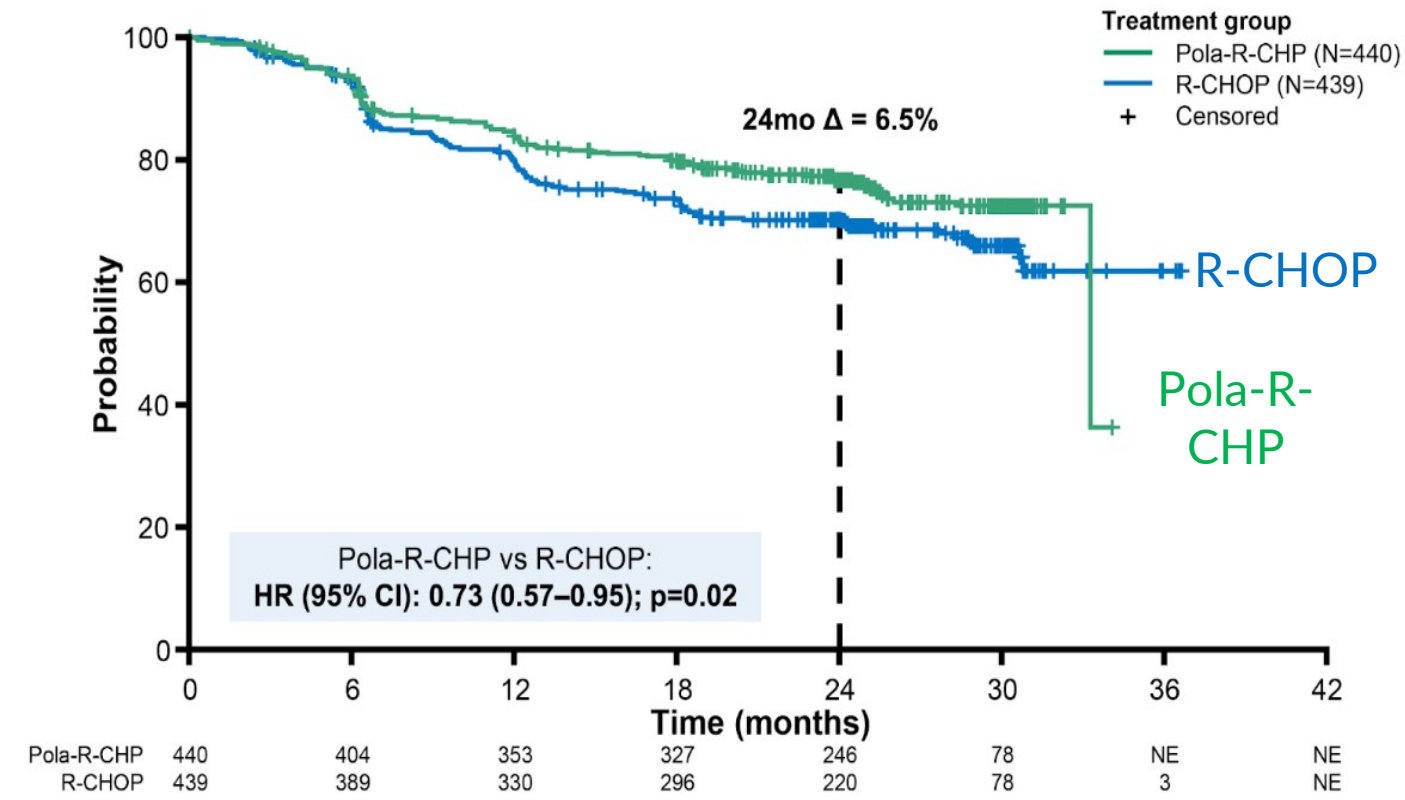


Table 7 Summary of investigator-assessed PFS (ITT population)

	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)

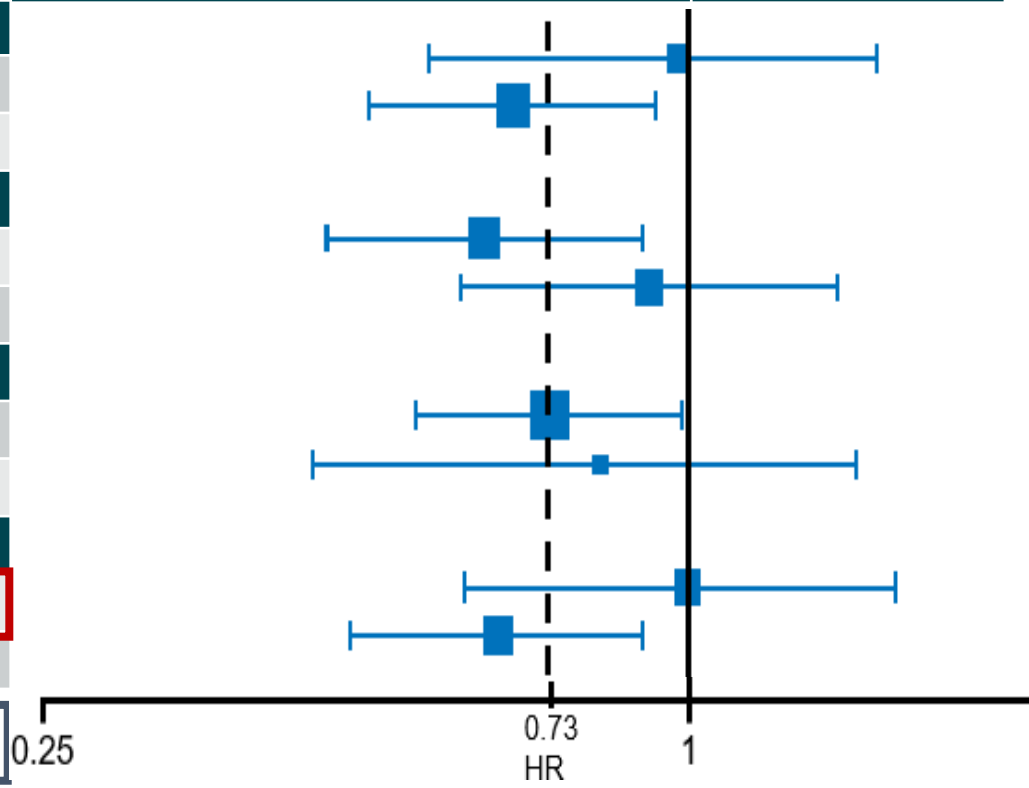
Abbreviations: CI, confidence interval; HR, hazard ratio, ITT, intention to treat; n, number; PFS, progression-free survival

POLARIX results – PFS by subgroup

Key issue: There was no difference in PFS for the IPI 2 subgroup

Table 8 Investigator-assessed PFS by subgroup (unstratified)

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		
Age group							
≤60	271	140	74.1	131	71.9	0.9	0.6–1.5
>60	608	300	77.9	308	69.5	0.7	0.5–0.9
Sex							
Male	473	239	75.9	234	65.9	0.7	0.5–0.9
Female	406	201	77.7	205	75.2	0.9	0.6–1.4
ECOG PS							
0–1	737	374	78.4	363	71.2	0.8	0.6–1.0
2	141	66	67.2	75	65.0	0.8	0.5–1.4
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



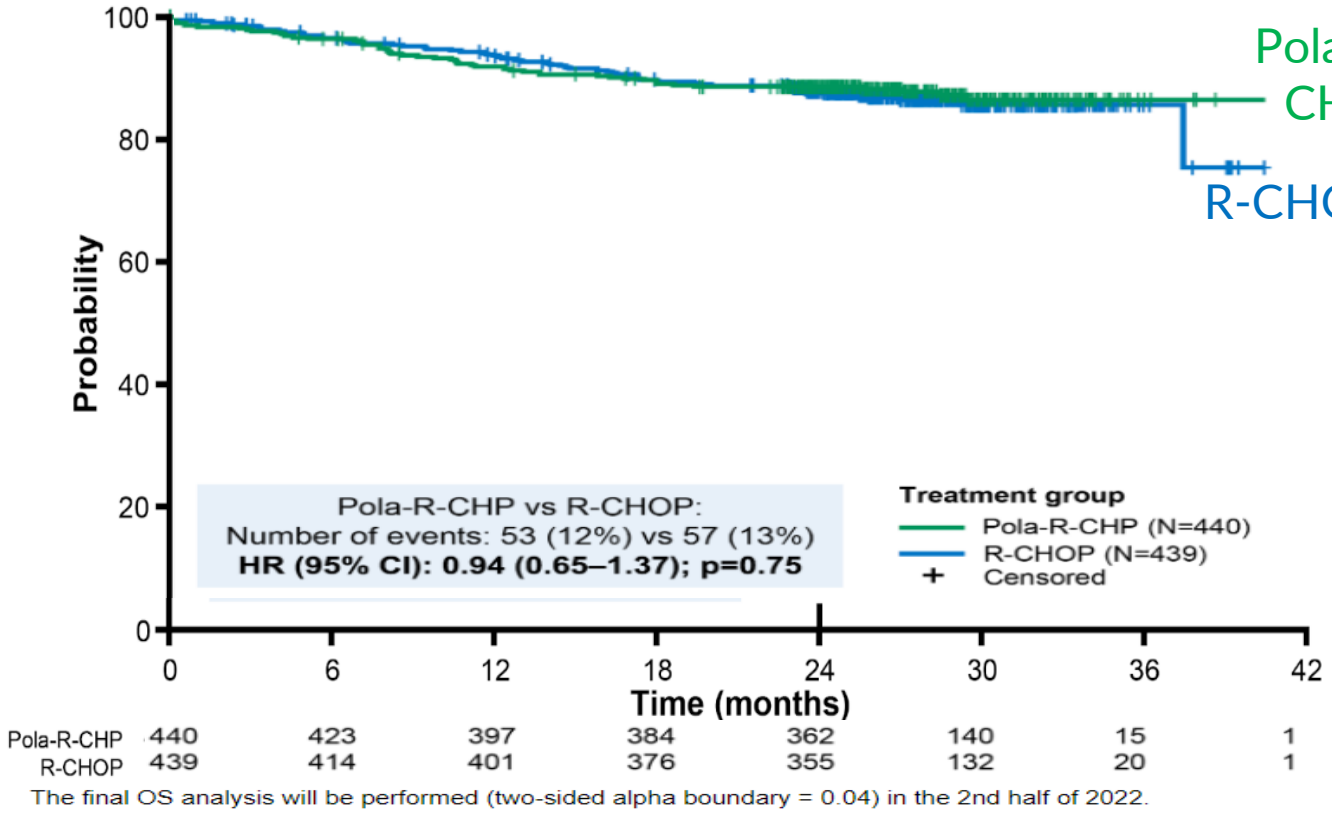
Trial subgroup analyses exploratory/signal seeking, not confirmatory

Should a subgroup of IPI3-5 be considered?

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index

POLARIX results - OS
Frequency of OS events (deaths) were low in both arms

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



The final OS analysis will be performed (two-sided alpha boundary = 0.04) in the 2nd half of 2022.

Table 9 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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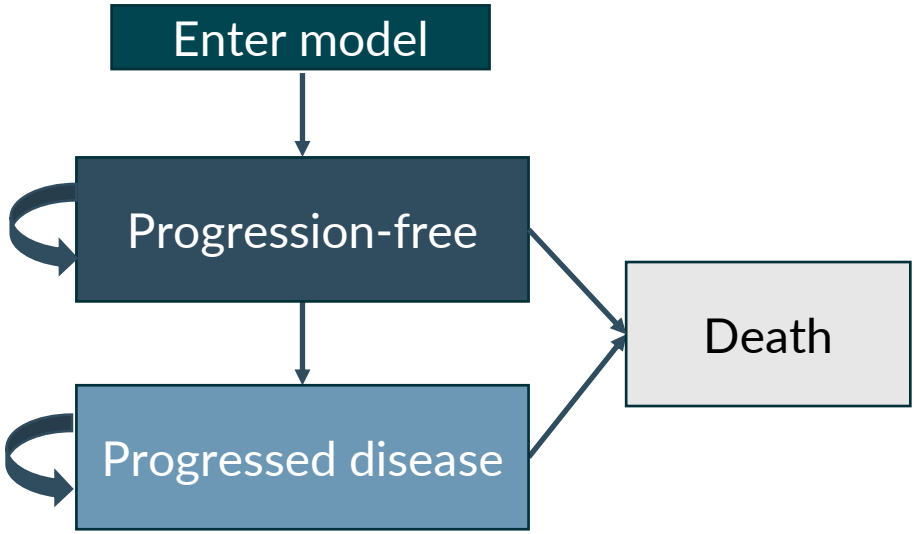
Company's model overview
Three state partitioned survival model was used

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:
  - Treatment effect waning assumption for OS; between 30 and 60 months
  - 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

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Mixture-cure modelling was used for OS extrapolation

OS data immature so not possible to directly estimate long term survival. Instead, OS was informed by long-term remission fraction (i.e. PFS cure fraction)

Figure 5 OS mixture-cure model pola+RCHP (informed by PFS)

Figure 6 OS mixture-cure model R-CHOP (informed by PFS)

NICE Abbreviations: OS, overall survival; PFS, progression-free survival.

Company and ERG use KM+generalised gamma OS extrapolations

Figure 7 OS Kaplan-Meier from POLARIX

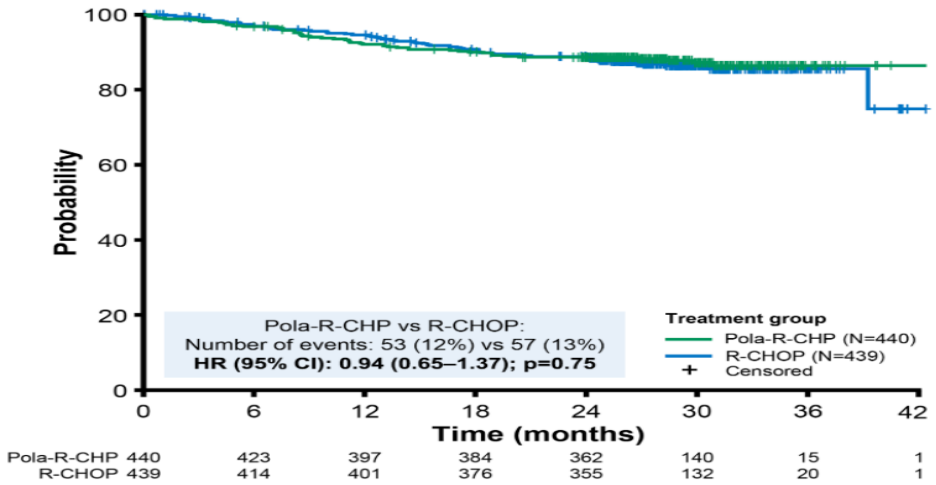


Figure 8 Extrapolations of OS for Pola-R-CHP and R-CHOP

[redacted]

Table 10 OS predictions for the generalised gamma vs the KM data from the POLARIX and GOYA trials

	Pola+R-CHP arm			R-CHOP arm			
Yr	Generalised gamma	KM+Generalised gamma[a]	POLARIX trial	Generalised gamma	KM+Generalised gamma[a]	POLARIX trial	GOYA trial
1	93.4%	92.2%	92.2%	94.6%	94.6%	94.6%	[redacted]
2	89.4%	88.7%	88.7%	89.3%	88.6%	88.6%	
5	81.0%	79.6%	-	78.7%	78.0%	-	
10	68.7%	66.0%	-	65.2%	64.6%	-	-

ERG and company base case extrapolation

Are OS extrapolations plausible?

[a]Includes treatment effect waning. Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Key issue: Treatment effect waning

ERG assume the treatment effect of pola+R-CHP would wane

Background

- No statistically significant OS difference between Pola+R-CHP and R-CHOP (HR 0.94 CI 0.65 to 1.37)
- Company's extrapolation assumes continued survival benefit for Pola+R-CHP over R-CHOP

Company: DLBCL is curable in 1L so does not wane - evidence from 1L and relapsed/refractory supports benefit is maintained

- Clinical expert advice to the company agreed in curative setting would not expect treatment effect waning
- OS informed by PFS, which means OS curves likely underestimating efficacy of Pola+R-CHP long-term

ERG comments

- Pola+R-CHP OS benefit would not last indefinitely – uncertain if there is an OS benefit, other treatments impact survival
- Evidence provided by company is in different treatment regimens, has different patient characteristics and study time periods which limits applicability but suggests survival benefit could be maintained
- In absence of more mature survival data take conservative approach - assume waning from 30 months and treatment benefit unlikely to last more than 5 years (after this point probability of death same in both arms)
- Waning is in context of mixture-cure model and applied to whole population (even cured)

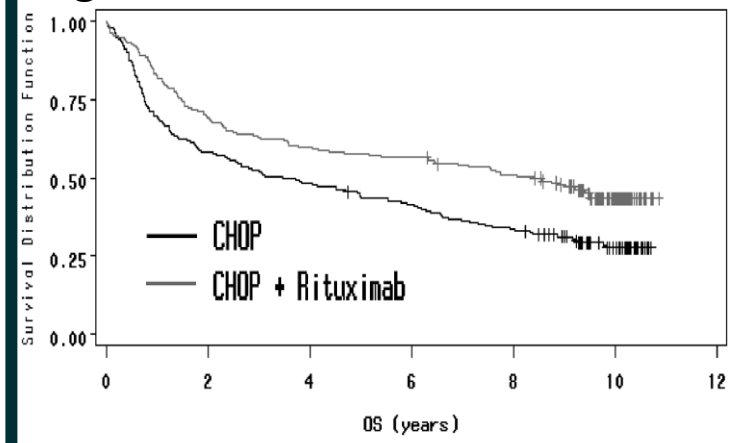
NICE: ERG approach is conservative. Applying waning only to uncured group, would increase separation of OS groups and benefit Pola+R-CHP

 Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Company evidence supporting treatment benefit

LNH-98.5 trial - 1L DLBCL (n =399)

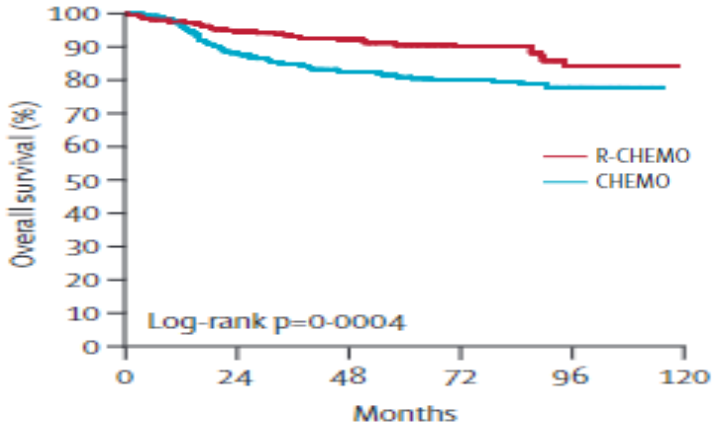
Figure 9 OS CHOP vs. R-CHOP



Benefit persists over 10 years

MInT trial - 1L DLBCL (n = 823)

Figure 10 OS CHEMO vs. R-CHEMO



Benefit persists over 6 years

GO29365 phase II trial - R/R DLBCL (n =331)

Figure 11 OS Pola+BR vs. BR

Benefit persisted over 5 years

Other considerations

- Previous appraisals in later line DLBCL do not include waning - no previous appraisals in untreated population
- Clinical experts: vast majority of death and relapse occurs within 2 years; will be significant toxicity from subsequent high dose treatments

Should the treatment benefit of pola+R-CHP be assumed to last indefinitely?

Abbreviations: BR, bendamustine and rituximab; R/R, relapsed or refractory

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Key issue: Supportive care costs (1/2)
Company prefer PD resource use based on TA649

Background
- Company health care resource use based upon estimates for 3rd and 4th-line treatment of DLBCL (TA649 which used TA306) → No NICE appraisals in untreated DLBCL

Company
- Accepted ERG values for PFS but not PD - in POLARIX people had ~2 more treatments after 1st line but company base-case does not account for additional resource costs beyond 2nd line so is conservative

ERG comments
- Resource and costs for untreated DLBCL overestimated:
  - 3rd and 4th-line patients may be in poorer health and require greater resource use
  - PD disease likely respond to subsequent treatment and no longer incur costs, as assumed in TA649
  - Company include end-of-life (EoL) costs in PD but also have one-off (EoL) cost (£6,950.29) – double counting costs
  - Costs higher than UK real world evidence study in UK[1] and other similar appraisals (TA513)
- Prefer to estimate resource use based on TA243 and clinical advice

Clinical expert comments
- Agree that resource use in 1st line would be less intense than 3rd and 4th line; PD needs intensive treatment

 Abbreviations: PD, progressed disease; PFS, progression free survival. [1] Wang et al. 2017. *Eur J Health Econ;18(2):255-67.*

Key issue: Supportive care costs (2/2)

Table 11 Average unit of resource per year for progressed disease

Procedure	Company base case	ERG base case
Residential care (day)	0.0	0.0
Day care (day)	24.4	0.0
Home care (day)	121.7	0.0
Hospice (day)	12.1	0.0
Oncologist (visit)	4.3	13.0
Haematologist (visit)	13.0	0.0
Radiologist (visit)	0.0	0.0
Nurse (visit)	2.1	0.0
Specialist nurse (visit)	32.6	0.0
GP (visit)	43.0	0.0
District nurse (visit)	52.2	0.0
CT scan	0	3.0
Inpatient day	2.7	0.0
Palliative care team	17.3	0.0
Full blood counts	13.0	13.0
LDH	4.3	13.0
Liver function	13.0	13.0
Renal function	4.3	13.0
Immunoglobulin	4.3	6.5
Calcium phosphate	13.0	6.5

Company estimations of resource use frequency are much higher than ERG estimates. This results in a significant increase in overall PD resource use costs.

Table 12 Cost of resource by treatment for progressed disease

Cost	Company base case		ERG base case	
	Pola+R-CHP	R-CHOP	Pola+R-CHP	R-CHOP
One-off cost	**£422.35**	**£624.14**	**£202.11**	**£281.27**
Cost per year	**£4,793.16**	**£4,793.16**	**£736.80**	**£736.80**

Do company resource use estimates reflect NHS practice?

Subsequent treatment costs
CAR-T therapies are approved in the CDF

Background
- CAR-T treatments are currently in the CDF and will be undergoing review for use in routine commissioning:
  - ID3980 [TA559 review] Axicabtagene ciloleucel (axi-cel) - guidance due in Jan 2023 (ACM1 – September 2022)
  - TA567 Tisagenlecleucel – guidance TBC (ACM not scheduled)
- Clinical experts - Large number of people proceed to CAR-T - fundamentally important to consider
- NICE's position statement - CDF recommendations should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals

Company
- Pola+R-CHP could be cost-saving in the long term because CAR-T is highly expensive but agree to exclude from model because they are in CDF

ERG
- Agree with removal of CAR-T

NICE
- CDF review ACM of axi-cel is 6th September. If recommended for routine use and if considered standard practice, inclusion as a subsequent treatment would be appropriate
- Committee is asked to note the relevance of the ongoing ID3980 appraisal to the present appraisal

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

Key issue: Redistribution of CAR-T subsequent treatment

Company redistributed people from CAR-T to other treatments

Background

- Company and ERG agreed CAR-T therapies should not be included as subsequent treatments at this time

Company

- Clinical advice suggests around [redacted] receive CAR-T in 3L+
- Redistributed [redacted] of people on CAR-T in original analysis to other 3L treatments.

ERG comments

- After the redistribution of people from CAR-T the total usage of subsequent treatments is 118% in company base case – implausible
- More appropriate to remove CAR-T without adjusting other treatments (total subsequent treatment usage 97%)

Table 13 Subsequent treatment costs based on UK clinical data (pola list price)

Subsequent treatment costs	Redistribution (company)	No redistribution (ERG)
Pola+R-CHP	£21,343	£17,816
R-CHOP	£43,310	£31,502

Should other subsequent treatments be adjusted when CAR-T therapies are removed?

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; 3L, 3rd line.

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Key issue: Health state utility values

Health state utility values from GOYA trial used in base case

Background

- Company use health state utilities from GOYA trial because of longer follow-up and clinician validation

Company

- 11 clinicians confirmed GOYA more representative than POLARIX
- POLARIX not representative because: [redacted] who progressed did not report HRQoL → those who reported had better outcomes; HRQoL data collected [redacted]; disease progressed rapidly after 1L

ERG comments

- GOYA utility values similar to PD utilities in TA649 → ERG agree to use GOYA utilities in base case
- ERG age-adjust PD utility values using Ara and Brazier
- Difference in OS contributes to QALY difference

Table 14 Summary of utility values for cost-effectiveness analysis

State	Mean utility value	
	GOYA	POLARIX
PFS	0.816	[redacted]
PD	0.734	[redacted]
PFS: long-term follow up	Age- and sex-matched general population utility values	
Treatment adverse event disutilities	Disutility values sourced from NICE TA306 and the literature.	

Are the utility differences plausible?

Abbreviations: HRQoL: health-related quality of life; PD, progressed disease; 1L, first-line; 2L, second-line.

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Summary of company and ERG base case assumptions

Table 15 Assumptions in company and ERG base

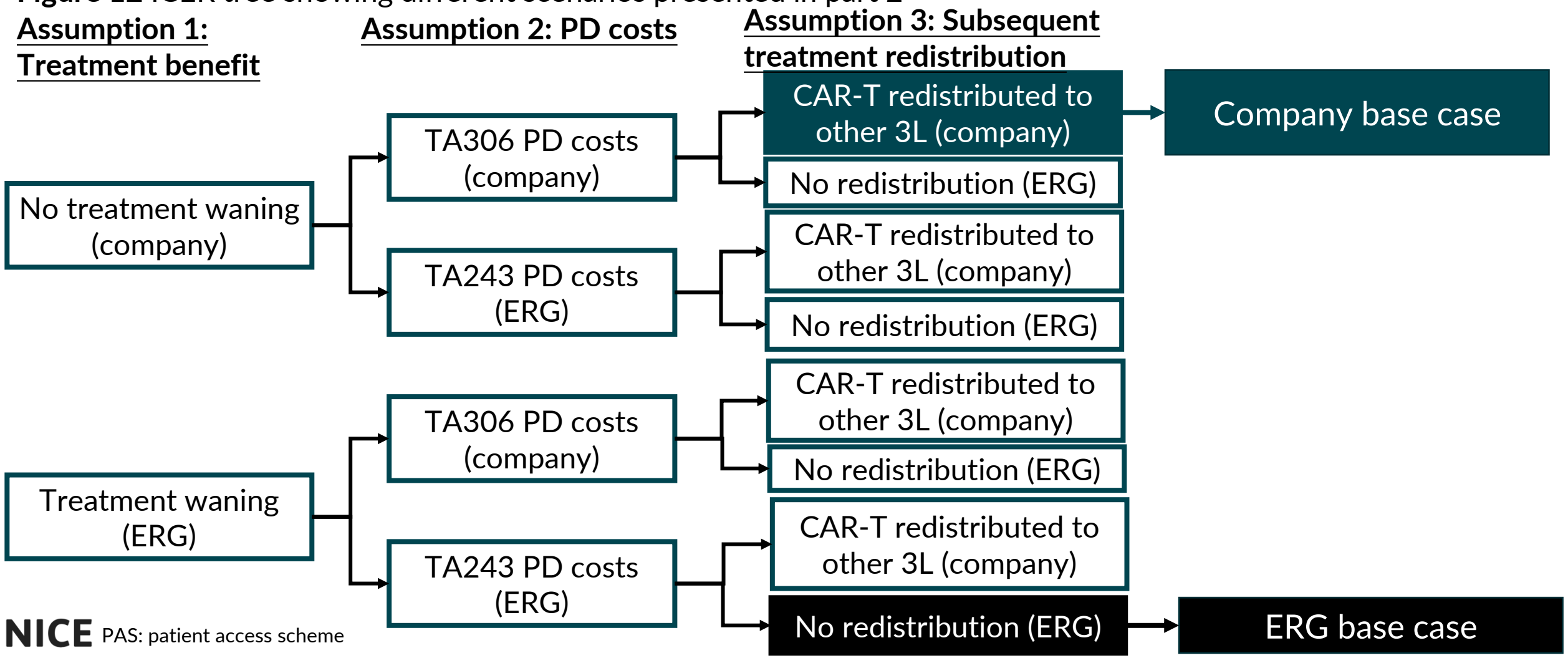
Assumption	Company base case	ERG base case
PFS extrapolation	Mixture-cure model with generalised gamma parametric curve	Mixture-cure model with generalised gamma parametric curve
OS extrapolation	Piecewise model - KM to month 30 then generalised gamma mixture-cure model.	Piecewise model - KM to month 30 then generalised gamma mixture-cure model.
Treatment effect waning	**Not included**	**Treatment effect waning between 30 and 60 months**
Health state utilities	GOYA trial	GOYA trial
AE disutility	Yes	Yes
Age-related disutility	Included after 2 years for PFS and PD	Included after 2 years for PFS and PD
Subsequent therapy costs	No CAR-T therapies	No CAR-T therapies
	People on CAR-T redistributed to other treatments (TE updated approach)	**People on CAR-T not redistributed to other treatments (TE updated approach)**
Resource use	PFS: 243; **PD: TA306**	PFS: TA243; **PD: TA243**
End of life cost	Yes	Yes

Abbreviations: CAR-T, Chimeric antigen receptor T-cell; KM, Kaplan Meier, OS, overall survival; PD, progressed disease; PFS, progression-free survival.

Cost-effectiveness results and scenarios

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

Figure 12 ICER tree showing different scenarios presented in part 2



NICE PAS: patient access scheme

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

NICE National Institute for Health and Care Excellence

Thank you.