Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy

Public observer slides, no confidential information

Second Appraisal Committee Meeting

Technology appraisal committee C [14 February 2022]

Chair: Stephen O'Brien

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Technical team: George Millington, Alex Filby, Ross Dent

Company: Kite, a Gilead company

Axicabtagene ciloleucel (Yescarta, Kite)

Table 1 Technology details

Marketing authorisation	• for treating 'adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy' • GB license extension granted in December 2022
Mechanism of action	Autologous CAR T-cell product that recognises and eliminates all CD19-expressing target cells, including B-cell malignancies and normal B-cells
Administration	• **Production**: patient T-cells are extracted via leukapheresis and activated with IL-2 and an anti-CD3 mAb, then transduced with the anti-CD19 CAR transgene-containing γ-retroviral vector • **Infusion**: Bag of axi-cel for IV infusion has target dose of 2 x 10^6 CAR-positive viable T-cells per kg of body weight • **Additional medication**: Lymphodepleting chemotherapy (cyclophosphamide and fludarabine). Premedication with paracetamol and diphenhydramine recommended
Price	• List price including shipping, engineering and generation of CAR T-cells: £280,451 • Patient access scheme discount available

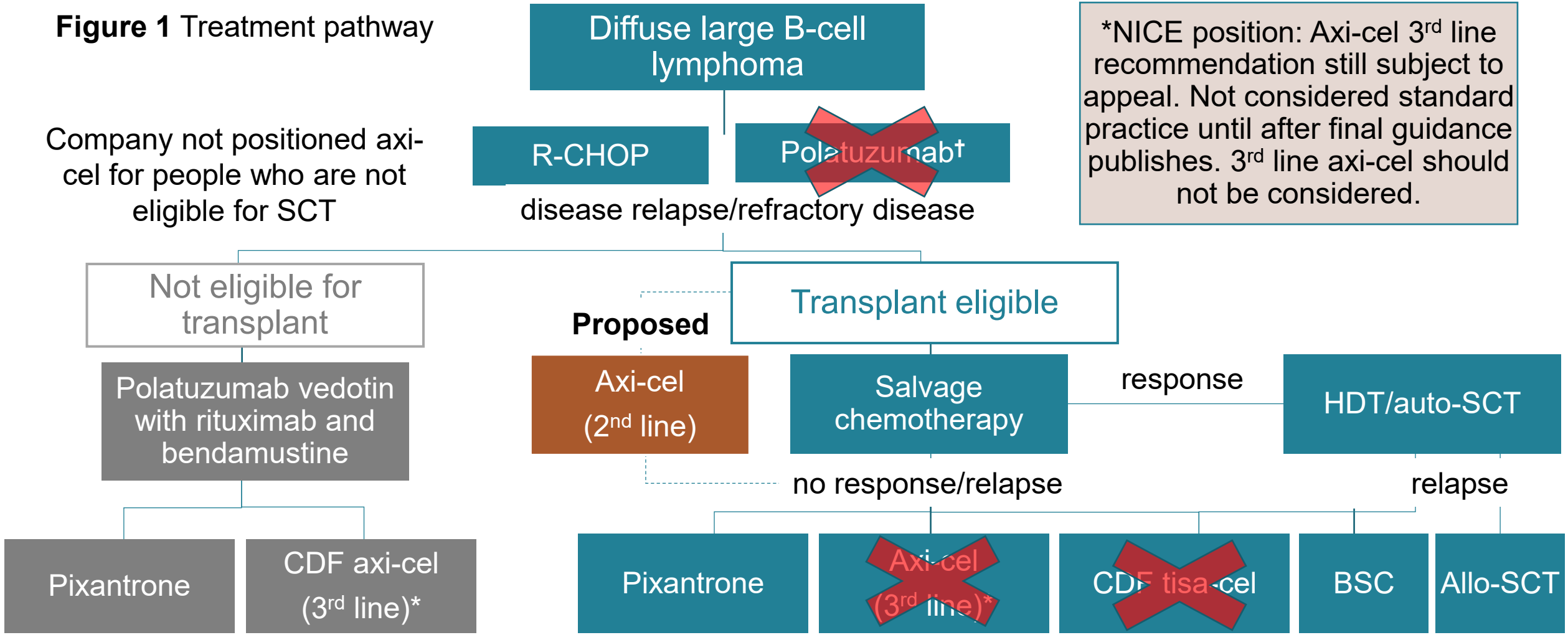
Population in appraisal is narrower 'Adults with primary refractory or early relapse (≤ 12 months) DLBCL **who are intended for transplant**'

Abbreviations: CAR T, chimeric antigen receptor T; CD3, cluster of differentiation 3; CD19, cluster of differentiation 19; CHMP, Committee for Medicinal Products for Human use; DLBCL, diffuse large B-cell lymphoma; IL-2, interleukin 2; kg, kilogram; mAb, monoclonal antibody

Treatment pathway

Proposed as 2nd line treatment for people who are transplant eligible

Figure 1 Treatment pathway



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† Not considered standard practice until final guidance publishes.
Abbreviations: allo-SCT, allogenic stem cell transplant; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; BSC, best supportive care; CDF, Cancer Drugs Fund; HDT, high dose therapy

Proposed positioning

- The company proposed axi-cel for a narrower population than its anticipated marketing authorisation
- It focused on adults with DLBCL that is primary refractory or early relapsed within 12 months of treatment, and **who are intended for autologous stem cell transplant** (auto-SCT)
- The marketing authorisation includes people not eligible for auto-SCT
- At ACM1, clinical experts commented that people who cannot have an autologous stem cell transplant have worse outcomes
- They explained some people could tolerate axi-cel but not auto-SCT
- They explained that it would be beneficial to have an additional treatment option for these people
- However, they also highlighted that there is no evidence for axi-cel in this population because they were not included in ZUMA-7
- At ACM1, committee agreed it was appropriate to position axi-cel for the narrower population.

Abbreviations: ACM, appraisal committee meeting; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma

Key clinical trial: ZUMA-7

Table 2 Clinical trial designs and outcomes

	ZUMA-7 [ongoing]
Design	Phase 3, randomised (1:1), open-label, parallel assignment
Population	Adults with histologically confirmed DLBCL • refractory to frontline treatment or relapsed ≤ 12 months after frontline chemoimmunotherapy • intended to proceed to high-dose therapy and auto-SCT • ECOG PS 0 or 1
Intervention	Axi-cel (lymphodepleting chemotherapy then IV axi-cel. Bridging therapy of corticosteroids permitted before chemotherapy for high disease burden)
Comparator	Standard of care (platinum-based 2nd-line combination chemotherapy followed by high dose therapy and autologous stem cell transplant)
Primary outcome	Event free survival
Secondary outcomes	ORR, OS, PFS, DoR

Clinical experts: Chemotherapy bridging was not allowed in ZUMA-7 but is conducted in NHS practice. The lack of option to bridge may have meant investigators did not recruit people with rapidly progressive disease. This may have biased results in favour of axi-cel.

Abbreviations: auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression free survival

Recap of key issues from ACM1

Table 3 Key issues from ACM1

Issue	Committee's ACM1 conclusion
Axi-cel 3rd line crossover adjustment (because it is not routinely commissioned in NHS) • Is the RPSFTM with full re-censoring the most appropriate cross-over adjustment for overall survival in the standard of care arm?	RPSFTM with full re-censoring is most clinically appropriate but uncertainty still present and may benefit axi-cel
Axi-cel retreatment costs • Should costs or benefits be adjusted to account for axi-cel retreatment?	Retreatment costs should be included to align modelled costs and benefits
Overall survival for axi-cel • Is generalised gamma or log-logistic extrapolation more appropriate?	Both were plausible but preferred slightly more conservative log-logistic because of uncertainty
End of life criteria • Is axi-cel a life extending treatment at the end of life?	Axi-cel met end of life criteria
CAR-T tariff • What are the most appropriate costs for axi-cel administration in the NHS?	See next slide

Abbreviations: auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; RPSFTM, rank preserving structural failure time model; SoC, standard of care

CAR-T tariff

- The administration costs for running a CAR-T service in the NHS are uncertain
- In ACM1, the company provided an estimate of around £28,000
- Previously, NHS England recommended an administration cost of £65,415 which was subject to review
- These figures have been reviewed by both the company and NHS England and both have agreed to a figure of **£41,101** (excluding costs for bridging therapy, consolidation SCT and hypogammaglobulinemia management)
- This figure was accepted by the committee in ID3980 - axicabtagene ciloleucel as a 3rd line treatment

Abbreviations: ACM, appraisal committee meeting

Patient and expert ACD consultation responses

Summary of consultation responses

There is unmet need in DLBCL patients

- Many commenters noted that currently available treatment fails in a large proportion of the population
- The severe side effects of the current standard of care were also noted
- Commenters would like to see another treatment option for DLBCL and believe that axi-cel is superior to current standard of care
- 2L axi-cel would mean earlier use of a potentially curative treatment. It can spare chemotherapy toxicity and healthcare costs as successive futile treatments and follow ups can be avoided.

Axi-cel treatment population

- Some commenters noted the potential for axi-cel to be used as a treatment option for people who were not eligible to receive auto-SCT
- One commenter noted that patients older than 70 are rarely offered auto-SCT but may be offered axi-cel, reducing age-related inequality

Comments received from: Kite (company), Anthony Nolan, Blood Cancer UK, Lymphoma Action, NCRI, ACP, RCP, RCR
Abbreviations: ACD, appraisal consultation document; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma

Key issues for ACM2

Table 4 Key issues for ACM2

Issue	ICER Impact
Uncertainty in long-term overall survival • Large differences in survival data based on RPSFTM method • At ACM1, committee stated that RPSFTM with full re-censoring was most plausible but uncertainty was still present and may benefit axi-cel	Uncertain 
Overall survival extrapolations for axi-cel • Company does not agree that log-logistic is most plausible • EAG preference aligned with committee's preferred assumptions from ACM1	Small 

Abbreviations: ACM, appraisal committee meeting; axi-cel, axicabtagene ciloleucel; EAG, external assessment group; RPSFTM, rank-preserving structural failure time model

Key issue: Uncertainty in long-term overall survival

Background

- In ZUMA-7, 56% of people in the SoC arm received CAR-T therapies as 3rd line treatment
- Because 3rd line CAR-T therapy is not usual treatment in England, crossover adjustment is needed
- Analysis included a full re-censoring RPSFTM and a RPSFTM that re-censored switchers only
- The full re-censoring RPSFTM implies better outcomes than the RPSFTM that re-censored switchers only
- At ACM1 the committee agreed that RPSFTM with full re-censoring is most clinically appropriate but uncertainty was still present and may benefit axi-cel

Company comments (pre ACM1 clarification)

- Explored various cross-over adjustment methods
- Believes RPSFTM with full re-censoring provides the most clinically plausible results

EAG comments

- RPSFTM with full re-censoring remains the most appropriate cross-over model for SoC
- There is uncertainty in SoC survival estimates until 3rd line axi-cel becomes standard practice

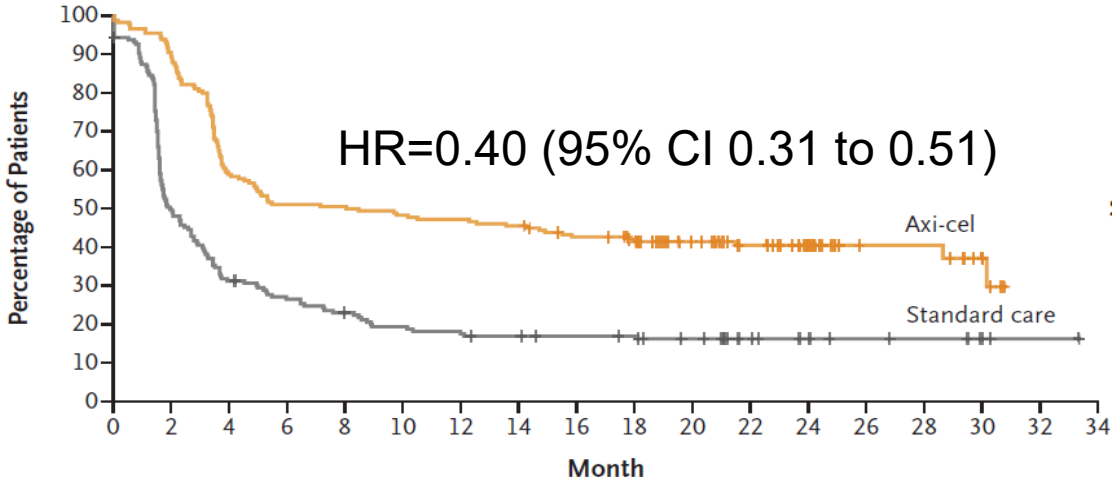
What is the impact of uncertainty in long-term overall survival?

Abbreviations: ACM, appraisal committee meeting; axi-cel, axicabtagene ciloleucel; EAG, external assessment group; OS, overall survival; RPSFTM, rank-preserving structural failure time model; SoC, standard of care

ZUMA-7 results

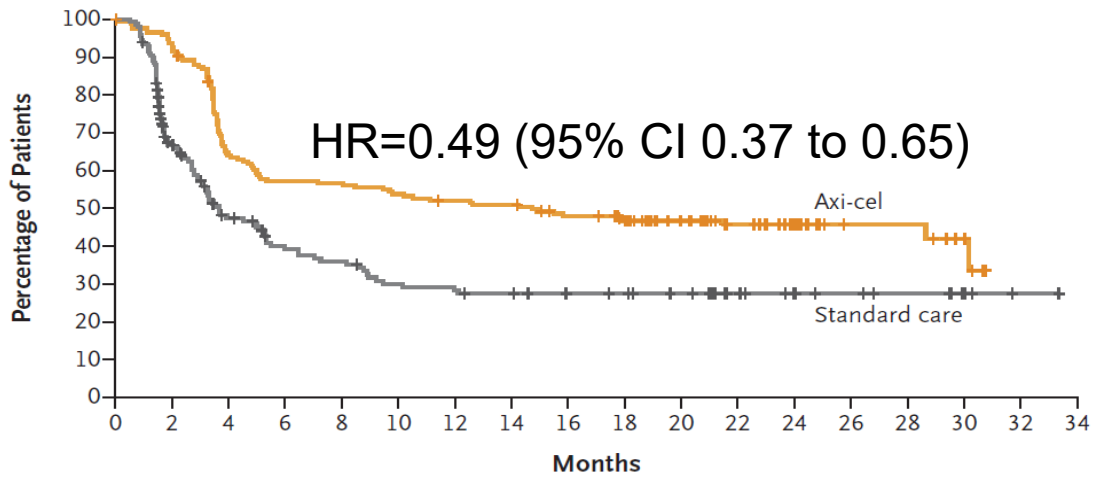
Median EFS and PFS were longer in axi-cel arm than SoC arm

Figure 2 Event free survival, ZUMA-7 full analysis set



No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

Figure 3 Progression free survival, full analysis set



No. at Risk																	
Axi-cel	180	166	112	100	99	94	90	88	80	73	56	43	28	12	12	6	
Standard care	179	94	61	47	43	35	33	31	28	27	24	15	11	9	7	4	1	0

Event free survival: [central assessment] time from randomisation to earliest date of disease progression, new lymphoma therapy, death from any cause, absence of response, or a best response

Progression free survival: [investigator assessment] time from randomisation to disease progression or death from any cause

What is the impact of uncertainty in long-term overall survival?

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Abbreviations: axi-cel, axicabtagene ciloleucel; CI, confidence interval; EFS, event free survival; HR, hazard ratio; PFS, progression free survival; SoC, standard of care

ZUMA-7 results

Figure 4 Overall survival, unadjusted ZUMA-7 full analysis set

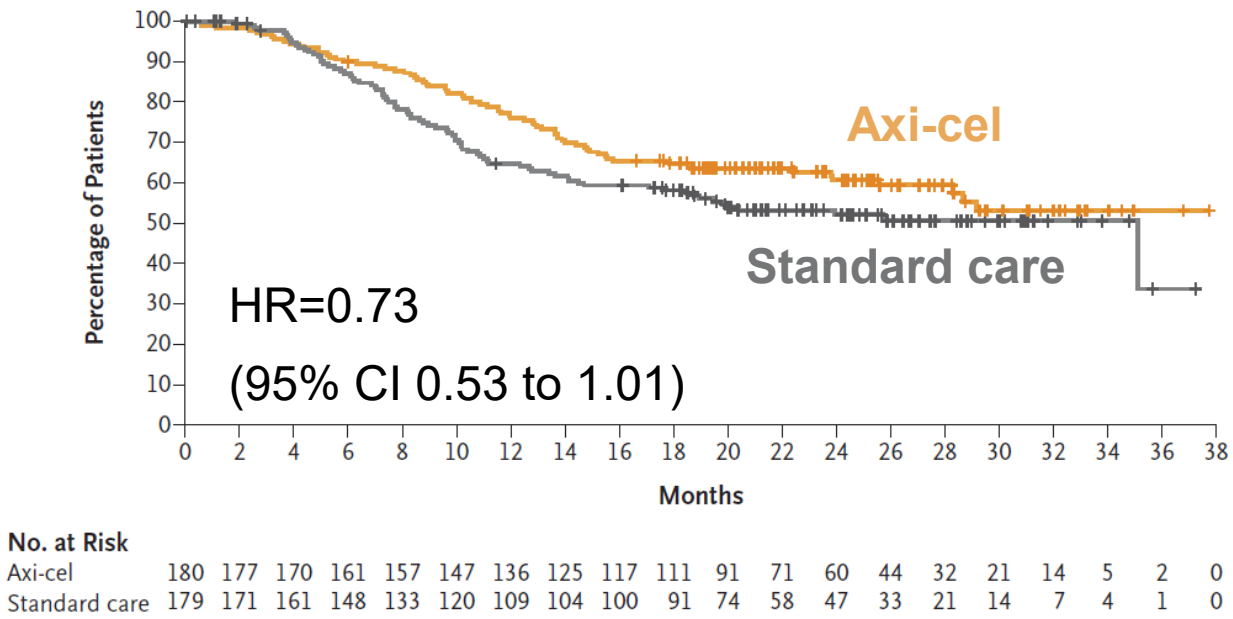
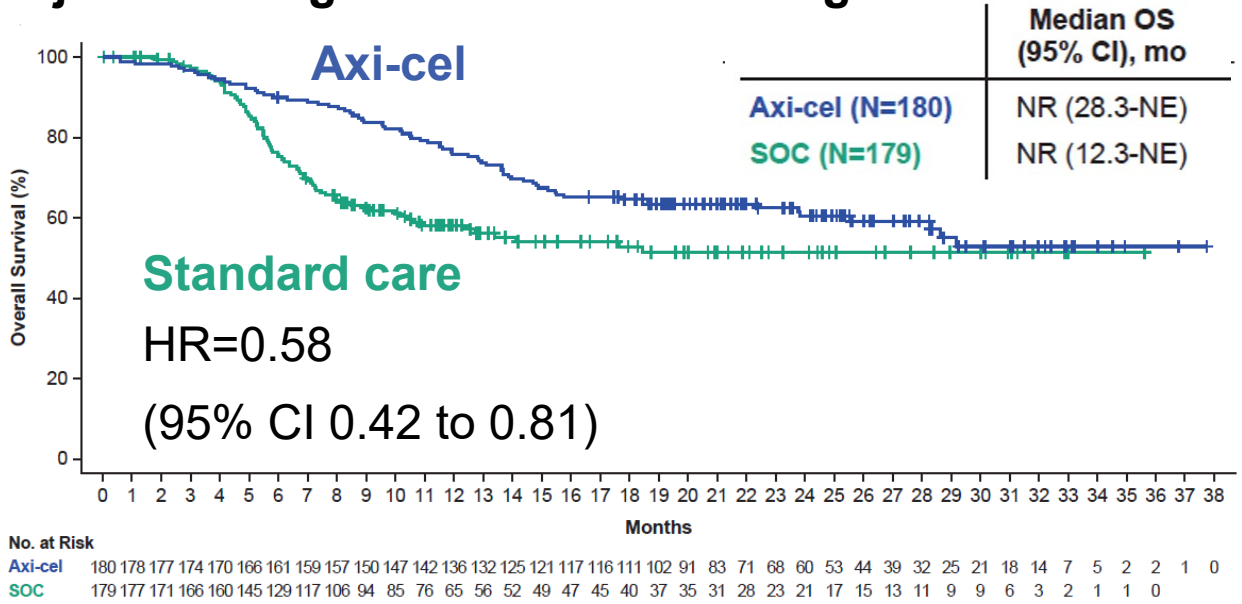


Figure 5 Overall survival, ZUMA-7 **full analysis set adjusted using RPSFTM re-censoring switchers***



*adjustment used in model is RPSFTM with full censoring

Crossover not permitted, but those on SoC could have subsequent cellular immunotherapy outside trial protocol, **56% of SoC had subsequent CAR T-cell therapy.** It is not routinely commissioned in NHS (only available in CDF)

ACD: ZUMA-7 provided the best available evidence for axicabtagene ciloleucel compared with standard care.

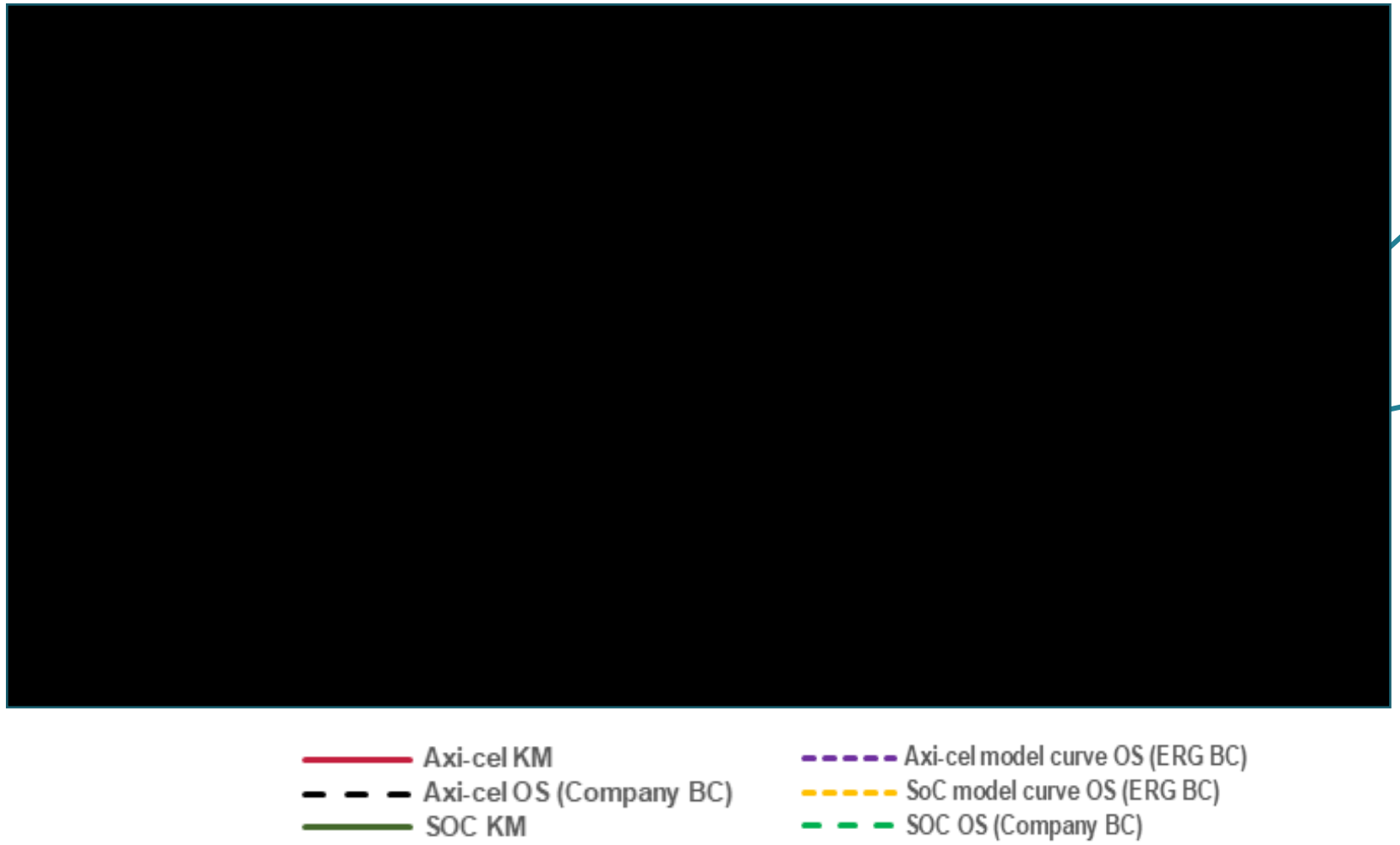
What is the impact of uncertainty in long-term overall survival?

NICE

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR T cell, chimeric antigen receptor T cell; CI, confidence interval; HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; RPSFTM, rank preserving structural failure time model; SoC, standard of care; 3L, 3rd line

Key issue: Uncertainty in long-term overall survival

Figure 6 Overall survival extrapolations from RPSFTM with full re-censoring



Axi-cel: Company base case – generalised gamma

Axi-cel: EAG base case – log-logistic

Graph uses Kaplan-Meier from RPSFTM with **full re-censoring**. This was the company's base case for the economic model and the EAG's preferred method.

What is the impact of uncertainty in long-term overall survival?

Key issue: Overall survival extrapolations for axi-cel

Background

- The company prefer the generalised gamma while the EAG prefer the more conservative log-logistic
- At ACM1, the committee preferred the log-logistic MCM due to uncertainty

Company's response to ACD

- Concerned about the clinical plausibility of the log-logistic model based on survival difference between 2nd line and 3rd or later line and believes generalised gamma produces more plausible estimates (see table)

EAG comments

- Maintains that most suitable MCM is uncertain but both log-logistic and generalised gamma are plausible
- Both have similar statistical fits and generate OS estimates above ZUMA-1, indicating clinical plausibility
- Prefers the more conservative log-logistic given substantial uncertainty of long-term OS outcomes

	2 years (OS)	5 years (OS)	
ZUMA-1 (3L or later axi-cel)	50%	43%	
ZUMA-7 (2L axi-cel)	61%	Log-log	**46%**
		Gen gamma	**51%**

Is the log-logistic or generalised gamma extrapolation most suitable?

Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting; axi-cel, axicabtagene ciloleucel; EAG, external assessment group; MCM, mixture-cure model; OS, overall survival

Axi-cel retreatment costs

Background

- [redacted] patients [redacted] in ZUMA-7 had axi-cel retreatment. Of these, [redacted] had a confirmed response to axi-cel but most were of short duration ([redacted] to [redacted] months), 1 had response of [redacted] months
- At ACM1, the committee stated retreatment costs should be included to align modelled costs and benefits

Company's response to ACD

- Believes that benefits but not costs should be included in the analysis
- Retreatment with axi-cel is not part of the marketing authorisation and would not be done in clinical practice
- Maintains that the benefit of retreatment is small and believes that including these patients is more conservative than an informed censoring removal

EAG comments

- Including benefits but not costs of retreatment biases the analysis
- Given that efficacy has not been adjusted, the most appropriate way to balance costs and benefits is to keep axi-cel re-treatment costs in the model

Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting; axi-cel, axicabtagene ciloleucel; EAG, external assessment group

Cost-effectiveness results

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

ICERs including confidential discounts will be presented in Part 2.

Summary

- Company's base case is **lower** than the upper end of what would usually be considered cost-effective use of NHS resources when considering end-of-life criteria
- EAG's base case is **lower** than the upper end what would usually be considered cost-effective use of NHS resources when considering end-of-life criteria

Abbreviations: EAG, external assessment group; ICER, incremental-cost effectiveness ratio

Impact of EAG preferred assumptions on company base case ICER

Small impact

Table 5 Impact of individual EAG preferred assumptions compared with company base case

SN.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
1	Log-logistic MCM for axi-cel OS	↓	↓	↑
2	Include re-treatment costs for axi-cel	↑	=	↑
3	**EAG base case** 1+2 combined	↑	↓	↑

Arrow indicates direction of change in costs, QALYs or ICER **compared to company post ACM1 base case**

Abbreviations: ACM, appraisal committee meeting; axi-cel, axicabtagene ciloleucel; EAG, external assessment group; ICER, incremental-cost effectiveness ratio; MCM, mixture-cure model; OS, overall survival; QALY, quality-adjusted life year; SN., scenario number

Managed access

Criteria for a managed access recommendation

Uncertainty	How uncertainty can be addressed
Axi-cel and SoC overall survival	ZUMA-7 longer term follow-up
Axi-cel and SoC event free survival	ZUMA-7 longer term follow-up
Generalisability of ZUMA-7 data to NHS e.g. bridging chemotherapy use	SACT data collection