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

Part 1– ACIC information redacted

Technology appraisal committee C [05th July 2022]

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NICE

Axi-cel for low-grade non-Hodgkin lymphoma

- ✓ **About**
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Points to consider (5)
  - 2 with large impact on ICER
  - 3 with small impact on ICER
- ❑ End-of-life criteria
- ❑ ICERs
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ❑ Summary

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

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Experts
Dr. Graham Collins (Oxford University Hospital NHS Foundation Trust)
Dr. Tobias Menne (The Newcastle upon Tyne Hospitals)

Organisation: Lymphoma Action

Low-grade non-Hodgkin lymphoma

Epidemiology

- Around 2,200 each year in the UK
- ~220 (10%) receive at least four lines of therapy (198 in England and Wales)

Diagnosis and classification

- Various grading and staging systems are used for follicular lymphoma (WHO/REAL, Cotswolds modified Ann Arbor and FLIPI score)

Symptoms and prognosis

- Lymph nodes, night sweats, fatigue, fever and weight loss
- Restricted movement, disfigurement, discomfort
- May develop anaemia, low white cell count & platelets
- Prognosis with 4L + relapsed/refractory is poor with no established standard of care

Abbreviations: FLIPI: Follicular Lymphoma International Prognostic Index; REAL: Revised European-American Lymphoma WHO: World Health Organisation

Patient experts' perspectives – Lymphoma Action

Unmet need for curative treatment with fewer side effects

Living with low-grade NHL

- Has a profound and devastating impact on all aspects of person's life
- Severity is wide ranging: from few symptoms to a wide variety
- Low grade disease can transform into a high-grade lymphoma

Limited options for people with relapsed/refractory follicular lymphoma

- No effective treatment available at relapse
- People feel dissatisfied with current treatments
- Side effects mentally and physically challenging

Axi-cel potential advantages over current standard of care

- Achieve remission in people who disease have relapsed after multiple treatments
- Responses to axi-cel appear durable and might be considered curative

"I've had to give up most of my active hobbies - at my worst I was only able to concentrate / plan/carry out a daytime activity of 2 hours - then I would be asleep the rest of the day. And night"

"The impact of the various treatments cannot be understated. Side effects of nausea, depression, chemo-brain as well as long-term, ever-present exhaustion"

"My quality of life has been immeasurably improved. CAR T-cell therapy has been a lifesaver for myself"

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor cell therapy

Clinical experts' perspectives

Aim of drug treatment for relapsed/refractory follicular lymphoma

- To induce long-term remission, stop progression and maintain good quality of life
- Relapsed/refractory disease is difficult to treat and there is no curative treatment

Current treatment options

- Range of treatments available with variation of initial sequencing in chemoimmunotherapy and lenalidomide/rituximab combination
- Most with relapsed/refractory disease have been previously treated bendamustine, anthracyclines, alkylating agents rituximab, lenalidomide and obinutuzumab
- After 3 lines of therapy the disease is mostly relapsed/refractory with no standard of care at 4th plus line

Axi-cel

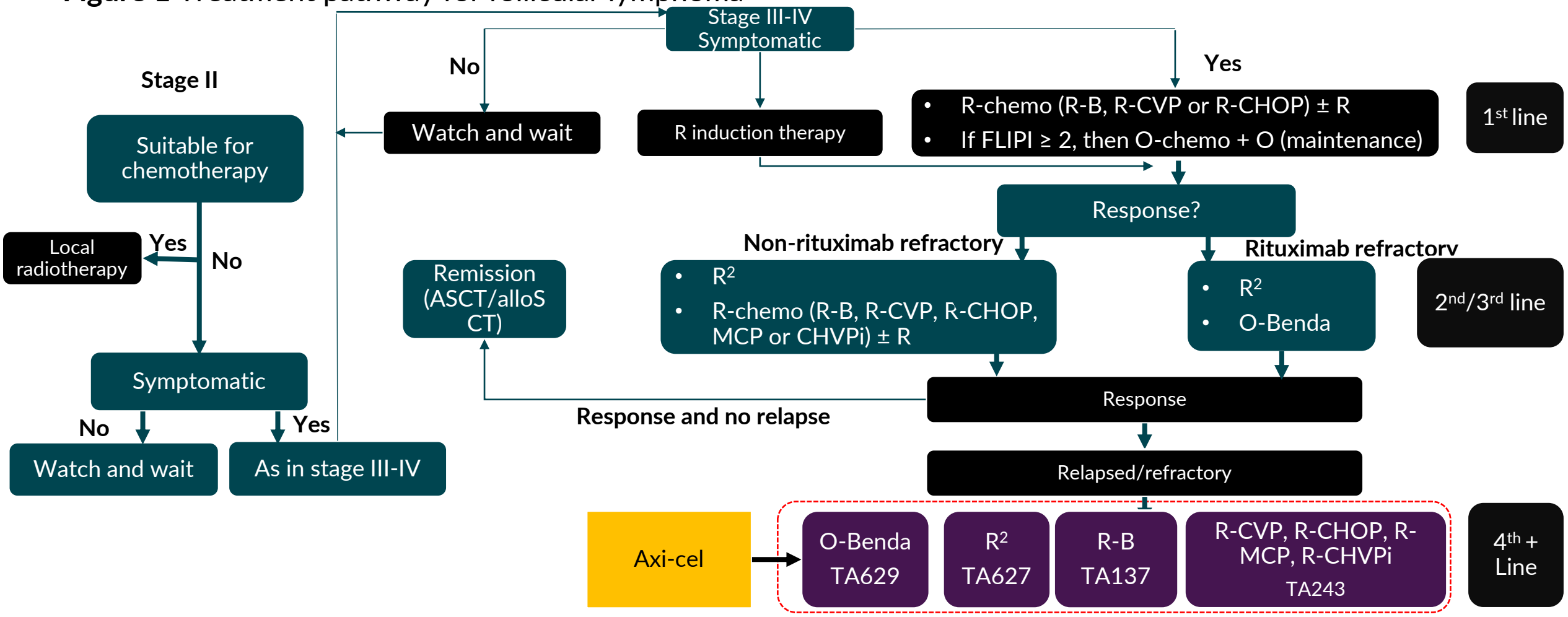
- Promising results with high response "rates durable remission and acceptable" toxicity profile
- Associated with significant rates of cytokine release syndrome and neuro toxicity
- Requires appropriate facilities and cannot be administered in general hospital: 10 approved CAR-T centres in England to provide care regionally

Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor cell therapy

Source: clinical expert submissions

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; R^2: lenalidomide with rituximab

Axicabtagene ciloleucel (Yescarta, Kite Pharma/Gilead)

Table 1 Technology details

Marketing authorisation	• "Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed/refractory follicular lymphoma after three or more lines of systemic therapy" • Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion following European Commission Decision Reliance Procedure
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

Decision problem

Table 2 Population, intervention, comparators and outcomes

	Final scope		Company
Population	Adults with relapsed or refractory non-Hodgkin lymphoma		As per scope
Intervention	Axicabtagene ciloleucel (axi-cel)		As per scope
Comparators	• Rituximab monotherapy • Rituximab in combination with chemotherapy • Obinutuzumab with bendamustine • Lenalidomide with rituximab • Clinical management without axi-cel • Best supportive care		• No established care for people who received 3+ prior therapies • Current 4L+ care → basket of therapies used in NHS practice • Treatments in 4L+ care basket were aligned with % distribution in SCHOLAR-5 (external study used for comparative evidence for axi-cel)
Outcomes	• OS • PFS • Response rates	• AEs • HRQoL	As per scope but HRQoL were informed by literature

ERG: Agreed company's decision problem appropriate and in line with the NICE final scope

Abbreviations: AEs: adverse events; axi-cel: axicabtagene ciloleucel; Benda: bendamustine; CVP: cyclophosphamide, vincristine and prednisolone; HRQoL, health-related quality of life; O: obinutuzumab; OS: overall survival; PFS: progression-free survival; R-B: rituximab with bendamustine; R^2: lenalidomide with rituximab

Source: Table 4, ERG report

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

Key clinical trials: ZUMA-5

Table 3 Clinical trial design and outcomes

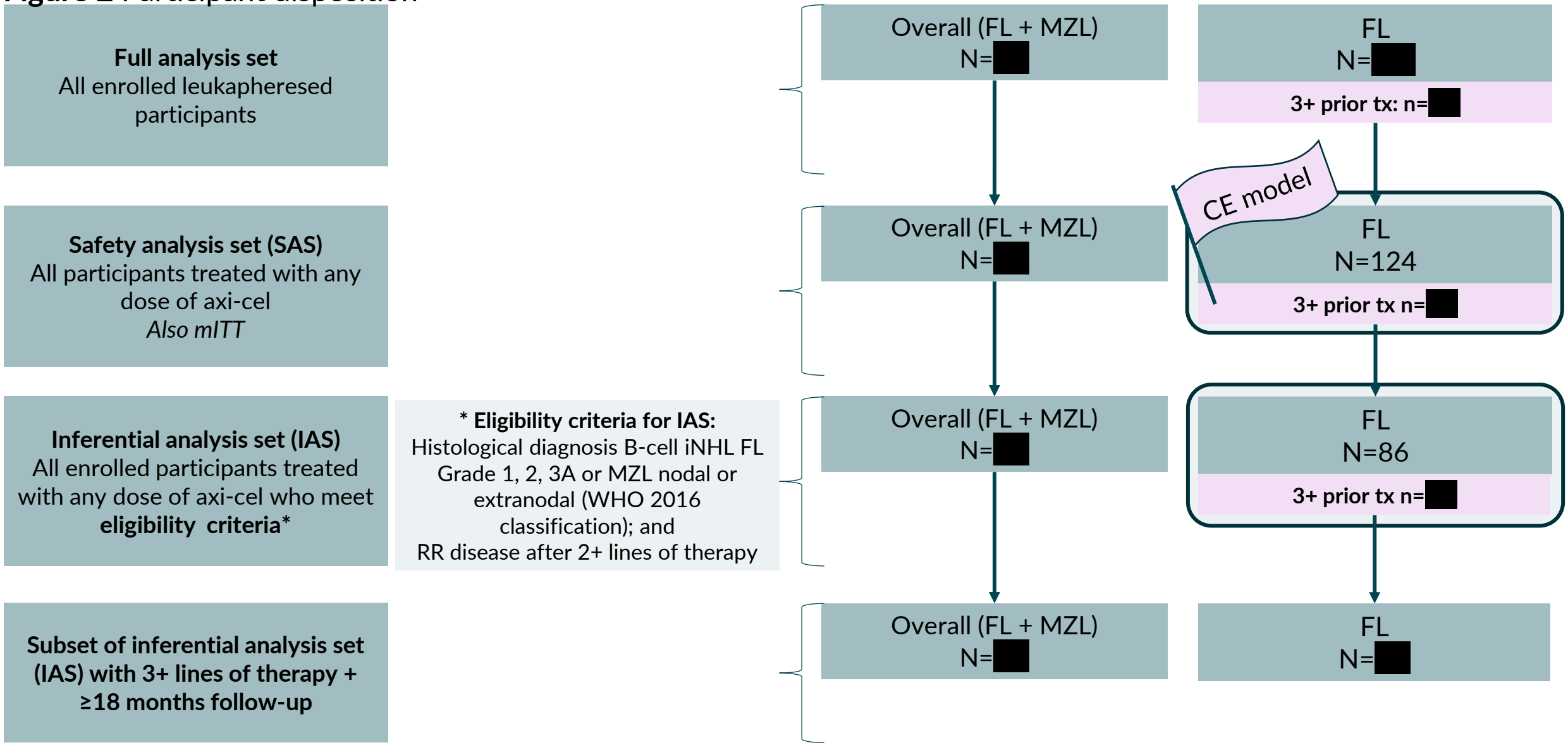
	ZUMA-5
Design	Phase II, multicentre, single-arm, open-label
Population	People with relapsed/refractory B-cell iNHL of FL or MZL histological subtypes who have received 2 or more prior lines of therapy
Intervention	Axi-cel
Comparator(s)	Not applicable
Follow-up time	PFS: [redacted] months; OS: [redacted] months (mITT)
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

Participant disposition: ZUMA-5

Figure 2 Participant disposition



Abbreviations: axi-cel: axicabtagene ciloleucel; FL: follicular lymphoma; iNHL: indolent non-Hodgkin lymphoma; mITT: modified intention-to-treat; MZL: marginal zone lymphoma; RR: relapsed/refractory; tx: treatment; WHO: World Health Organization

ZUMA-5: baseline characteristics

Table 4 Baseline characteristics from ZUMA-5

Baseline characteristics		SAS/mITT: 3+ prior therapies	IAS: 3+ prior therapies
N		[redacted]	[redacted]
Median age, years (min-max range)		[redacted]	[redacted]
ECOG performance status, n (%)	0	[redacted]	[redacted]
	1	[redacted]	[redacted]
Disease status	Relapsed	[redacted]	[redacted]
	Refractory	[redacted]	[redacted]
	Double-refractory	[redacted]	[redacted]
No. of prior lines of therapy, n (%)	3	[redacted]	[redacted]
	4	[redacted]	[redacted]
	≥5	[redacted]	[redacted]
Time to relapse from first therapy, n (%)	≥24 months	[redacted]	[redacted]
	<24 months	[redacted]	[redacted]
Median no. of prior therapies (range)		[redacted]	[redacted]
Prior lenalidomide, n (%)		[redacted]	[redacted]

Are these baseline characteristics generalisable to NHS clinical practice?

Abbreviations: ECOG: Eastern Cooperative Oncology Group; FL: follicular lymphoma; mITT: modified intention-to-treat; SAS: safety analysis set; tx: treatment

ZUMA-5: Response rates

Table 5 Response rates

Outcome	SAS/mITT: 3+ prior therapies	IAS: 3+ prior therapies
N	[redacted]	[redacted]
ORR (CR+PR), n (%)	[redacted]	[redacted]
Best objective response		
CR, n (%) [95% CI]	[redacted]	[redacted]
PR, n (%) [95% CI]	[redacted]	[redacted]
SD, n (%) [95% CI]	[redacted]	[redacted]
PD, n (%) [95% CI]	[redacted]	[redacted]
Duration of response		
Median duration of response in all responders, months(range)	[redacted]	[redacted]
Median duration of response in CRs, months (range)	[redacted]	[redacted]

- [redacted] of people achieved complete response (mITT)
- [redacted] of people achieved complete response (IAS)

Abbreviations: CR: complete response; IAS inferential analysis set; mITT: modified intention-to-treat; NE: not evaluated; ORR: objective response rate; PD, progressed disease; PR: partial response; SAS: safety analysis set; SD: stable disease

Source: Table 5, CS

ZUMA-5: Progression-free and overall survival

Table 6 PFS and OS for mITT and IAS population

	mITT: 3+ prior therapies [redacted]	IAS: 3+ prior therapies [redacted]
Progression-free survival		
Median 95% CI PFS	[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]
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]

OS is defined as the time from the axi-cel infusion date to the date of death from any cause.
PFS is defined as the time from the axi-cel infusion date to the date of disease progression per Lugano assessment or death from any cause

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, and CSR

ZUMA-5: Progression-free and overall survival mITT ([redacted])

Figures 3 and 4 Kaplan-Meier plots of PFS and OS

Abbreviations: mITT: modified intention-to-treat; NE: not evaluable; FL: follicular lymphoma; OS: overall survival; PFS: progression free survival

Source: Figure 8 and 10, CS

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 7 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

Current 4th line plus care

Table 8 Distribution of current 4L+ care therapies

Removed treatments

Treatment	SCHOLAR-5 distribution	Comparator	Re-weighted distribution
O-Benda	5.3%	Yes	13.3%
R-B	10.7%	Yes	26.7%
R-CVP	6.0%	Yes	15.0%
R^2	9.0%	Yes	22.5%
R-CHOP	9.0%	Yes	22.5%
Idelalisib	12%	No	0%
Radioimmunotherapy	3.0%	No	0%
CVP	19.0%	No	0%
Experimental	26.0%	No	0%

- SCHOLAR-5 included people who received treatments not used in NHS (e.g. idelalisib)
- Company reweighted distribution of SCHOLAR-5 treatments to calculate blended comparator costs
- No corresponding adjustment was made to efficacy estimates

ERG

- No adjustment for efficacy was possible, redistributed participants may have experienced poorer outcomes e.g. 19% CVP
- Difficult to predict overall direction and magnitude of bias caused by mismatch between SCHOLAR-5 distribution and the treatment distribution used in the NHS
- Assuming better outcomes with idelalisib is likely to favour comparator (against axi-cel)

Abbreviations; axi-cel: axicabtagene ciloleucel; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: cyclophosphamide, vincristine, and prednisone; O-Benda: Obinutuzumab plus bendamustine; R-B, rituximab with bendamustine: R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SCT: stem cell transplant.

Source: Table 40, CS

ZUMA-5 and SCHOLAR-5: Inclusion/exclusion criteria

Table 9 Inclusion/exclusion criteria for ZUMA-5 and SCHOLAR-5

	ZUMA-5	SCHOLAR-5

Inclusion criteria	• Local histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL grade 1, grade 2 or grade 3a or MZL nodal or extra-nodal, based on criteria established by the WHO 2016 classification
	• People with r/r disease after two or more prior therapies
	  • Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent
	  • Stable disease (without relapse) >1 year from completion of last therapy is not eligible
		• People with histologically confirmed diagnosis of iNHL, with histological subtype limited to FL grade 1, grade 2, or grade 3a or MZL nodal or extra nodal based on criteria established by the WHO 2016 classification
		• People with RR disease starting third or more therapies

Exclusion criteria	• Transformed FL or MZL • FL histological Grade 3b • History of infection with HIV or Hepatitis B • History of a seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, cerebral oedema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement • Presence of fungal, bacterial, viral or other infection that is uncontrolled or requiring IV antimicrobials for management	• Transformed FL • FL Histological Grade 3b • Prior anti-CD19 CAR T-cell therapy or other genetically modified T-cell therapy • Eligible within 12 months before the last updated version of the database

Abbreviations: CAR-T, chimeric antigen receptor cell therapy: CNS: central nervous system; FL: follicular lymphoma; iNHL: indolent non-Hodgkin lymphoma; MZL: marginal zone lymphoma; HIV: human immunodeficiency virus; RR: relapsed/refractory; WHO: World Health Organisation

Source: Table 6, CS; clinical Study Report, Section 5.3

Axi-cel survival outcomes vs. current 4L+ care

Figures 5 and 6 Kaplan-Meier plots of PFS and OS for axi-cel (ZUMA-5 [mITT]) and current 4L+ care (SCHOLAR-5, **excluding DELTA**)

- Axi-cel (ZUMA-5) demonstrates higher survival benefit compared with current 4L+care (SCHOLAR-5)

Source: CS Figure 14 and 15

Abbreviations: axi-cel: axicabtagene ciloleucel; NE: not estimated; OS: overall survival; PFS: progression free survival

Axi-cel for low-grade non-Hodgkin lymphoma

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

How company incorporated evidence into model

Table 10 Inputs and evidence sources used in the model

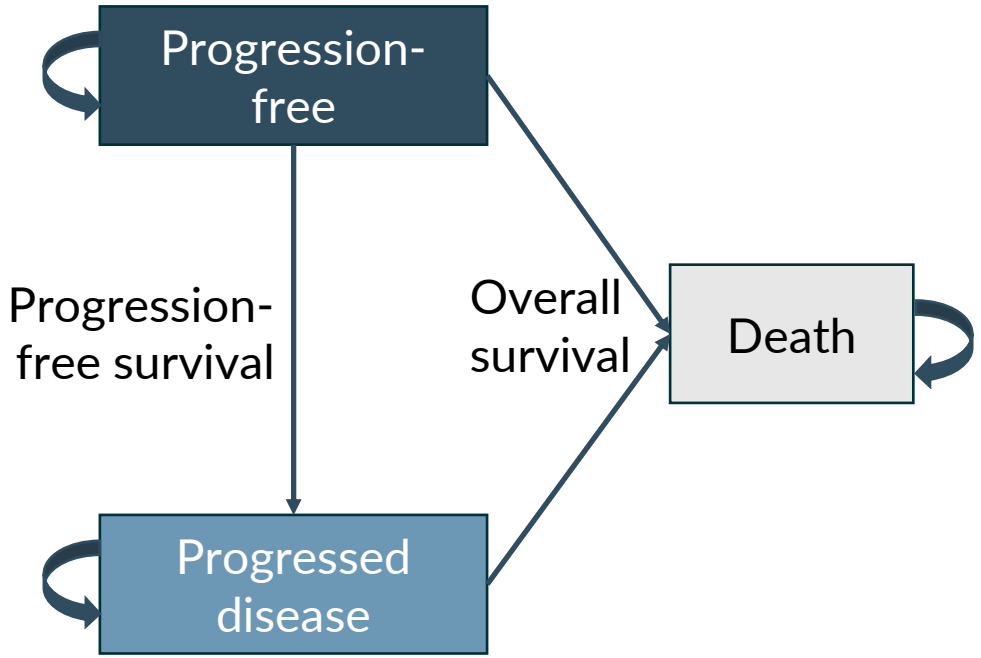
Input	Evidence source
Baseline characteristics	• ZUMA-5
Intervention efficacy	• ZUMA-5, mITT population (n=78),UK life tables, Maurer et al. 2014, clinical opinion
Comparator efficacy	• SCHOLAR-5 effectiveness matched to ZUMA-5, UK life tables
Utilities	• Wild et al. 2006
Costs and resource use	• Monthly Index of Medical Specialities (MIMS) • The drugs and pharmaceutical electronic market information tool (eMIT) for generic treatment costs • NHS reference costs 2019/20 for service/healthcare activity costs • The PSS Research Unit (PSSRU) Unit Costs of Health and Social Care 2020 for staff costs and inflation indices • Published literature sources
Adverse events	• ZUMA-5 (axi-cel) • Clinical trial data (reported in previous NICE TAs)
Discounting	• 3.5% for costs and health effects

 Abbreviations: axi-cel: axicabtagene ciloleucel: mITT: modified intention to treat; TA: technology appraisal

Company's model overview

A three-state partitioned survival model was used

Figure 7 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

Is the company's model acceptable for decision making?

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

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Key issues

Table 11 Key issues at technical engagement

Issue #	Issue	Resolved?	ICER impact
1	**Differences between ZUMA-5 and SCHOLAR-5 cohorts**	**Partially – for discussion**	**Large**
2	Proportion of people who can be considered long-term survivors	Partially – for discussion	Small
3	PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Partially – for discussion	Small
4	Health state utility values used in the model	Partially – for discussion	Small
5	Capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Partially – for discussion	Large

Abbreviations: axi-cel: axicabtabgene ciloleucel; ICER: incremental-cost effectiveness ratio; OS: overall survival; PFS: progression-free survival

Key issue 1: Difference between ZUMA-5 and SCHOLAR-5 (1)

Uncertainty around generalisability of SCHOLAR-5 to UK practice

Background

- No indirect comparison was conducted. SCHOLAR-5 was used as a comparative arm for axi-cel
- Some treatments used in SCHOLAR-5 are not in line with NHS practice

ERG comments

- Noted difference between ECOG score (0 and 1) between ZUMA-5 and SCHOLAR-5
- People in DELTA cohort received treatment (idelalisib) not approved for routine use by the NHS which may have overestimated SCHOLAR-5 OS for current 4L+ treatments
- SMR weighting improved comparability between the ZUMA-5 and SCHOLAR-5 but company's approach was not transparent
- Because progression dates were not present in DELTA, ERG suggested removing DELTA cohort from OS curves. DELTA was excluded from PFS analysis which means [redacted] fewer people inform PFS relative to OS

Clinical experts

- No major concern about generalisability, prior treatments were similar but sequencing may differ
- Most patients would have been exposed to very similar therapies before reaching 4th line and expect outcomes for SCHOLAR-5 to be generalisable to NHS clinical practice

Is SCHOLAR-5 generalisable to NHS clinical practice?

Abbreviations: axi-cel: axicabtagene ciloleucel; ECOG: Eastern Cooperative Oncology Group OS: overall survival; PFS: progression-free survival; SMR: standardised mortality ratio

Key issue 1: Difference between ZUMA-5 and SCHOLAR-5 (2)

Uncertainty around generalisability of SCHOLAR-5 to UK practice

Company TE response

- Updated its base case and removed DELTA cohort from OS and PFS analyses prior to propensity score weighting to match ZUMA-5
- Acknowledged removing DELTA cohort does not fully resolve uncertainties related to:
  - differences between ZUMA-5 and SCHOLAR-5 cohorts in terms of prior treatment received
  - generalisability of SCHOLAR-5 to the NHS clinical practice
- Expect survival with current 4L+ care available to be less than 3 years and selected gamma curve for its base case

ERG comments

- Removing DELTA prior to propensity score weighting had a minimal impact on PFS and resulted in more pessimistic OS curves (short life expectancy: increased QALY gain for axi-cel and reduced ICER)
- Noted DELTA cohort was used in SCHOLAR-5 from point of progression on idelalisib: representing people with prior exposure to idelalisb which could have better outcomes than people without prior exposure
- Generalised gamma, log-logistic and log-normal provided best statistical fits but company selected gamma for its base case without any justification for OS
- Evidence suggests an inverse relationship between treatment line and OS

Does removing DELTA cohort resolve uncertainties?

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

Key issue 1: Difference between ZUMA-5 and SCHOLAR-5 (3)

Figures 8 and 9 PFS and OS incl/excl DELTA cohort before propensity score weighting for current 4L+ care

Is the company's extrapolation for PFS and OS for current 4L+ care appropriate?

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

Key issues

Table 12 Key issues at technical engagement

Issue #	Issue	Resolved?	ICER impact
1	Differences between ZUMA-5 and SCHOLAR-5 cohorts	Partially – for discussion	Large 
5	**Capping of time on treatment for comparator therapies, and modelling subsequent treatment costs**	**Partially – for discussion**	**Large** 
2	Proportion of people who can be considered long- term survivors	Partially – for discussion	Small 
3	PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Partially – for discussion	Small 
4	Health state utility values used in the model	Partially – for discussion	Small 

Abbreviations: axi-cel: axicabtabgene ciloleucel; ICER: incremental-cost effectiveness ratio; OS: overall survival; PFS: progression-free survival

Key issue 5: Capping of time on treatment and subsequent treatment

Background

- Time on treatment curves were not consistent with PFS and OS for comparators in company's original base case: capped time on treatment assuming it continues beyond disease progression
- Company recycled comparator costs and applied as a one-off treatment cost when progressed in each cycle
- ERG considered this could overestimate comparator costs as treatment would be stopped on progression

Company

- Accepted its original base case may have overestimated comparator and subsequent treatment costs
- Agreed with ERG that comparator treatment should be capped on PFS rather than OS
- Updated its base case to cap comparator time on treatment at PFS

ERG comments

- Satisfied with company's approach and associated changes in the model
- However, time on treatment with comparator therapies at 4th line and beyond are not well informed in the model and remain uncertain

Clinical experts

- Treatment beyond progression is not a standard approach

Is the company's updated modelling of time on treatment for comparators appropriate ?

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

Key issues

Table 13 Key issues at technical engagement

Issue #	Issue	Resolved?	ICER impact
1	Differences between ZUMA-5 and SCHOLAR-5 cohorts	Partially – for discussion	Large 
5	Capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Partially – for discussion	Large 
2	**Proportion of people who can be considered long-term survivors**	**Partially – for discussion**	**Small** 
3	PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Partially – for discussion	Small 
4	Health state utility values used in the model	Partially – for discussion	Small 

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental-cost effectiveness ratio; OS: overall survival; PFS: progression-free survival

Key issue 2: Long term survivors following axi-cel

Company

- Assumed 25% people treated with axi-cel are long-term survivors and experienced SMR adjusted general population mortality from 5 years onwards of 1.09: provide scenarios with varied SMR
- Acknowledged uncertainties due to lack of data and suggested further data collection through Cancer Drugs Fund to inform model inputs: [redacted]

ERG

- No data available for this population to validate company's 25% long-term survivor assumption, but accepted company's long-term survivor proportion and timing assumptions in its base case.
- Long-term survivor proportion and mortality assumptions for long-term survivors represent key uncertainties in model: scenarios should be considered carefully by the committee
- Consider not possible to resolve these issues with additional data collection through Cancer Drugs Fund

Table 14 Standardised mortality ratio (SMR) and extrapolation time point

Long-term survivorship SMR		Time point	
Base-case	**Scenario**	**Base-case**	**Scenario**
1.09	1 and 1.20	5 years	5, 7 and 10 years

Clinical experts: mixed opinion from clinical experts:

- One expert suggesting 25% achieving long-term survivorship reasonable. Second expert highlighted 25% never relapse, [redacted] alive at 10 years based on Weibull extrapolation is unrealistic

Would a more robust estimate of the proportion who have progressed/not progressed by year 5 sufficiently resolve the uncertainty around the proportion of long-term survivors?

Key issues

Table 15 Key issues at technical engagement

Issue #	Issue	Resolved?	ICER impact
1	Differences between ZUMA-5 and SCHOLAR-5 cohorts	Partially – for discussion	Large
5	Capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Partially – for discussion	Large
2	Proportion of people who can be considered long-term survivors	Partially – for discussion	Small
3	**PFS and OS extrapolation assumptions for axi-cel non-long-term survivors**	**Partially – for discussion**	**Small**
4	Health state utility values used in the model	Partially – for discussion	Small

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost effectiveness ratio; OS: overall survival; PFS: progression-free survival

Key issue 3: Extrapolation for non-long-term survivors

Background
- Uncertainty around extrapolation to model hazard progression and death for non-long-term survivors

ERG
- Noted parametric curves were fitted to PFS and OS data from overall ZUMA-5 population which also included 25% long-term survivors who achieved a reduced hazard for mortality
- From 5 years onwards company fitted PFS and OS curves which could underestimate hazard of progression and death for non-long-term survivors because it also included long-term survivors
- Noted proportion of surviving model cohort who are considered long-term survivors was fixed over time in model instead of increasing because non-long-term survivors face higher risk of death

Company
- During TE the company updated its base-case to address the ERG's concerns as follows:
  - allowed the proportion of non-long term survivors to reduce over time
  - uplifted the hazard of progression and death for non-long-term survivors from the timepoint that the long-term survivor proportion and assumptions are applied (SMR 1.2 inline with ERG)
  - ensured hazard of death for non-long-term survivors never falls below that of long-term survivors

ERG
- Satisfied with company's revised approach but considers uncertainties remain in the economic analyses

Is the committee satisfied with the company and ERG's approach?

OS: overall survival; PFS: progression-free survival; SMR: standardised mortality ratio

Key issues

Table 16 Key issues at technical engagement

Issue #	Issue	Resolved?	ICER impact
1	Differences between ZUMA-5 and SCHOLAR-5 cohorts	Partially – for discussion	Large
5	Capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Partially – for discussion	Large
2	Proportion of people who can be considered long-term survivors	Partially – for discussion	Small
3	PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Partially – for discussion	Small
4	**Health state utility values used in the model**	**Partially – for discussion**	**Small**

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost effectiveness ratio; OS: overall survival; PFS: progression-free survival

Key issue 4: Utilities used in model [1]

Background

- No health-related quality of life data collected in ZUMA-5 or SCHOLAR-5
- Uncertainty in utility values due to lack of quality of life data available at 4th line and beyond

Company

- Used utility values in line with TA627 from AUGMENT trial in its original base case and capped utilities to ensure progression-free remained below age-adjusted general population
- General population utilities were used for progression-free disease and applied utility decrements to progressed disease

Table 17 Utility inputs

Heath state	Original base case	AUGMENT (TA627)		Wild et al /Pettengell et al (TA604)- revised base case	GADOLIN (TA629)
		R^2	R-mono		
Pre-progression	0.829	0.847	0.840	0.805	0.822[a] ,0.807[b]
Progressed disease	0.803	0.821[a] 0.791[b]	0.813[a] 0.784[b]	0.736	0.758

[a:] off-treatment; [b:] on-treatment

ERG

- AUGMENT included more people at earlier stage: 2nd line (54%) vs 4th line (24%)
- People receiving 2nd line treatment have a higher quality of life than receiving treatment at 4th line and beyond
- Considers utility values uncertain and used lower values from Wild et al. in line with TA604 in its base case

Abbreviations: R-mono: rituximab monotherapy; R^2:lenalidomide with rituximab; TA: technology appraisal

updated base case

Key issue 4: Utilities used in model [2]

Clinical experts

- People receiving 2nd line treatment have better quality of life than 4th line treatment but do not expect a big difference

Company TE response

- Updated its base case using lower utility values from Wild et al. in line with ERG base case
- Inconsistent to consider that long-term survivors would suffer a utility decrement compared with general population for rest of life based on prior CAR-T cell therapy topics
- In line with TA559 and TA677, the company assumed health-related quality of life for alive and free of progression at 5 years and beyond returns to that of general population

ERG

- Agreed with company's revised approach (Wild et al. utilities) for progression-free and progressed disease
- Consider it's inconsistent to assume that long-term survivors achieve health state utilities in line with general population while experiencing elevated mortality risk
- Highlights uncertainty around utility values and suggested it's import to explore range of assumptions around long-term survivor utility values

What source of utility values is more appropriate?

 Abbreviations: axi-cel: axicabtagene ciloleucel: TA: technology appraisal

Axi-cel for low-grade non-Hodgkin lymphoma

- ❑ About
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Points to consider (5)
  - 2 with large impact on ICER
  - 3 with small impact on ICER
- ✓ **End-of-life criteria**
- ❑ ICERs
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ❑ Summary

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

End-of-life criteria

Table 18 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] 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

Axi-cel survival outcomes vs. current 4L+ care

Figures 10 and 11 Kaplan-Meier plots of PFS and OS for axi-cel (ZUMA-5 [mITT]) and current 4L+ care (SCHOLAR-5, excluding DELTA)

- Axi-cel demonstrates higher survival benefit compared with SCHOLAR-5 current 4L+care

Source: CS Figure 14 and 15

Abbreviations: axi-cel: axicabtagene ciloleucel; NE: not estimated; OS: overall survival; PFS: progression free survival

Axi-cel for low-grade non-Hodgkin lymphoma

- ❑ About
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- ❑ 2 with large impact on ICER
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- ❑ End of life criteria
- ✓ **ICERs**
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ❑ Summary

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

Summary of company and ERG base case assumptions

Table 19 Assumptions in company and ERG base case

Assumption		Company base case	ERG base case
PFS extrapolation	4L+	Exponential	Exponential
	Axi-cel	Weibull	Weibull
OS extrapolation	4L+	Gamma	Gamma
	Axi-cel	Weibull	Weibull
Long-term survivor proportion (after axi-cel treatment)		25%	25%
Long-term survivor SMR		1.09	1.09
Long-term survivorship time point		5 years	5 years
Health related utility values source		Wild et al (general population utility values for alive and progression free beyond 5 years)	Wild et al

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

Company and ERG deterministic base case

Including and excluding DELTA cohort

Table 20 Company Deterministic incremental base-case results (axi-cel PAS, list price for all other treatments)

Technology	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company base case (including DELTA cohort)			
Current 4L+ care	[redacted]	[redacted]	£55,383
Axi-cel			
Company base case (excluding DELTA cohort)			
Current 4L+ care	[redacted]	[redacted]	£47,905
Axi-cel			

Table 21 ERG Deterministic incremental base-case results (axi-cel PAS, list price for all other treatments)

Technology	Incr. costs	Incr. QALYs	ICER (£/QALY)
ERG base case (including DELTA cohort)			
Current 4L+ care	[redacted]	[redacted]	£56,332
Axi-cel			
ERG base case (excluding DELTA cohort)			
Current 4L+ care	[redacted]	[redacted]	£48,606
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 and ERG probabilistic base case results

Revised base case after technical engagement excluding DELTA cohort

Table 22 Company probabilistic incremental base case results (axi-cel PAS, list price for all other treatments)

Technology	Total costs (£)	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	[redacted]	£49,906
Axi-cel	[redacted]	[redacted]			

Table 23 ERG probabilistic incremental base case results (axi-cel PAS, list price for all other treatments)

Technology	Total costs (£)	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	[redacted]	£50,861
Axi-cel	[redacted]	[redacted]			

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	£41,898
			Current 4L+ care, Weibull; Axi-cel, Weibull	£48,636
	Long-term survivorship	25%	[redacted] of treated patients (i.e. all in PFS at 5 years)	£44,717
			10% of treated patients	£55,643
	Long-term survivorship SMR	1.09	1.00	£47,394
			1.20	£48,502
	Long-term survivorship time	5 years	2 years	£44,769
			10 years	£53,050
	Health state utilities source	Progression-free and progressed disease (Wild et al)	Progression-free, general population (TA627) Progressed, general population with AUGMENT decrement (TA627)	£46,833
			GADOLIN	£47,354
			AUGMENT, R^2	£46,316
			AUGMENT, R-mono	£46,524
	Utility value for alive and progression-free beyond-5 years	General population	Adjusted general population utility (98.6%)	£48,253

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

ERG scenario analyses around company base case

ERG scenarios

	Base case	Scenarios	ICER (£/QALY)
Axi-cel extrapolation	OS: Weibull PFS: Weibull	OS, Weibull (no long-term survivorship)	£56,533
		PFS, generalised gamma (no long-term survivorship)	
Current 4L+ care Extrapolation	OS, gamma PFS, exponential (excl. Delta)	OS, gamma; PFS, exponential (incl. DELTA)	£55,383
		OS, lognormal; PFS, exponential	£55,998
Utility values for long-term survivors	Age/sex match general population	Progression free utility from Wild et al.	£48,606
Comparator costs	Capped on PFS	Capped on OS	£42,471
Long-term survivor proportion	25%	15%	£52,810
		20%	£50,242
Mortality ratio for non-long term survivors	1.2	1.09	£46,805
		1.5	£50,552
		2	£54,064

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

Axi-cel for low-grade non-Hodgkin lymphoma

- ❑ About
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Points to consider (5)
- ❑ 2 with large impact on ICER
- ❑ 3 with small impact on ICER
- ❑ End of life criteria
- ❑ ICERs
- ✓ **Other considerations: Equality; innovation; Cancer Drugs Fund**
- ❑ Summary

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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

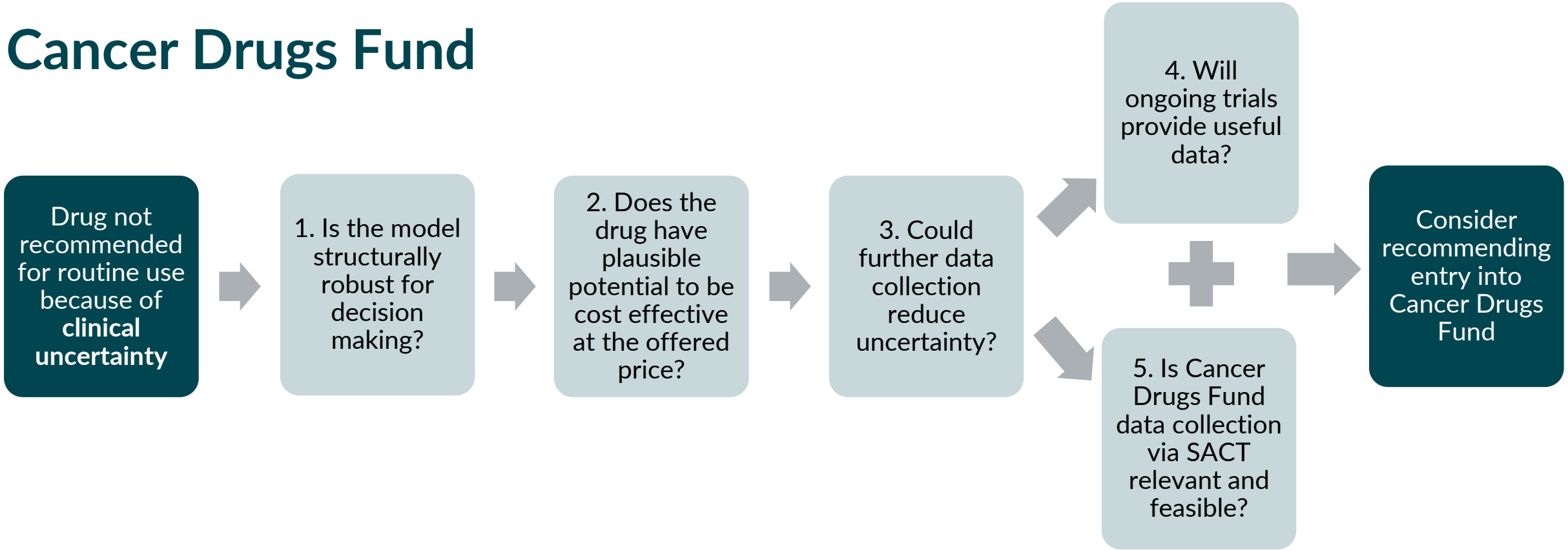
Innovation

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?
- Would a more robust estimate proportion who have not progressed by year 5 sufficiently resolve the uncertainty around proportion of long-term survivors?

Is axi-cel a candidate for the CDF?

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

ZUMA-22

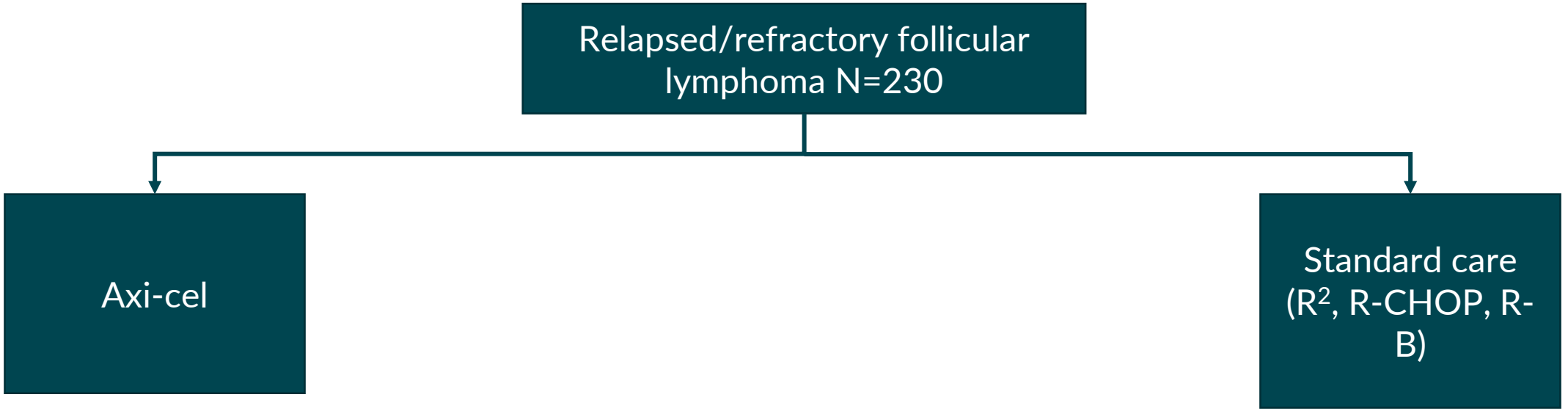


Table 24 ZUMA-22 study details

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

Axi-cel for low-grade non-Hodgkin lymphoma

- ❑ About
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- ❑ Modelling
- ❑ Points to consider (5)
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- ❑ End of life criteria
- ❑ ICERs
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ✓ **Summary**

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

Key issues

Table 25 Key issues at technical engagement

Issue #	Issue	Resolved?	ICER impact
1	Differences between ZUMA-5 and SCHOLAR-5 cohorts	Partially – for discussion	Large 
5	Capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Partially – for discussion	Large 
2	Proportion of people who can be considered long-term survivors	Partially – for discussion	Small 
3	PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Partially – for discussion	Small 
4	Health state utility values used in the model	Partially – for discussion	Small 

Abbreviations: axi-cel: axicabtagene ciloleucel; ICER: incremental cost effectiveness ratio; OS: overall survival; PFS: progression-free survival

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Thank you.