Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Part 1– ACIC information redacted

Second appraisal committee meeting

Technology appraisal committee C [06th September 2022]

Chair: Stephen O'Brien

Evidence review group: Aberdeen HTA Group

Technical team: Harsimran Sarpal, Louise Crathorne, Jasdeep Hayre

Company: Kite

NICE

Recommendation in Appraisal Consultation Document (ACD)

Axicabtagene ciloleucel is **not recommended** for treating relapsed or refractory follicular lymphoma after 3 or more systemic therapies in adults

Key changes from last meeting

Clinical effectiveness data

- Updated data from 18-month to 36-month data cut of ZUMA-5 to support extrapolations
- Post-hoc sensitivity analyses to explore subsequent treatments impact on overall survival

Company's response to address uncertainties highlighted in ACD

- Clarification on SCHOLAR-5 alignment to ZUMA-5
- Explored sensitivity analyses and other methods to adjust SCHOLAR-5 data
- Justification for utilities used in the model
- Presented a graph with modelled overall survival stratified by long-term and non-long-term survivors
- Seeking further clarity and highlighted the importance of transparency for the inclusion of NHS England CAR-T delivery tariff
- Comment on committee's end-of-life assessment to reiterate burden of disease and positioning as end-of-life care and note lack of flexibility with old methods that new methods (severity modifier) would have offered

Revised patient access scheme

- Cost of axi-cel to the NHS reduced

Abbreviations: ACD: appraisal consultation document; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor cell therapy

Axi-cel for low-grade non-Hodgkin lymphoma

- ✓ **About**
- ❑ Clinical evidence
- ❑ Points to consider:
  - Consultation responses
- ❑ End-of-life criteria
- ❑ ICERs
- ❑ Other considerations: equality; innovation; Cancer Drugs Fund

NICE National Institute for Health and Care Excellence

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio

Axicabtagene ciloleucel (Yescarta, Kite Pharma/Gilead)

Table 1 Technology details

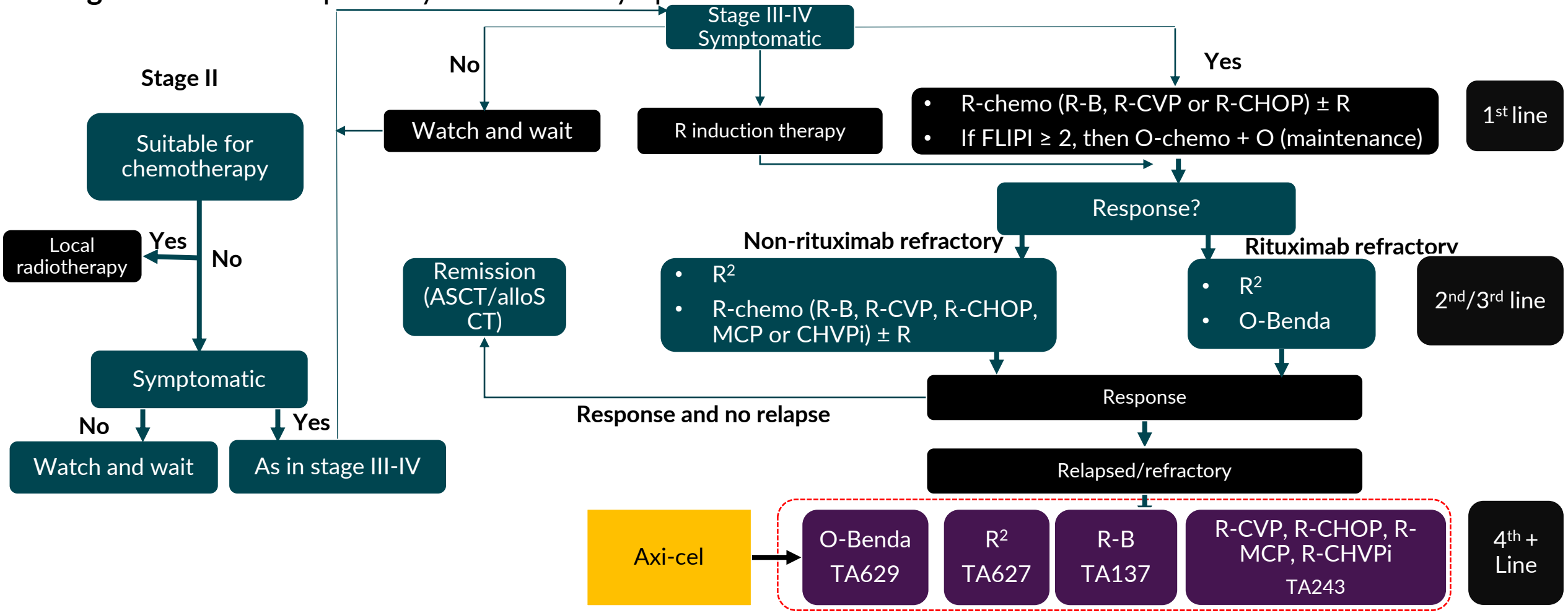
Marketing authorisation	• Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after three or more lines of systemic therapy
Mechanism of action	• Axicabtagene ciloleucel is an autologous anti-CD19 CAR-T cell product that recognises and eliminates all CD19 expressing target cells, including B-cell malignancies and normal B-cells
Administration	• Intravenous infusion: 2 x 10^6 CAR-positive viable T-cells per kg of body weight (range: 1 x 10^6 to 2 x 10^6, or maximum of 2 x 10^8 CAR-positive viable T-cells for patients who are 100 kg and above) in approximately 68 mL dispersion
Price	• List price: £280,451 per treatment • Patient access scheme discount in place (confidential) per treatment including leukapheresis, bridging therapy, conditioning chemotherapy, acquisition and infusion and monitoring hospitalisation costs

Source: Table 2, CS

Abbreviations: CAR-T: chimeric antigen receptor cell therapy; CD19: cluster of differentiation 19; CRS: cytokine release syndrome

Treatment pathway and proposed positioning

Figure 1 Treatment pathway for follicular lymphoma



Which are the most appropriate comparators for axi-cel?

Notes: *Includes rechallenging with second/third line therapies based on response

Source: Figure 3, CS

Abbreviations: alloSCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplant; Benda: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi: cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP: cyclophosphamide, vincristine and prednisolone; FLIPI: Follicular Lymphoma International Prognostic Index; MCP: mitoxantrone, chlorambucil and prednisolone; O: obinutuzumab; R: rituximab; R-B: rituximab with bendamustine; R2: lenalidomide with rituximab

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Key clinical trials: ZUMA-5

Table 2 Clinical trial design and outcomes

	ZUMA-5
Design	Phase II, multicentre, single-arm, open-label
Population	People with relapsed/refractory B-cell iNHL of FL or MZL histological subtypes who have received 2 or more prior lines of therapy
Intervention	Axi-cel
Comparator(s)	Not applicable
Primary outcome	ORR (not relevant for this appraisal)
Key secondary outcomes	CR, ORR, DOR, PFS, OS and safety assessments (AEs and clinically significant changes in laboratory values)
Locations	19 centres in France and US
Used in model?	CR, ORR, DOR, PFS, OS and safety assessments (AEs and clinically significant changes in laboratory values)

Abbreviations: AEs: adverse events; axi-cel: axicabtagene ciloleucel; CR: complete response; DOR: duration of response; FL: follicular lymphoma; iNHL: indolent non-Hodgkin lymphoma; mITT: modified intention-to-treat; MZL: marginal zone lymphoma; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

Source: Table 6, CS

ZUMA-5: Progression-free and overall survival

Table 3 PFS and OS

	mITT: 3+ prior therapies [redacted]	IAS: 3+ prior therapies [redacted]	FAS: 3+ prior therapies[a] (N=75)
Data cut	[redacted]	[redacted]	[redacted]
Progression-free survival			
Median 95% CI PFS	[redacted]	[redacted]	[redacted]
Median follow-up months	[redacted]	[redacted]	-
Progression/death n (%)	[redacted]	[redacted]	-
Estimated PFS rate at Month 12 (95% CI)	[redacted]	[redacted]	-
Estimated PFS rate at Month 18 (95% CI)	[redacted]	[redacted]	-
Overall survival			
Death from any cause, n (%)	[redacted]	[redacted]	-
KM median (95% CI) OS time months	[redacted]	[redacted]	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]	[redacted]	-
Estimated OS rate at Month 12 (95% CI)	[redacted]	[redacted]	-
Estimated OS rate at Month 18 (95% CI)	[redacted]	[redacted]	-

[a]For 5 of the 80 patients enrolled (locally diagnosed FL, a central laboratory assessment did not confirm a diagnosis of FL

Abbreviations: CI: confidence interval; IAS: inferential analysis set; KM: Kaplan-Meier; mITT: modified intention-to-treat; NE: not evaluable; OS: overall survival; PFS: progression free survival

Source: Table 10 ERG report, Section 2.6.2.6 CS, Company ACD response

SCHOLAR- 5*: external cohort (comparative evidence)

- SCHOLAR-5 was a multicentre, external control cohort study designed to provide comparative evidence for axi-cel in people with relapsed or refractory follicular lymphoma meeting ZUMA-5 eligibility criteria
- SCHOLAR-5 was also designed to help characterise the natural history of follicular lymphoma and current treatment patterns to provide comparative data for ZUMA-5
- SCHOLAR-5 cohorts were created from multiple data sources

Table 4 SCHOLAR-5 data sources

Cohort	Description
Cohort A (IQVIA)	Retrospective cohort created from electronic medical records of six sites, including university hospitals and cancer centres with two sites based in the UK and other sites based in France, Spain, Portugal and the US
Cohort B (VUMC SD)	Retrospective cohort created from the Vanderbilt University Medical Center's Synthetic Derivative: a fully de-identified database derivative of electronic medical records from the university
Cohort C (DELTA)	Prospective cohort created from an open-label phase II study, DELTA, that enrolled patients with relapsed/refractory follicular lymphoma who had not responded to or were refractory to rituximab and an alkylating agent and were treated with idelalisib

 Abbreviations: axi-cel: axicabtagene ciloleucel

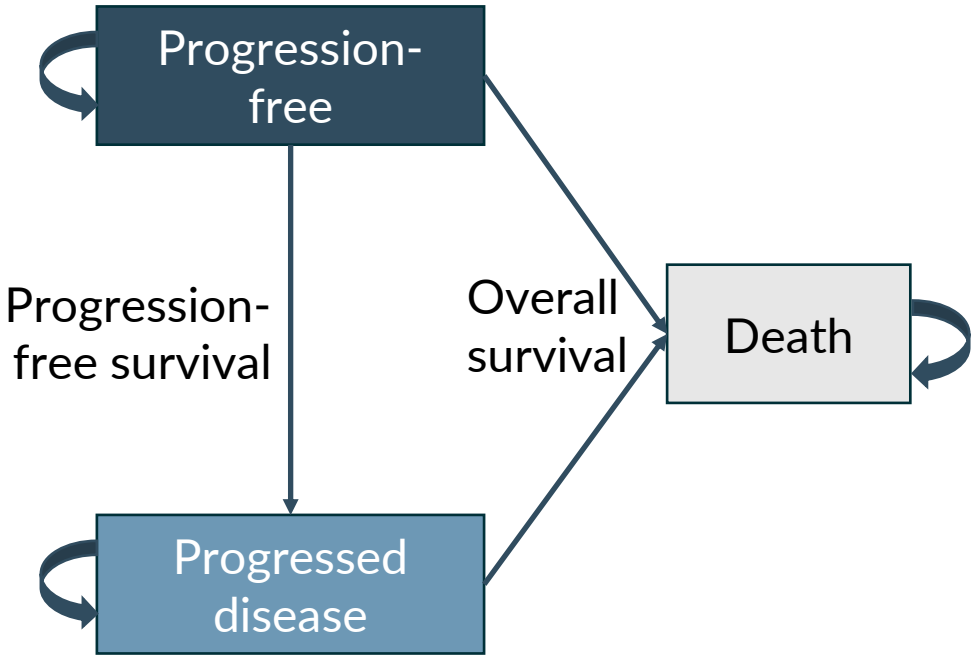
* Funded by Kite Pharma/Gilead

Source: Section B.2.9.1, CS

Company's model overview

A three-state partitioned survival model was used

Figure 2 Model structure



- **Axicabtagene affects costs by:**
  - Having higher acquisition costs
  - Delaying or preventing progression of disease
  - Higher modelled rate of adverse events
  - Longer survival time in pre and post progression states
- **Axicabtagene affects QALYs by:**
  - Delaying or preventing progression of disease
  - Increasing overall survival
- **Assumptions with greatest ICER effect:**
  - Parametric curve selection for OS in the technology and comparator arm of the model
  - Proportion of long-term survivors
  - OS extrapolation assumptions applied to axicabtagene-ciloleucel long-term survivors and non-long-term survivors
  - Capping of time on treatment for comparator therapies on overall survival rather than progression free survival

 Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life-year

ACD conclusions and uncertainties

	Committee conclusion	Discuss?	ACD
Treatment pathway	• Axi-cel's positioning appropriate	No	3.3
	• Blended comparator suitable for this appraisal	No	3.4
Clinical evidence	• ZUMA-5 generalisable to NHS clinical practice	No	3.5
	• Axi-cel likely to be effective but benefit uncertain	Yes	3.6
Comparator data	• SCHOLAR-5 study was acceptable to inform comparative • effectiveness	No	3.7
SCHOLAR-5 alignment to NHS	• SCHOLAR-5 population is not fully aligned with the ZUMA-5 population	Yes	3.8
Adjusting for SCHOLAR-5 data	• Approach was uncertain: explore other methods in detail or address uncertainties of unanchored indirect comparison	Yes	3.9
Model structure	• Appropriate for decision making	No	3.10
Extrapolation OS/PFS	• OS and PFS extrapolations for standard care were uncertain	Yes	3.11

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

ACD conclusions and uncertainties

	Committee conclusion	Discuss?	ACD
Long-term survivor assumption	• Uncertain if the company's long-term survival assumptions were appropriate	Yes	3.12
Utility values	• ERG's approach of using a utility decrement for long-term survivors was more appropriate	Yes	3.13
Time on treatment	• Time on treatment uncertain with comparator therapies	No	3.14
NHS tariff cost	• NHS tariff estimate is the best source available to inform cost that NHS is currently paying	Yes	3.15
End-of-life	• Axi-cel not considered a life-extending treatment at end of life	Yes	3.16
Cost-effectiveness estimates	• Not cost effective – ICER should be between £20-£30K • Cancer Drug Fund- criteria not met	Yes	3.17-3.18

Abbreviations: axi-cel: axicabtabgene ciloleucel; ICER: incremental-cost effectiveness ratio

Axi-cel for low-grade non-Hodgkin lymphoma

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- ✓ **Consultation responses**
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Consultation responses

Comments received from

- **Kite/Gilead (company)**
- **Royal College of Physicians**

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Key issue: Survival data are immature and uncertain (1)

ACD

- Committee concluded that axi-cel likely to clinical effective but immature survival data, inclusion of subsequent therapies and lack of comparator data mean the size of this benefit is uncertain

Company

- Agreed with the committee that survival data are immature and uncertain: highlighted that axi-cel is suitable for Cancer Drug Fund while further evidence is collected
- Evidence indicates that 43% people treated with CAR-T therapies remain progression-free at five years suggesting company estimate of [redacted] remain progression-free at 5 years following axi-cel is conservative
- Provided updated 36-month data cut of ZUMA-5: showing OS curve plateau at [redacted] survival after 3 years aligns with [redacted] overall survival at 5 years estimated from survival modelling for axi-cel
- Median OS is [redacted] and median PFS is [redacted] vs OS [redacted] and [redacted] for SCHOLAR-5
- Post-hoc analyses indicate that subsequent allo-SCT does not have a positive impact on OS: censoring at time of allo-SCT in 24-month overall rate estimate of [redacted] vs. without censoring [redacted]

ERG comments

- 43% progression free at 5 years estimate is uncertain as it is based on small number of people at risk, with PFS outcomes affected by censoring and only 6 people were at risk from 3 years
- Noted slight difference in number at risk at time zero in updated analyses FAS [redacted] vs. mITT [redacted]

NICE

Abbreviations: : alloSCT: allogeneic stem cell transplantation; axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor cell therapy; FAS: full analyses set; NE: not evaluable; FL: follicular lymphoma; OS: overall survival; PFS: progression free survival

Key issue: Survival data are immature and uncertain (2)

Figures 3 and 4 Kaplan-Meier (KM) plots of PFS and OS (IAS)

ERG comments

- KM estimates from ZUMA-5 aligns with extrapolations out to five years but PFS slightly underestimated
- Noted curves flattening from 3 years but data was heavily affected by censoring, making projections uncertain
- Consider data is immature and 24 months are too early to determine if allo-SCT following CAR-T therapy had a positive impact on OS
- If allo-SCT used in practice following CAR-T therapies its costs should also be included
- Unclear what % of relevant cohort had SCT following axi-cel and in SCHOLAR-5

Abbreviations; NE: not evaluable; FL: follicular lymphoma; IAS: inferential analysis set; OS: overall survival; PFS: progression free survival

Key issue: SCHOLAR-5 population alignment to ZUMA-5

ACD

- Committee concluded that SCHOLAR-5 population is not fully aligned with the ZUMA-5 population

Company

- Non-alignment of SCHOLAR-5 and ZUMA-5 due to inclusion of DELTA cohort which was resolved at technical engagement by removing DELTA cohort
- Removing DELTA favoured axi-cel because people in DELTA lived longer than people who received standard of care more aligned to NHS England current practice

ERG comments

- Agreed with the company and reiterated that DELTA cohort was used in SCHOLAR-5 overall survival analysis from the time of progression on idelalisib not from initiation of idelalisib
- DELTA overall survival outcomes ungeneralisable to NHS England were less clear than ERG's original views
- Consider inclusion of DELTA cohort still provides a useful scenario analysis given the uncertainty around overall survival outcomes

 Abbreviations: axi-cel: axicabtagene ciloleucel

Key issue: Company approach to adjusting SCHOLAR-5 data

ACD

- Committee concluded that the company's approach and use of the propensity score weighting method was highly uncertain. It would like to see other methods explored or uncertainties resolved

Company

- Statistical analysis plan for SCHOLAR-5 followed NICE TSD 17 and 18 guidelines
- Acknowledged propensity score weighting should adjust for all treatment effect modifiers and prognostic variables but has to be balanced with sample size
- Given limited patient numbers in SCHOLAR-5 it was considered appropriate to focus on identification and inclusion of covariates which strongly correlated with outcomes
- Conduced sensitivity analyses using propensity score matching methods, inverse probability treatment weighting. Explored other methods including G-estimation and the E value
- All methods favoured axi-cel and were consistent with company's original base case

ERG comments

- Challenging to estimate comparative effectiveness from real world data due to small sample size meaning that not all prognostic and effect modifying variables can be adjusted for
- Follicular lymphoma subtype was not included in propensity score: more lower grade subtypes in SCHOLAR-5 than in ZUMA-5 and failure to adjust may bias in favour of current 4L+ care
- Noted there will be substantial uncertainty around relative and absolute survival benefit regardless of method used
- Consider approach to extrapolation of weighted Kaplan-Meier data for current 4L+ care and inclusion/exclusion of DELTA cohort contribute to substantial uncertainty for long-term survival for current 4L+ care in NHS

Abbreviations: axi-cel: axicabtagene ciloleucel; TSD: technical support document: 4L+: fourth line plus treatment

Key issue: Utilities used in the model

ACD

- Committee concluded that the ERG's approach of using a utility decrement for long-term survivors who experience elevated mortality risk was more appropriate
- It would consider the scenarios presented in its decision making

Company

- Committee has not followed precedent regarding the rebound to general population utility after achieving long-term survival
- Assumption was applied and accepted by the committee consistently in previous appraisals where long-term survival is modelled (TA559)

ERG comments

- Acknowledged company's concern and highlighted provided scenario using progression free utility for long-term survivors which had a minimal impact on incremental cost-effectiveness ratio (ICER)

	Base case assumption	Scenario analysis
TA559	2 yrs PFS assumed to be in long-term remission and have equal utility values as the age and gender matched general population after this point. • Maurer et al. (2014) → DLBCL patients who were disease-free at 24 months, there was no significant difference in subsequent survival compared with that for the general population	In scenario analyses, a percentage decrement to the age and gender matched general population utility values are applied.

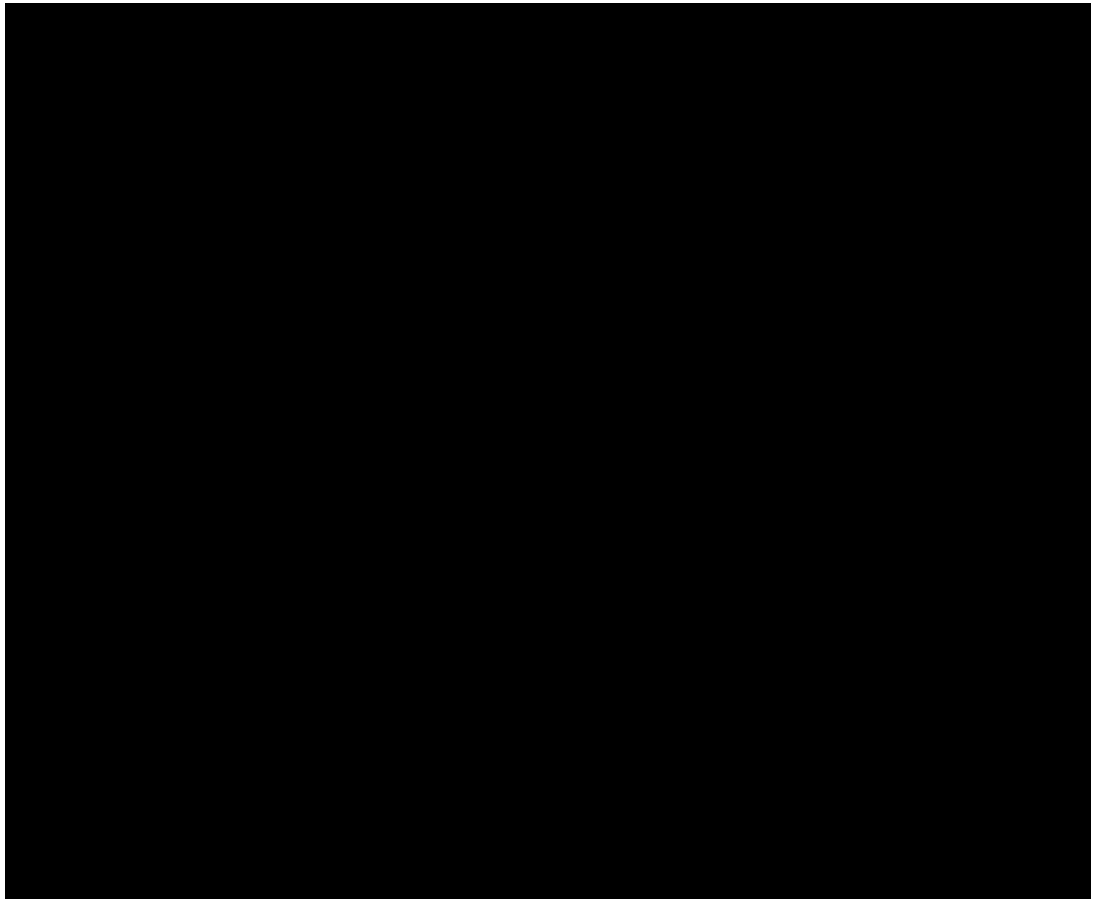
Is it appropriate to assume long-term survivors can achieve utilities in line with general population?

Abbreviations: DLBCL, diffuse large B-cell lymphoma; PFS, progression free survival; TA: technology appraisal

Key issue: Long-term survivor predictions (1)

ACD

- Committee concluded that based on the immature survival data from ZUMA-5 and uncertainties in SCHOLAR-5 data, it was uncertain company's long-term survival assumptions were appropriate



Figures 5 OS extrapolations stratified by long-term and non-long-term survivors

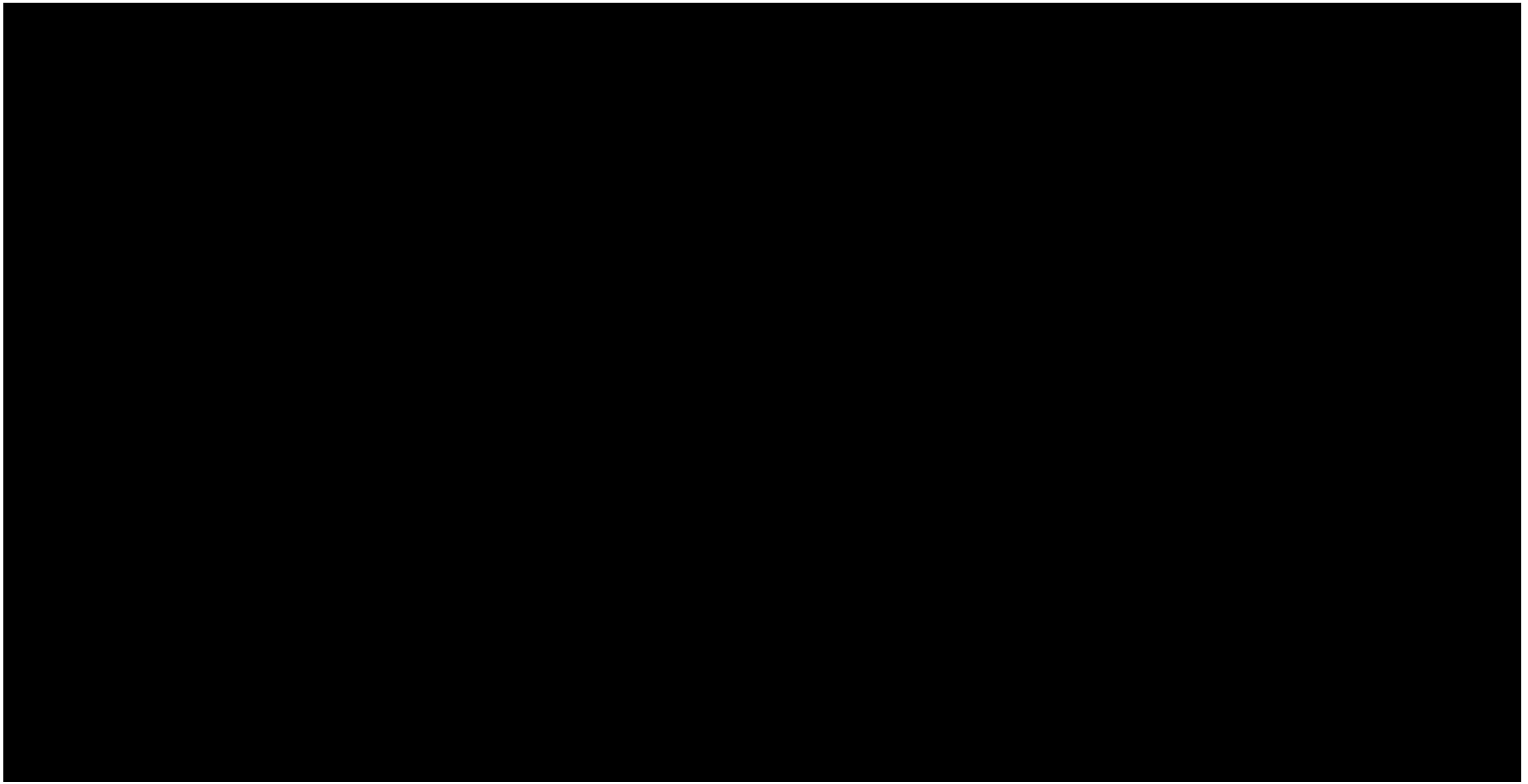
Company

- Presented a graph with overall survival stratified by long-term survivor (LTS) and non-long-term survivors (NLTS)

ERG comments

- Noted hazard of death remained lower in NLTS than current 4L+ care over survival duration
- Weibull extrapolated hazard of mortality for NLTS, tends to the SMR adjusted general population mortality of LTS by 25 years but is adjusted to remain 1.2 times higher
- Explored increases to adjustment factor applied to curve to 1.5 and 2
- Implemented a more pessimistic scenario using generalised gamma curve for extrapolation of axi-cel OS but on without upward adjustment of extrapolated mortality for NLTS:
- Predicting a steeper OS curve for NLTS with cycle specific mortality of exceeding current 4L+ care from 11.3 years

Key issue: Long term survivor predictions (2)



Key issue: Inclusion of NHS England CAR-T delivery tariff (1)

ACD

- Committee concluded that tariff estimate was best available source to inform the cost that NHS is paying currently (£96,016 [cost year 2021/2022])

Company

- Concerned about inclusion of NHS England CAR-T delivery tariff in terms of fair and transparent procedure and resultant impact on access to CAR-T therapies in England
- Company followed NICE recommended methods including systematic identification of relevant evidence and clinical validation. NICE must consider what the true cost of the treatment to the NHS in line with methods guide
- Highlighted that transparency is required on methods used to derive the tariff cost or evidence used to substantiate the value to the NHS tariff
- NHS tariff was not considered for TA677 in final decision: if adopted for axi-cel should be justified by clear reasoning
- Due to lack of transparency, uncertainties, opinion from clinicians and approach followed in previous appraisals of CAR-T therapies: recommendation based on NHS tariff would clearly be procedurally unfair and unreasonable

NHS England CAR-T tariff (2)

NHS England communication to NICE

The CAR-T tariff was developed by a CAR-T Finance Working Group in 2018

- Designed to cover all costs of care from point of identification through to 100 days post infusion but excludes the following:
  - CAR-T product itself
  - Any associated chemotherapy drugs and treatment costs
  - Any other high-cost tariff excluded drugs
  - Any intensive care needs
- CAR-T products are funded on a pass-through basis, currently by the Cancer Drug Fund
- Rest of exclusions fall under the standard specialised commissioning contractual arrangements
- Tariff is uplifted each year (£97,598 for 2022/23 [1.7% increase]) in line with National Tariff Payment system and remains under review

Abbreviations: CAR-T: chimeric antigen receptor cell therapy

Key issue: Inclusion of NHS England CAR-T delivery tariff (3)

Royal College of Physicians

- Concerned about the use of NHS tariff instead of NHS costing tool
- Noted NHS tariff was not considered in TA677
- Highlighted that previous CAR-T therapies have been approved using estimated cost NHS costing tool
- Any change in calculating delivery cost would be inconsistent and will disadvantage current and future CAR-T funding applications

ERG comments

- Agreed with the company that further clarity on the derivation of the tariff cost was needed and a detailed costing study as suggested by the company could be beneficial
- Considered company's approach to calculate costs based on malignant lymphoma may have underestimated full economic cost of the infusion and monitoring admission
- Clinical experts to ERG: delivery of CAR-T therapies requires increased staffing and infrastructure compared to other malignant lymphoma which may not have been captured adequately
- Not clear if increased staffing and infrastructure could explain the large difference between company's cost calculation and the tariff price [redacted] vs. £96,016 [year 2021/2022])
- Company's cost analysis using length of stay data for people receiving CAR-T therapy in real world setting (including UK) aligns with its calculation based on ZUMA-5
- Explored in scenario analyses

 Abbreviations: CAR-T: chimeric antigen receptor cell therapy; TA: technology appraisal

Axi-cel for low-grade non-Hodgkin lymphoma

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- ✓ **End-of-life criteria**
- ❑ ICERs
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End-of-life criteria

Table 5 End-of-life

Criterion 1 – treatment is indicated for patients with a short life expectancy (normally less than 24 months)	**Company:** current care survival estimates from SCHOLAR-5: median is [redacted] months ERG: mean life expectancy of [redacted] in the current 4L+ care arm	Not met?
Criterion 2 – sufficient evidence to indicate that treatment offers an extension to life (normally at least an additional 3 months) compared to current NHS treatment	Model output suggests incremental life year gain of [redacted] years	Met?

Company

- Clinicians will adopt axi-cel for people with lower life expectancy at 4L+ positioning as an end-of-life treatment in NHS England

Abbreviations: axi-cel: axicabtagene ciloleucel

End-of-life criteria

ACD

- Committee concluded that axi-cel does not meet the criteria to be a life-extending treatment at end-of-life

Company

- Accepted current survival for people treated with best support care is marginally greater than 24 months
- Axi-cel would be adopted by clinicians as end-of-life therapy in England when other treatments are no longer effective in people with shorter life expectancy
- Considered revised NICE methods may have provided greater flexibility in considered of end-of-life and suggested that severity modifier >1 would be applicable

Royal College of Physicians

- Average life expectancy between 30-36 months based on SCHOLAR-5 is an overestimate due to data collected from large academic centres which may included fitter and healthier people
- Estimate average life expectancy around 2 years or even less

ERG comments

- Heterogeneity in life-expectancy of this population: no case made for people with shorter life-expectancy
- Based on clinical advice to the ERG, axi-cel would be used for people within r/r 4L+ follicular lymphoma but based on SCHOLAR-5 data, it does not meet end of life criteria
- Acknowledged revised NICE methods would have provided greater flexibility in the consideration of end-of-life but suggested that severity modifier >1 would not be applicable

 Abbreviations: axi-cel: axicabtagene ciloleucel; r/r: relapsed or refractory; QALY: quality-adjusted life year

Axi-cel for low-grade non-Hodgkin lymphoma

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- ✓ **ICERs**
- ❑ Other considerations: Equality; innovation: Cancer Drugs Fund

NICE National Institute for Health and Care Excellence

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio

Summary of company's revised base case

Table 6 Assumptions in company's revised base case

Assumption		Company base case	Changed post ACD?
PFS extrapolation	4L+	Exponential	No change
	Axi-cel	Weibull	
OS extrapolation	4L+	Gamma	
	Axi-cel	Weibull	
Long-term survivor proportion (after axi-cel treatment)		25%	
Long-term survivor SMR		1.09	
Long-term survivorship time point		5 years	
Health related utility values source		Wild et al	
Patient access discount		Confidential	Increased

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival; PFS: progression-free survival; SMR: standardised mortality ratio

Company revised deterministic and probabilistic base case

Table 7 Company deterministic incremental base-case results

Technology	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company revised base case			
Current 4L+ care	[redacted]	[redacted]	£40,584
Axi-cel			

Table 8 Company probabilistic incremental base-case results

Technology	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company revised base case			
Current 4L+ care	[redacted]	[redacted]	£42,291
Axi-cel			

Note: Results do not include confidential commercial discounts for comparators

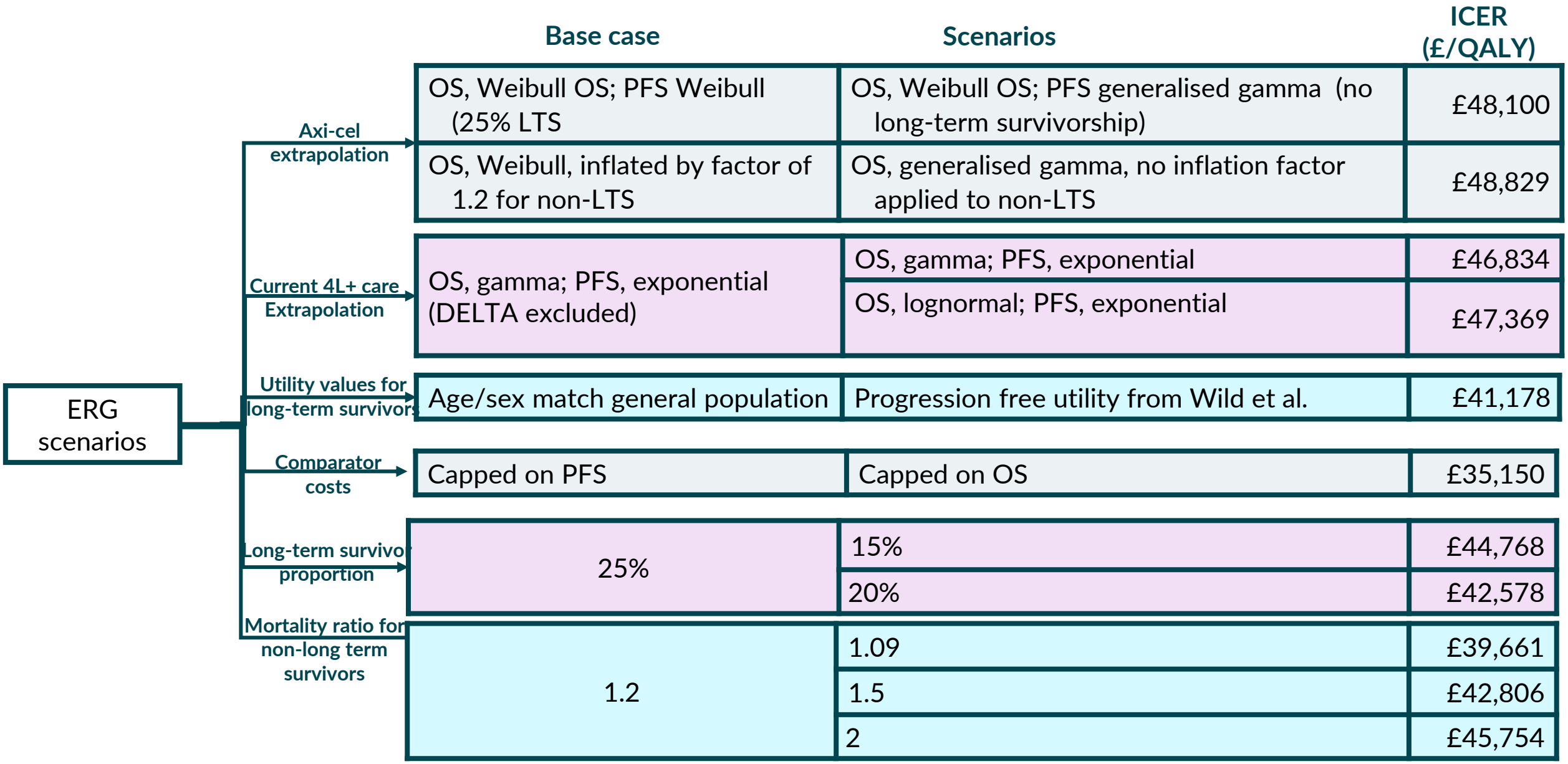
Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio: PAS: patient access scheme; QALY: quality-adjusted life year

Company scenario analyses

	Base case	Scenarios	ICER (£/QALY)
Company scenarios → OS extrapolations	Current 4L+ care: gamma :Axi-cel: Weibull	Current 4L+ care, gamma; Axi-cel, log-logistic	£35,549
		Current 4L+ care, Weibull; Axi-cel, Weibull	£41,198
Company scenarios → Long-term survivorship	25%	[redacted] of treated patients (i.e. all in PFS at 5 years)	£37,865
		10% of treated patients	£47,185
Company scenarios → Long-term survivorship SMR	1.09	1.00	£40,151
		1.20	£41,090
Company scenarios → Long-term survivorship time	5 years	2 years	£37,695
		10 years	£42,491
Company scenarios → Health state utilities source	Progression-free and progressed disease (Wild et al)	Progression-free, general population (TA627) Progressed, general population with AUGMENT decrement (TA627)	£39,676
		GADOLIN	£40,117
		AUGMENT, R^2	£39,238
		AUGMENT, R-mono	£39,414
Company scenarios → Utility value for alive and progression-free beyond-5 years	General population	Adjusted general population utility (98.6%)	£40,879

Abbreviations: axi-cel: axicabtagene ciloleucel; ; ICER: incremental-cost effectiveness ratio; OS: overall survival; PFS: progression-free survival; R^2: lenalidomide with rituximab; R-mono: rituximab monotherapy; SMR; standardised mortality ratio; QALY: quality-adjusted life year: TA: technology appraisal

ERG scenario analyses around revised company base case



	Base case	Scenarios	ICER (£/QALY)
Axi-cel extrapolation	OS, Weibull OS; PFS Weibull (25% LTS	OS, Weibull OS; PFS generalised gamma (no long-term survivorship)	£48,100
	OS, Weibull, inflated by factor of 1.2 for non-LTS	OS, generalised gamma, no inflation factor applied to non-LTS	£48,829
Current 4L+ care Extrapolation	OS, gamma; PFS, exponential (DELTA excluded)	OS, gamma; PFS, exponential	£46,834
		OS, lognormal; PFS, exponential	£47,369
Utility values for long-term survivors	Age/sex match general population	Progression free utility from Wild et al.	£41,178
Comparator costs	Capped on PFS	Capped on OS	£35,150
Long-term survivor proportion	25%	15%	£44,768
		20%	£42,578
Mortality ratio for non-long term survivors	1.2	1.09	£39,661
		1.5	£42,806
		2	£45,754

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival; PFS: progression-free survival; ICER: incremental-cost effectiveness ratio; QALY: quality-adjusted life year

ERG scenario analyses around NHS tariff

ERG scenarios →

Base case	Scenarios	ICER (£/QALY)
[redacted]	[redacted] increase (£16,569.38)	£41,306
	[redacted] increase (£19,915.65)	£42,028
	[redacted] increase (£26,554.51)	£43,472
	[redacted] increase (£96,016 [year 2021/2022]))	£58,582

- Increase in the cost of admission increases the ICER for axi-cel upwards

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental-cost effectiveness ratio; QALY: quality-adjusted life year

Axi-cel for low-grade non-Hodgkin lymphoma

- ❑ About
- ❑ **Clinical evidence**
- ❑ **Points to consider:**
- ❑ **Consultation responses**
- ❑ End-of-life criteria
- ✓ **ICERs**
- ✓ **Other considerations: equality; innovation: Cancer Drugs Fund**

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Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost-effectiveness ratio

Other considerations

Equality

- There are no known equality issues relating to the use of axi-cel in people with relapsed/refractory non-Hodgkin lymphoma

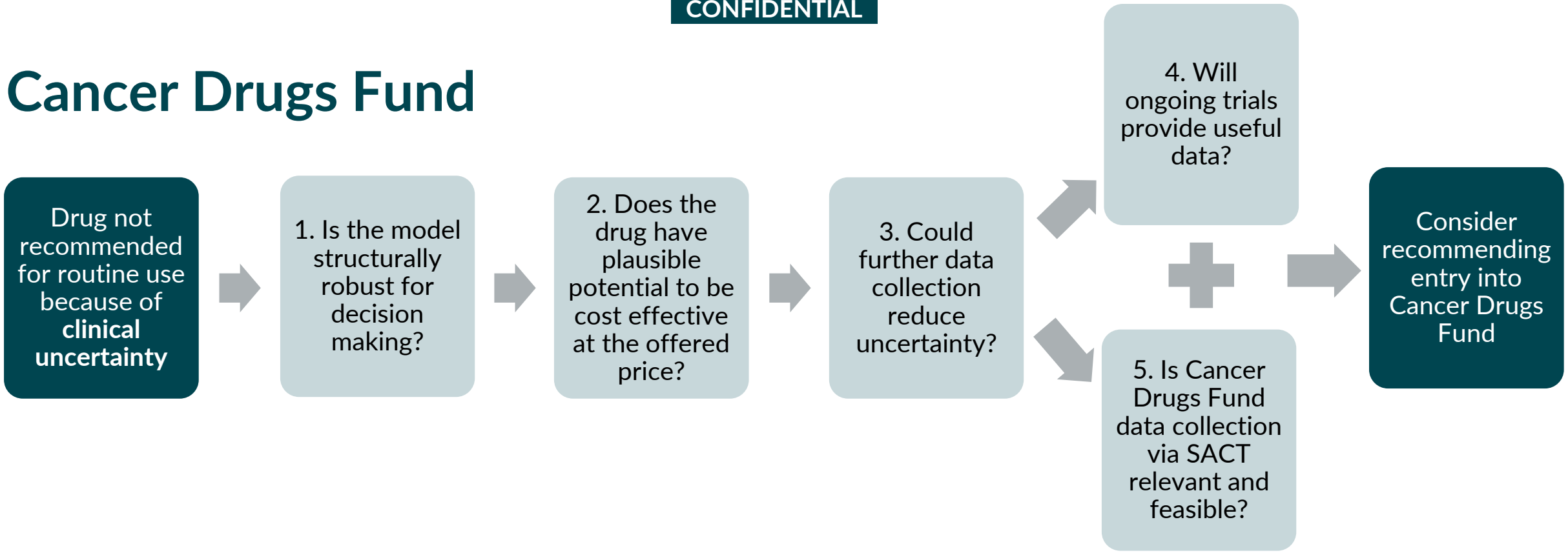
Innovation

Company considers axi-cel to be innovative:

- Offers a significant extension to life expectancy: difference axi-cel could make to lives is difficult to capture in QALY calculation
- Single CAR-T infusion versus recurrent cyclic nature of conventional treatments
- Innovation of axi-cel has been previously recognised by NHS England and NICE in diffuse large B-cell lymphoma: similar step change could be achieved with the introduction of axi-cel to follicular lymphoma pathway

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor cell therapy: QALY: quality-adjusted life year

Cancer Drugs Fund



- Company: axi-cel is a suitable candidate for the CDF: [redacted]
- Would the issues discussed be resolved through further data collection?

Is axi-cel a candidate for the CDF?

 Abbreviations: axi-cel: axicabtagene ciloleucel; CDF: Cancer Drugs Fund; RCT: randomised controlled trial

Axi-cel: ZUMA-5 overall survival

Figures 10 Axi-cel ZUMA-5 overall survival (18 months, provisional 36 months, applied model extrapolation)

Abbreviations: axi-cel: axicabtagene ciloleucel; OS: overall survival; KM: Kaplan-Meier

ZUMA-22

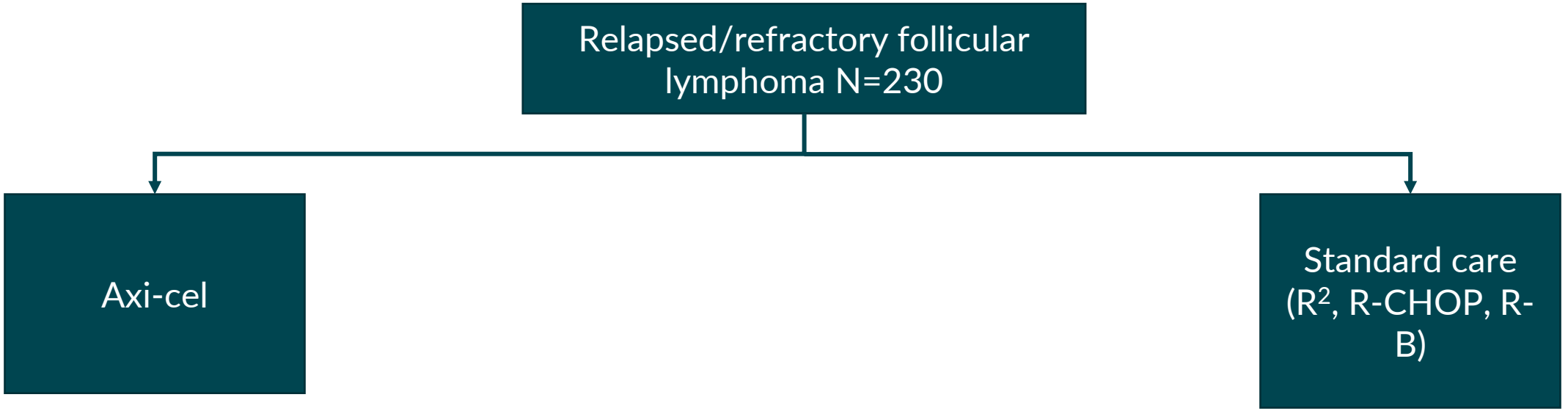


Table 9 ZUMA-22 study details

ZUMA-22	Description
Design	Randomised, parallel assignment, open-label
Population	N=230, relapsed refractory follicular lymphoma • after first-line chemoimmunotherapy and high-risk disease with relapse or progression within 24 months or • Relapsed or refractory disease after ≥ 2 prior systemic lines of therapy
Start date	• July 2022
Primary completion	• April 2027

Abbreviations: axi-cel: axicabtagene ciloleucel; R-B: rituximab with bendamustine; R2: lenalidomide with rituximab; R: CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone

Source: clinicaltrials.gov

NICE National Institute for Health and Care Excellence

Thank you.