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Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Technology appraisal committee C [08 August 2023]

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Company: Roche

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

- ✓**Background**
- ❑Clinical evidence and key clinical issues to consider
- ❑Modelling and key cost effectiveness issues to consider
- ❑Other considerations and base case assumptions
- ❑Summary

NICE National Institute for Health and Care Excellence

Background on diffuse-large B-cell lymphoma (DLBCL)

How many people have DLBCL?

- Around 4,850 people diagnosed with DLBCL in 2019 | accounts for ~40% of non-Hodgkin Lymphoma (NHL) cases | More common age 60 years or older and in men

Diagnosis and classification

- DLBCL is an aggressive (fast growing) form of NHL | Biopsy and testing confirms diagnosis | Staging determines treatment options and prognosis

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, Eastern Cooperative Oncology Group performance status ≥2, age over 60 years

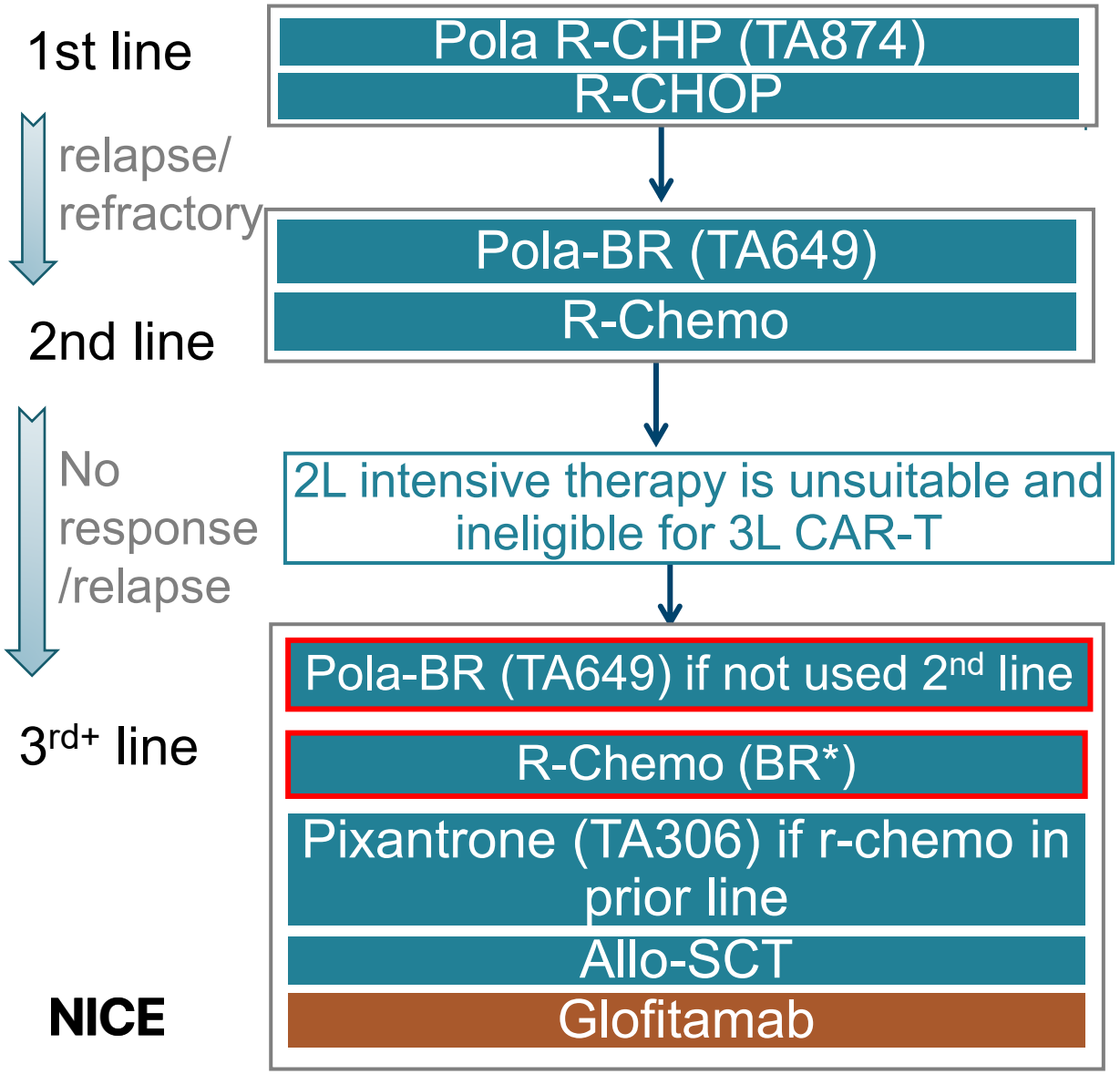
Glofitamab (Columvi, Roche)

Proposed marketing authorisation	For 'treatment of adult patients with relapsed or refractory DLBCL, after two or more lines of systemic treatment' (EMA) • Has Early Access to Medicines scheme designation
Mechanism of action	Bispecific monoclonal antibody activates a patient's own T-cells to multiply and eliminate cancerous B-cells that express CD20 antigens
Administration	Intravenous infusion
Price	List price: £687 (2.5 mg vial) | £2,748 (10 mg vial) Average course of glofitamab treatment, per patient, based on a median of 5 cycles: £46,536 (including obinutuzumab pre-treatment) Confidential simple discount patient access scheme available

Abbreviations: DLBCL, diffuse large B-cell lymphoma; EMA, European medicines agency

Treatment pathway for DLBCL

Pathway for when intensive therapy is unsuitable for patients

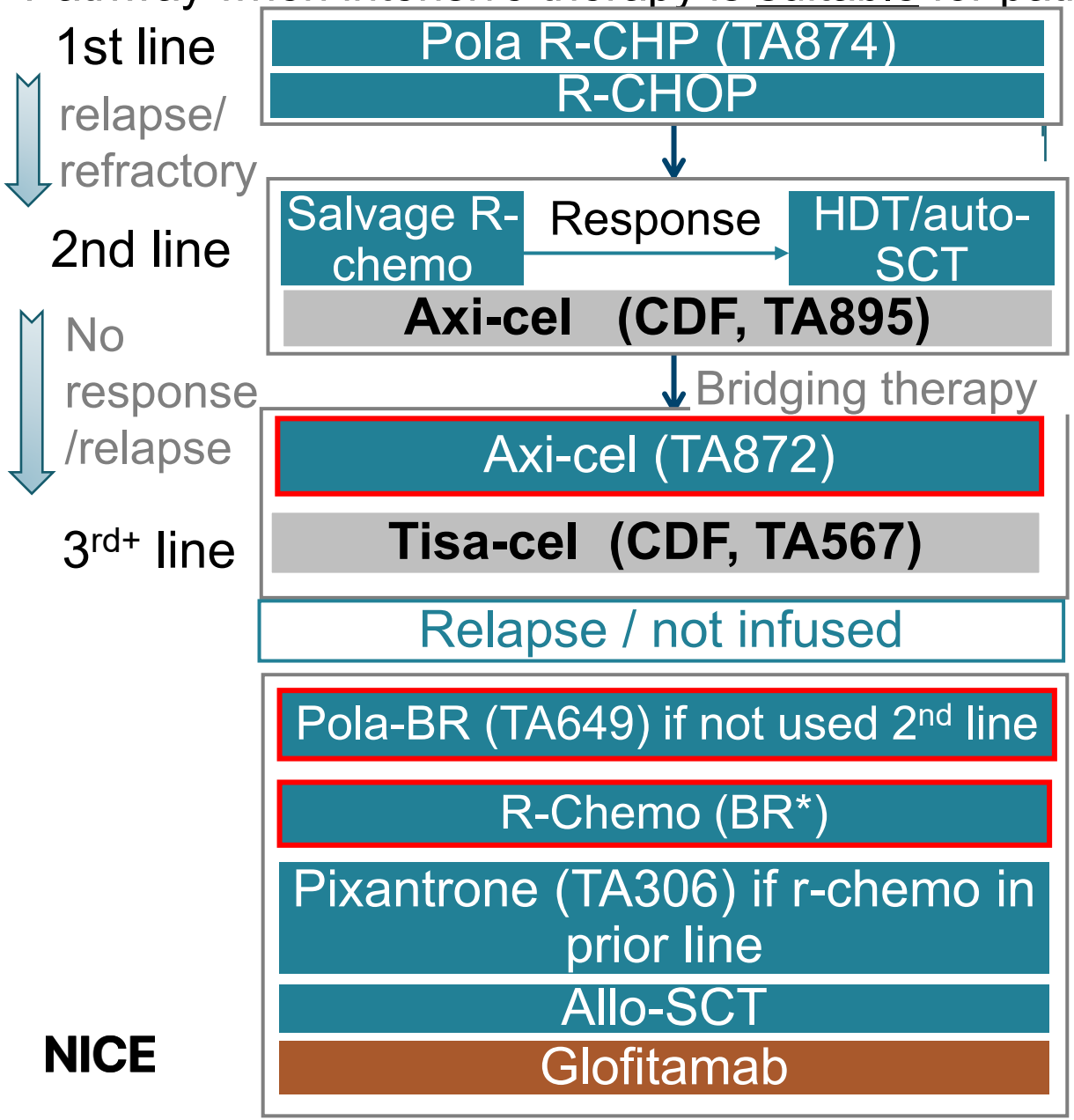


Included in company submission as relevant comparators

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 (BR*), rituximab based chemotherapy (*BR used as proxy for RGemOx due to lack of data); R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Treatment pathway for DLBCL

Pathway when intensive therapy is suitable for patients



Included in company submission 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 (BR*), rituximab based chemotherapy (*BR used as proxy for RGemOx due to lack of data); R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; tisa-cel tisagenlecleucel

Perspectives on living with DLBCL

DLBCL affects patients and carers with unmet needs for treatment options

Thanks to Lymphoma Action for submission and engagement

Symptoms

- Lumps in the neck, armpit or groin; symptoms vary with location
- Systemic symptoms include fevers, night sweats, weight loss, fatigue, loss of appetite and severe itching

Impact on daily life

- Significant impact on quality of life for both patients and carers
- Treatment can have debilitating side effects and take a long time to administer

Current treatment options

- Need more treatment options with fewer side effects
- Distribution of CAR-T therapy centres limits access

"I was…first and last person in the Chemo suite as R-CHOP takes…a long time to receive via IV."

"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."

Abbreviations: CAR T, chimeric antigen receptor T-cell; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Professional group perspectives

High unmet need in third-line treatment landscape

Thanks to NCRI-ACP-RCP-RCR for submission and engagement

Unmet need

- Poor rates of complete remission, overall survival and progression-free survival for people who have had 2 prior lines of treatment
- No standard of care in third+ line | CAR-T not always an option

Benefits of glofitamab

- Major advance in treatment of relapsed DLBCL due to 40% CR rate | Durable remission for most patients achieving CR
- Safety profile is manageable
    - Events are very rare beyond 1st cycle
    - Risk of cytokine release syndrome and ICANS are much lower than axi-cel

"up to 60% of patients have suboptimal response or progress post CAR-T and better treatment options are needed for these patients"

"don't yet have long enough follow up from the pivotal glofitamab trial to say with confidence that patients are cured but durable CRs are clearly seen"

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR T, chimeric antigen receptor T-cell; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome

Summary of key issues

Issue	Resolved?	ICER impact
Long-term remission/survivorship: Cure-point assumed after progression-free for 3 years • Is excess mortality of 9% appropriate? • For which treatments is a cure plausible?	For discussion	Large 
Average cohort age	For discussion	Small 
Uncertainty from indirect treatment comparison	Unresolvable uncertainty	Unknown 

Abbreviations: ICER, incremental cost effectiveness ratio

Other issues for consideration

Issue	ICER impact
Axi-cel and pola-BR may no longer be relevant 3rd line comparators due to being used in earlier lines • Rapidly moving pathway, issue is unresolvable	Unknown 
Key axi-cel trial excluded people who did not receive infusion • Biases analysis in favour of axi-cel as rapid progressors not included • Not possible to fully know or adjust for impact	Unknown 
Unadjusted and adjusted analyses used different methods for calculating confidence intervals (CIs) for indirect treatment comparisons • Same methods applied following technical engagement but remaining concern that adjusted analyses may be overestimating certainty	Small 
Immune effector cell-associated neurotoxicity syndrome (ICANS) not captured in cost-effectiveness analysis • Monitoring costs of ICANS not included in model • Rates of grade ≥2 ICANS are low ([redacted]) in people receiving glofitamab • Clinical experts agree ICANS rare in people receiving glofitamab	Small 

Abbreviations: axi-cel, axicabtagene ciloleucel; Pola-BR, polatuzumab vedotin with rituximab and bendamustine

Relevant third-line comparators

Treatment landscape is changing rapidly and substantially

Background

- Company included 3 comparators: R-based chemotherapy (BR*), pola-BR and axi-cel
- Changes to treatment landscape | polatuzumab and axi-cel now options in earlier lines
- [redacted] of people in NP30179 trial received prior CAR-T therapy
- Second-line axi-cel not considered in this appraisal as only available in CDF

Company (after TE)

- Agree that third-line use of pola-BR and axi-cel is declining
- No standard of care in third-line, experts advise that pola-BR use is already uncommon

EAG comments

- Issue cannot be resolved further but key area of uncertainty

Clinical experts

- Pola-BR and axi-cel use declining in third-line but still relevant comparators

What are the relevant comparator treatments for third-line?

*BR used as proxy for RGemOx due to lack of data

Abbreviations: axi-cel, axicabtagene ciloleucel; CDF, Cancer Drugs Fund; Pola-BR, polatuzumab vedotin with rituximab and bendamustine; R-Chemo, rituximab based chemotherapy

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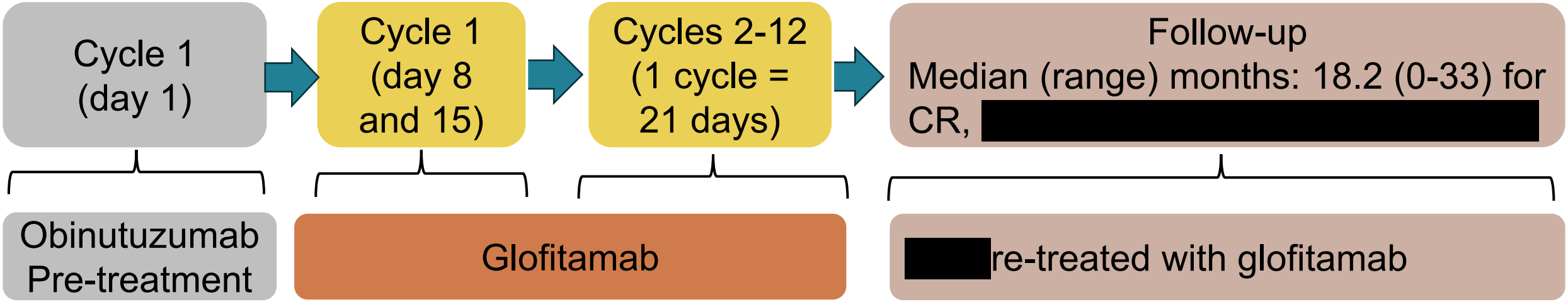
NP30179 key clinical trial

Company submission uses data from 3 cohorts of single-arm trial

Trial schematic



Study details

Participants	3 cohorts (combined =155, 154 received at least one dose) • Cohort 1: N=7 fixed glofitamab dosing • Cohort 2: N=108 step-up glofitamab dosing • Cohort 3: N=40 step-up dosing with pre-treatment dexamethasone
Key outcomes	CR, duration of response, overall response (OR), OS, PFS, safety
Location	Europe, US, Australia, New Zealand and Canada

Abbreviations: CR, complete remission; OS, overall survival; PFS, progression free survival

NP30179 results

High rate of complete response and people on 4th+ line of treatment

Efficacy results of NP30179

	Combined population (N=155)*
CR rate (95% CI)	[redacted]
OR rate (95% CI)	[redacted]
Median PFS (95% CI)	[redacted]
Median OS (95% CI)	[redacted]
3 or more prior lines of therapy	[redacted]
Prior auto-SCT	[redacted]
Prior CAR T-cell therapy	[redacted]
Any grade ≥3 adverse event	[redacted]
Adverse event leading to discontinuation	[redacted]

* N=155 for efficacy N=154 for safety outcomes

** Outcome assessed by investigator

Abbreviations: Auto-SCT, autologous stem cell transplant; CAR T, chimeric antigen receptor T cell; CR, complete remission; OR, Overall response; OS, overall survival; PFS, progression free survival

Indirect treatment comparison (ITC) methodology

Indirect comparison made against one key trial for each comparator

Background

ITCs using individual patient data for NP30179, weighted to match prognostic factors and effect modifiers of one key trial for each comparator

Treatment	Key trial in ITC	EAG points of criticism
Glofitamab	NP30179 (N=154) 3rd+ line; single-arm	Single-arm trial and using different data-cuts for each comparison leads to inherent bias
Axi-cel (unanchored MAIC)	ZUMA-1 (N=101) 3rd+ line; single-arm	Patients who progressed before infusion were excluded, may bias analysis in favour of axi-cel
Pola-BR (propensity score IPTW)	GO29365 (N=152) Randomised trial vs BR; 2nd+ line	May be more suitable source for BR than Hong **Company:** leads to balancing issues and effective sample size <10
BR (unanchored MAIC)	Hong 2018 (N=58) Retrospective analysis; 2nd+ line	Took place in South Korea only

Abbreviations: axi-cel, axicabtagene ciloleucel; Pola-BR, polatuzumab vedotin with rituximab and bendamustine; BR, bendamustine and rituximab; IPTW, inverse probability treatment weighting; MAIC, matching-adjusted indirect comparison)

Glofitamab compared against axicabtagene ciloleucel (axi-cel)

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Comparative evidence overview vs axi-cel

Comparison biased in favour of axi-cel

Background

- ZUMA-1 trial informed axi-cel arm; excluded people who did not receive CAR-T treatment
- Treatment-related Grade ≥3 adverse events considered in analysis, discontinuation due to adverse events not available

Participants characteristics before and after matching

- Matching reduced participants in glofitamab arm from 116 to an effective sample size of 34
- Participants were well matched for key baseline characteristics

Outcomes from matching-adjusted indirect comparison (MAIC)

	Adjusted base-case (95% CI)	Unadjusted(95% CI)
OR rate odds ratio	[redacted]	[redacted]
CR rate odds ratio	[redacted]	[redacted]
PFS hazard ratio*	[redacted]	[redacted]
OS hazard ratio	[redacted]	[redacted]

*per investigator assessment (as opposed to independent review committee)

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; OS, overall survival; PFS, progression-free survival; OR, overall response; CR, complete response

Comparative Evidence – From base case MAIC

Axi-cel has longer PFS and OS than glofitamab but comparisons have limitations

PFS for glofitamab compared with axi-cel

OS for glofitamab compared with axi-cel

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Abbreviations: axi-cel, axicabtagene ciloleucel; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

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Glofitamab compared against polatuzumab vedotin with rituximab and bendamustine (pola-BR)

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Comparative evidence overview vs pola-BR

Used individual patient data for both treatments, allowing better matching

Background

- Pola-BR arm informed by GO29365, which compared pola-BR to BR
- Analysis used individual patient data from both trials, allowing for better matching

Participants characteristics before and after matching

- Participants were excluded from each trial to make them more homogenous, then matched using inverse probability of treatment weighting, reducing number of glofitamab participants from 149 to [redacted], and pola-BR from 84 to [redacted]
- Participants were well matched for key baseline characteristics

Outcomes from MAIC

	Adjusted base-case (95% CI)	Unadjusted(95% CI)
OR rate odds ratio*	[redacted]	[redacted]
CR rate odds ratio*	[redacted]	[redacted]
Discontinuation due to adverse events odds ratio	[redacted]	[redacted]
PFS hazard ratio*	[redacted]	[redacted]
OS hazard ratio	[redacted]	[redacted]

*per investigator assessment (as opposed to independent review committee)

Abbreviations: CI, confidence interval; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; OR, overall response; CR, complete response Pola-BR, polatuzumab vedotin with rituximab and bendamustine; BR, bendamustine and rituximab

Comparative Evidence – From base case MAIC

No significant difference in outcomes but glofitamab curve shows slight benefit

PFS for glofitamab compared with pola-BR

[redacted]

OS for glofitamab compared with pola-BR

[redacted]

Abbreviations: MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; Pola-BR, polatuzumab vedotin with rituximab and bendamustine

Glofitamab compared against r-chemo (BR)

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Comparative evidence overview vs R chemo

Uses single arm trial to inform BR arm

Background

- Comparison used as a proxy for R-chemotherapies used in third-line treatment of DLBCL
- Analysis informed by Hong 2018 trial, which enrolled ~30% second-line patients

Participants characteristics before and after matching

- Matching reduced the number of participants in glofitamab arm from 139 to 67.5, not possible to control for second-line usage

Outcomes from MAIC

	Adjusted base-case (95% CI)	Unadjusted (95% CI)
OR rate odds ratio	[redacted]	[redacted]
CR rate odds ratio	[redacted]	[redacted]
PFS hazard ratio*	[redacted]	[redacted]
OS hazard ratio	[redacted]	[redacted]

*per investigator assessment (as opposed to independent review committee)

EAG: GO29365 comparing Pola-BR to BR showed larger hazard ratio favouring pola-BR:

- PFS HR: 0.39 (0.23, 0.66)
- OS HR: 0.42 (0.24, 0.72)

suggests there should be even stronger evidence in favour of glofitamab

Abbreviations: BR, bendamustine and rituximab; CI, confidence interval; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; OR, overall response; CR, complete response Pola-BR, polatuzumab vedotin with rituximab and bendamustine; R-chemo, Rituximab based chemotherapy

Comparative Evidence – From base case MAIC

Glofitamab improved PFS and OS compared with BR

PFS for glofitamab compared with BR

OS for glofitamab compared with BR

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Abbreviations; BR, bendamustine and rituximab; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression free survival

Summary of ITC informing economic model

Glofitamab less effective than axi-cel, more effective than BR and not significantly different to pola-BR

Comparator	Source	Sample sizes (after adjustment)	OS	PFS	OR rate	CR rate
Axi-cel	ZUMA-1	Glofitamab: ~34 Axi-cel: 101	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	GO29365	Glofitamab: ~[redacted] Pola-BR: ~[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	Hong et al 2018	Glofitamab: ~67.6 BR: 58	[redacted]	[redacted]	[redacted]	[redacted]

EAG: Using single-arm trials, with different data cuts of glofitamab trial brings inherent bias. Adjustments had minimal impact on results so a naive and unadjusted comparison may be relevant for decision-making

Abbreviations; axi-cel, axicabtagene ciloleucel; CR, complete remission; ITC, indirect treatment comparison; OR, overall response; PFS, progression free survival; MAIC, matching adjusted indirect comparison; Pola-BR, polatuzumab vedotin with rituximab and bendamustine; BR, bendamustine and rituximab

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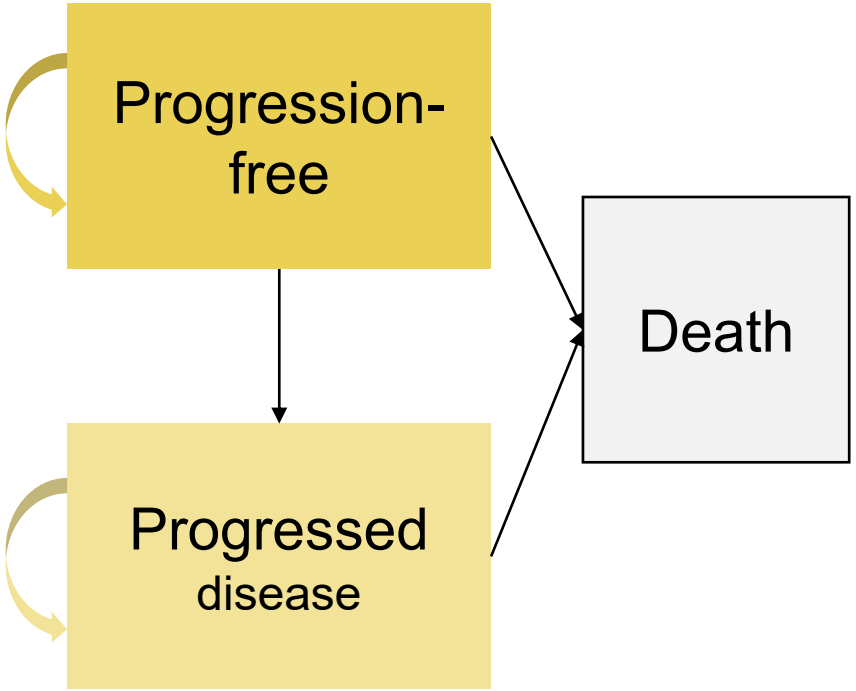
Company's model overview

Partitioned survival model

Model structure



Technology affects costs by:

- Accruing drug acquisition and administration costs
- Modifying time in each health state and related costs
- Modifying adverse events and related treatment costs

Technology affects QALYs by:

- Modifying time in each health state and related utilities
- Modifying adverse events and related disutilities

Assumptions with greatest ICER effect:

- Whether there is a cure-point
- HRQoL decrement & excess mortality after cure-point

- Efficacy informed by the PFS and OS curves generated by the MAIC
- Adverse event disutility not included in base-case explored in scenario analyses
- Assumed distribution of post-progression treatments as per NP30179 safety population. Same distribution assumed for all comparators

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Abbreviations: QALY quality adjusted life year; MAIC, matching adjusted indirect comparison; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival

Extrapolations of glofitamab (adjusted) vs. axi-cel

Axi-cel consistently more effective in extrapolation period

Background

- MAIC adjusted glofitamab (n=34) compared with unadjusted axi-cel (n=101) population

PFS and OS company base-case extrapolations with cure at 3 years

[redacted]

EAG

- Most of benefit conferred by axi-cel is during extrapolation period and data from ZUMA-1 are immature.

Abbreviations: axi-cel, axicabtagene ciloleucel; OS, overall survival; PFS, progression-free survival

Extrapolations of glofitamab (adjusted) vs pola-BR

Glofitamab outcomes slightly improved after initial period

Background

- Informed by adjusted glofitamab (n=[redacted]) and pola-BR (n=[redacted]) populations
- Pola-BR has much longer follow-up (>80 months) than glofitamab and other comparators

PFS and OS company base-case extrapolations with cure at 3 years

EAG: long-term PFS and OS extrapolations are truncated by cure assumption at 3 years. PFS curve from pola-BR trial shows beginning of a plateau from 60-62 months but number of patients still at risk is likely too small to be sure

Abbreviations: OS, overall survival; Pola-BR, polatuzumab vedotin with rituximab and bendamustine; PFS, progression-free survival

Extrapolations of glofitamab (adjusted) compared to BR

Glofitamab consistently more effective than BR

Background

- MAIC adjusted glofitamab (n=67.5) compared with unadjusted BR (n=58) population

PFS and OS company base-case extrapolations with cure at 3 years

Company: Unable to correct for all imbalances between populations

EAG: concerned with immaturity of PFS and OS observed data for BR, (3.5 years for PFS, 3 years for OS)

Abbreviations: BR, bendamustine and rituximab; OS, overall survival; PFS, progression-free survival

Key issue: Cure assumptions in all treatment arms

Assumptions have large impact on ICERs

Background

- Company base-case made two key assumptions around ‘cure’:
  - People not progressed by 2 years are ‘cured’ (no progression and 10% utility decrement compared to UK general population)
  - People still alive at 3.5 years (most people progressed have died by this time-point), return to mortality near that of UK general population: Standardised mortality rate (SMR): 1.09

EAG

- Preferred using cure time-point of 3-year for both assumptions but no cure should also be considered
- More evidence needed to support cure, utility decrement is uncertain and SMR is likely higher

Company

- Company base case adjusted for cure to be at same time-point: 3-years PFS, in line with EAG
- Provided evidence from numerous studies (including updated NP30179 trial data) to show a plateau forming for progression and survival, implying cure in people not receiving CAR-T
- 10% utility decrement reflects continued impact of former disease, is a conservative estimate

Abbreviations: CAR-T; chimeric antigen receptor T-cell therapy; ICERs; incremental cost-effectiveness ratios; PFS, progression-free survival

Cure-assumptions: Evidence of plateau after initial period (1)

Company provided evidence to show plateau forming, implying cure

Trial	Summary
NP30179 (updated)	Jan 23 data-cut: CR [redacted], 67% of which lasted 18 months
SCHOLAR-1	Retrospective study (n~600), none of whom received CAR-T
CORAL	297 people who progressed after second-line salvage therapy • 205 used as external control in comparison with JULIET
JULIET	167 people given CAR-T (tisangenlecleucel); 115 infused
ZUMA-7	Received standard of care (2-3 cycles chemotherapy followed by high-dose therapy and auto-SCT if complete or partial response) • ~44.2% received subsequent axi-cel therapy
GOYA/POLARIX	People receiving second or later-line treatment – none received CAR-T
HMRN	UK study (2004-2019) newly diagnosed DLBCL (subgroup for third-line) • [redacted]

Company: Evidence shows emergence of plateau after 1-3 years, which is maintained for subsequent years

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Abbreviations: auto-SCT, autologous stem cell transplant; CAR-T; chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; PFS, progression free survival

Cure assumptions: Evidence of plateau after initial period (2)

Company and EAG base-case

- Assumes long-term remission and survivorship after 3-years in all treatment arms

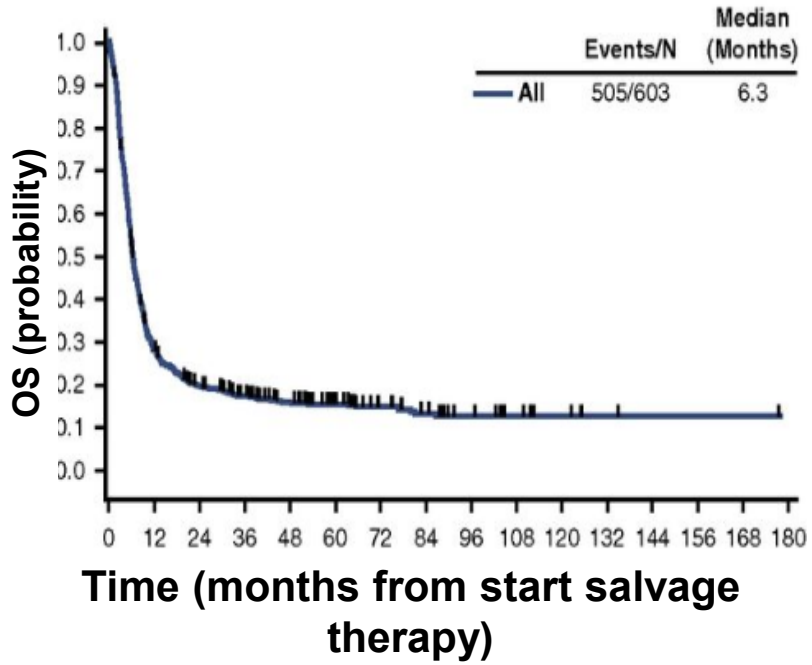
NP30179: Jan 23 data-cut OS

[redacted]

HMRN: OS from third-line therapy

[redacted]

SCHOLAR-1: OS from salvage therapy



Clinical expert: Would consider patient remaining in CR at 2 years cured; longer follow-up needed to be sure of cure proportion

EAG: unable to critique study methodology or generalisability

Company: SCHOLAR-1 shows similar plateau

Abbreviations: CR, complete response; OS, overall survival

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Is a cure plausible? For which treatments should cure be assumed?

Cure-assumptions: SMRs

SMR differs considerably between sources

SMRs after 2 years PFS in people with newly diagnosed DLBCL (updated company model applies cure-point after 3 years)

Source	Population	SMR after 2 years PFS	Comments
Mauer 2014	France (N=820)	1.09 (0.69,1.74)	**Company updated base case.** Considered SMR estimates >1.09 likely too pessimistic
	US (N=767)	1.18 (0.89, 1.57)	
Howlader 2017	SEER dataset (N=18,047)	1.41 (1.35, 1.48)	**EAG updated base case** Howlader 2017 was largest study and was considered generalisable in previous TAs
Jakobsen 2017	Denmark (N=1621)	1.27 (1.12, 1.44)	People who have CR after first line R-CHOP (or similar)

Expert: Studies suggest people remission-free 5 years after SCT have life-expectancy close to general population

Abbreviations: CR, complete remission; DLBCL; diffuse large B-cell lymphoma; PFS, progression free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; SMR, standardised mortality ratio;

Cure-assumptions: SMRs

HMRN registry suggests people with DLBCL who are progression-free after 2 years have only slightly increased mortality risk compared to general population

Background

- HMRN registry of UK patients (2004-2019)
- Newly diagnosed DLBCL

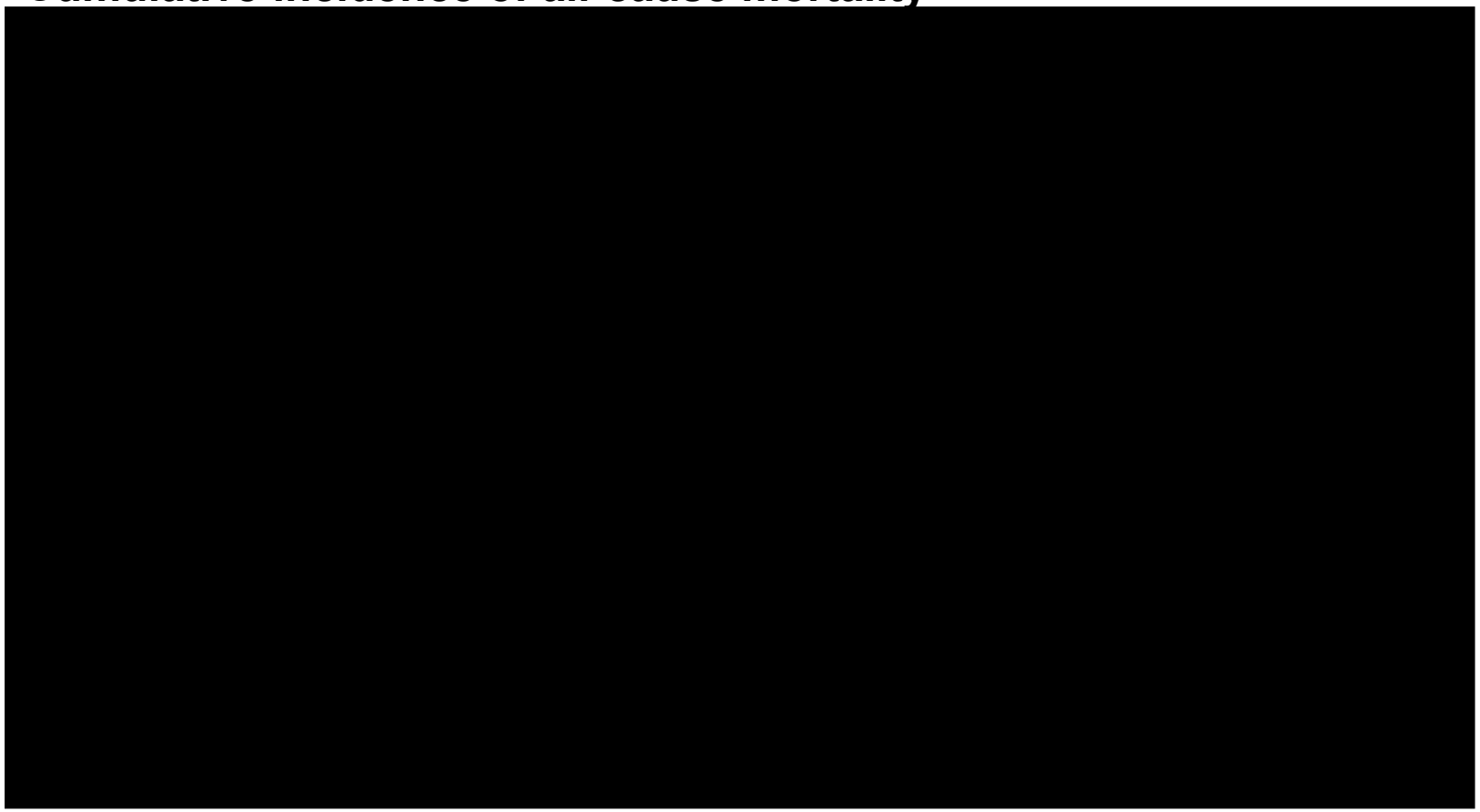
Company

- TA874 (pola-R-CHP in untreated DLBCL) assumed no excess mortality based on HMRN

EAG

- Unable to critique study's methodology and assess generalisability

Cumulative incidence of all-cause mortality



What SMR should be applied to people in long-term remission?

Abbreviations: DLBCL, diffuse large B-cell lymphoma; OS, overall survival; Pola-BR, polatuzumab vedotin with rituximab and bendamustine; SMR, standardised mortality rate

Key issue: Average age of the modelled cohort

Method has small impact on ICER

Background

- Background mortality modelled as a function of the age distribution seen in the NP30179 study, as opposed to assuming mortality corresponds to that of the mean cohort age.
- Age distribution approach only applied to all-cause mortality

EAG comments

- Prefers applying the mean cohort age of NP30179 into model
- Age-distribution approach could better account for heterogeneity in survival outcome but would also need to be applied to other outcomes (cancer-related survival, age-adjusted HRQoL) and impact in other areas (HRQoL, costs) should be considered

Company (during technical engagement)

- Expanded approach to also apply to age-adjusted distribution general population utility

Was the company's approach correctly implemented?

Abbreviations: HRQOL, health-related quality of life; ICER, incremental cost effectiveness ratio

Summary of key issues

Issue	Resolved?	ICER impact
Long-term remission/survivorship: Cure-point assumed after progression-free for 3 years • Is excess mortality of 9% appropriate? • For which treatments is a cure plausible?	For discussion	Large 
Average cohort age	For discussion	Small 
Uncertainty from indirect treatment comparison	Unresolvable uncertainty	Unknown 

Abbreviations: ICER, incremental cost effectiveness ratio

QALY weighting for severity (1)

NICE methods now include a QALY weighting system based on disease severity

Severity reflects future health lost by people living with a condition who have current standard care

Health: length and quality of life (QALYs)

QALYs people without the condition (A)

QALYs people with the condition (B)

Health lost by people with the condition: QALY shortfall

Absolute shortfall: total = A – B

Proportional shortfall: fraction = (A – B) / A

Criteria used to decide QALY weighting

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

- QALY weightings can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

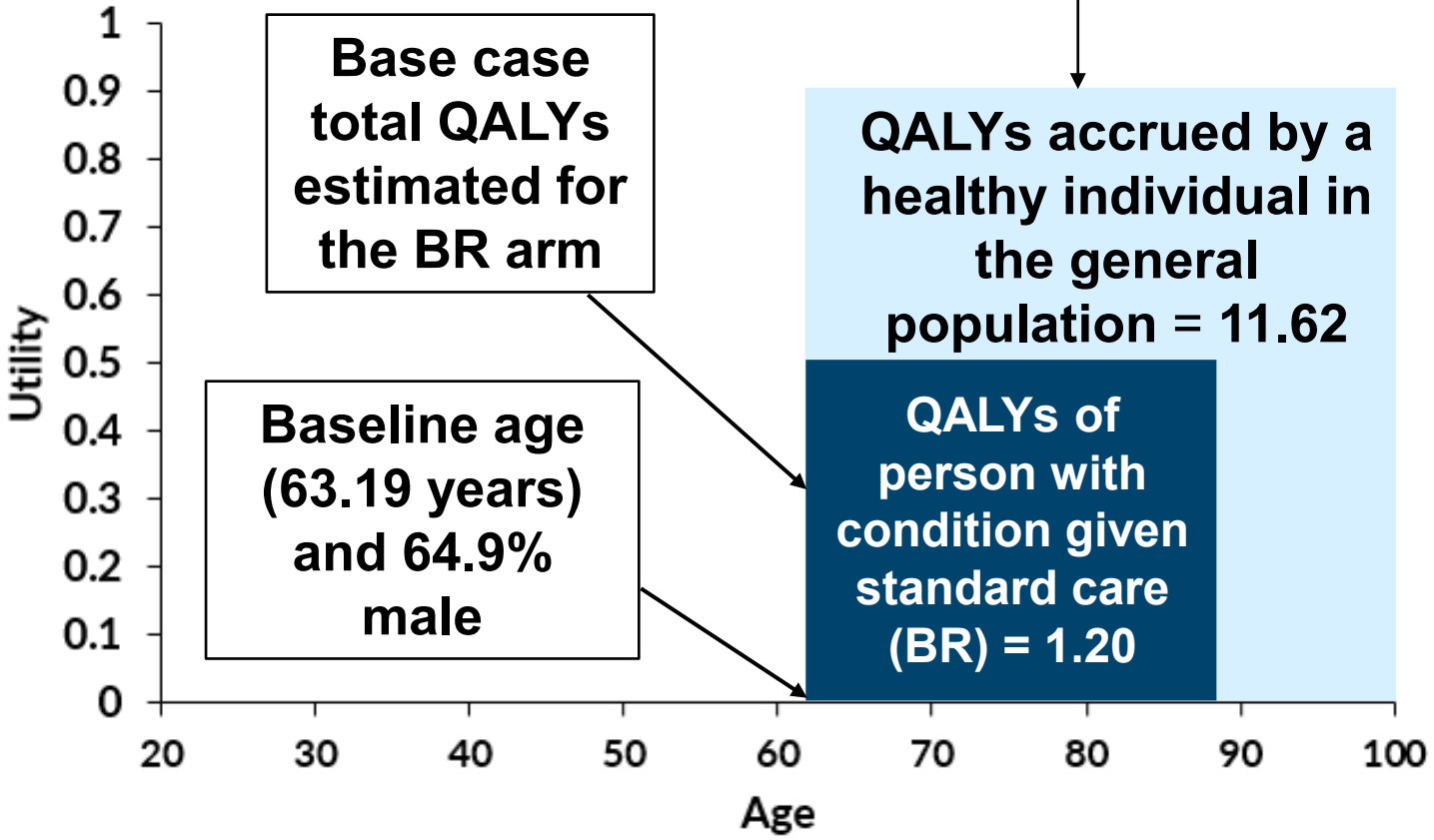
Abbreviations: QALY, quality-adjusted-life-year

QALY weighting for severity (2)

NICE methods now include a QALY weighting system based on disease severity

Example shown for BR (company base case assumptions)

Calculated using Schneider *et al.* (2021) QALY shortfall calculator



Absolute shortfall

- 11.62 – 1.20 = 10.42 (1.0x QALY weight)

Proportional shortfall

- 10.42/11.62 = 0.897 (1.2x QALY weight)

The higher weight of x1.2 was applied

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

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Abbreviations: QALY, quality-adjusted life years; BR; bendamustine and rituximab

QALY weighting for severity (3)

Severity modifier should be applied to certain treatments

QALY shortfall analysis*

Treatment	Expected total QALYS without disease	Total QALYs with condition, under current treatment	Absolute shortfall	Proportional shortfall	QALY weight
Not assuming long-term remission/survivorship (no cure)					
Axi-cel	11.62	5.03	6.59	56.71%	1
BR		0.74	10.88	93.63%	1.2
Pola-BR		1.52	10.10	86.92%	1.2
Company base-case assumptions (cure at 3 years)					
Axi-cel	11.62	4.98	6.64	57.14%	1
BR		1.20	10.42	89.67%	1.2
Pola-BR		2.63	8.99	77.36%	1

*Estimates based on company base case provided during technical engagement, EAG amended company's analysis to apply QALY weights to the total QALYs of both treatments

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: QALY, quality-adjusted life years

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Equality issues

- Company: there are barriers related to the delivery of CAR-T cell therapies, with many patients being unable, or having to travel long distances, to access therapy centres
- EAG outlines that previous appraisals for CAR-T therapies (TA567, TA559) concluded that no relevant equality issues are related to these treatments in the UK
    - Recommendations would not have a different effect on people protected by the equality legislation compared to the wider population

Innovation

- Company does not make a case for benefits not captured in the QALY calculations

Managed Access

- Company have not submitted a managed access proposal

Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Other considerations and base case assumptions
- ✓ **Summary**

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Summary of company and EAG base case assumptions

Key differences centre around cure assumption

Assumptions in company and EAG base case

Model feature	Company final base-case	EAG preferred assumptions	Key scenario analysis to consider	Effect of scenario analysis on ICER
Age	Background mortality modelled using age-distribution of NP30179	Modelled using average age of NP30179	Average age used for background mortality	Small increase (all comparisons)
Cure-point	3-year for both progression and mortality risk	Agree with changes but "no-cure" should also be considered	No cure point	Large increase (all comparisons)
SMR	1.09	1.41	1.41	Small increase (all comparisons)
Discontinuation	Based on Hong 2018	Agree with change	-	-

What are committee's preferred assumptions?

Abbreviations: ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

- Company and EAG ICERs are within the range normally considered as an effective use of NHS resources, for most scenarios, when compared with BR and pola-BR
- Scenario with no-cure has largest impact on ICER
- Glofitamab costs less than axi-cel but produces fewer QALYs

Abbreviations: axi-cel, axicabtagene ciloleucel; BR, bendamustine and rituximab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; Pola-BR, polatuzumab vedotin with rituximab and bendamustine

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Thank you.

Abbreviations

General

CI	Confidence interval	CR	Complete response
HRQoL	Health-related quality of life	ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio	IPCW	inverse probability of censoring weighting
ITT	Intention to treat	MAIC	Matching adjusted indirect comparison
OR	Overall response	OS	Overall survival
PFS	Progression-free survival	QALY	Quality-adjusted life year
TTOT	Time to off-treatment		

Treatment names

Auto-SCT	autologous stem cell transplant	Auto-SCT	autologous stem cell transplant
BR	Bendamustine and rituximab	CAR-T	chimeric antigen receptor T-cell
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