Poster EE27

A Best Practice Guide to Cost-Effectiveness Modelling of CAR Ts in Large B-Cell Lymphoma

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BACKGROUND

- Axicabtagene ciloleucel (**axi-cel**) is the first chimeric antigen receptor T-cell (CAR T) therapy to receive a positive recommendation by multiple country health technology assessment (HTA) agencies for the treatment of diffuse large B-cell lymphoma (DLBCL) at second-line (2L).[1-9]

Axi-cel key clinical trials

ZUMA-7[10]
Pivotal trial
Phase 3, dual-arm trial that investigated axi-cel as a 2nd line DLBCL treatment

ZUMA-1[11]
Supportive evidence
Phase 2, single-arm trial that investigated axi-cel as a 3rd line DLBCL treatment.

- Appraisals were based on **ZUMA-7**, where axi-cel exhibited superior overall survival (OS) vs. standard of care (SoC; salvage chemoimmunotherapy then high-dose chemotherapy with autologous stem-cell transplant for responders).
- However, different ZUMA-7 data cuts were used for the HTA assessments. The **Interim** analysis used 25-month follow up and the **Primary** analysis used 47-month follow up (Figure 1).
- **ZUMA-1** data were available as supportive evidence, which is a later-line trial with 5-year follow-up in the same indication (Figure 1), demonstrating the plausibility of cure and high levels of precision regarding the estimated cure fraction. Relative to ZUMA-7, the ZUMA-1 population is expected to have a higher risk of mortality and increased DLBCL disease progression.
- The company's choice of OS extrapolation for the HTA assessments was based on goodness-of-fit criterion (AIC and BIC), long-term considerations of visual and statistical fit, and the exclusion of clinically implausible distributions for axi-cel in the Interim analysis based on the ZUMA-1 survival data.
- The ZUMA-7 curves determined clinically implausible were those where the cure fraction or survival curve were lower than (or matched) those in ZUMA-1. This included exponential, log-logistic and log-normal (see Figure 1).
- In the SoC arm of ZUMA-7 a high number of participants received subsequent CAR T treatment. For countries where CAR T was not approved for routine use for 3L+ DLBCL treatment, crossover adjustments were available for use.

OBJECTIVES

- To summarise how different agencies with cost-effectiveness analysis as part of the HTA process assessed the key available evidence, with the aim to understand how the uncertainty in survival extrapolations were considered, the role of relevant supportive evidence (ZUMA-1) and other considerations.
- Provide recommendations to improve practice and consistency in approaches for future assessments.

METHODS

- The company submissions and feedback provided by agencies was reviewed for eight 2L DLBCL axi-cel appraisals: Australia, Canada, Denmark, France, England, the Netherlands, Norway, and Sweden.
- A qualitative assessment was undertaken for the way in which the evidence was considered by the HTA agencies, with a focus on the uncertainty around modelling methods for long-term survival and how these impact access to treatment.

RESULTS

- **Figure 1** displays the evidence for the Interim submissions: Interim ZUMA-7 axi-cel OS distributions and cure fractions, alongside ZUMA-1 data that was used to validate ZUMA-7.
- All Primary ZUMA-7 OS extrapolations and cure fractions for axi-cel, overlaid with the company and HTA agency preferred Interim ZUMA-7 OS analysis curves are plotted in **Figure 2**.
- **Table 1** summarises key considerations from each appraisal.

Figure 1: Interim ZUMA-7 and ZUMA-1 axi-cel OS

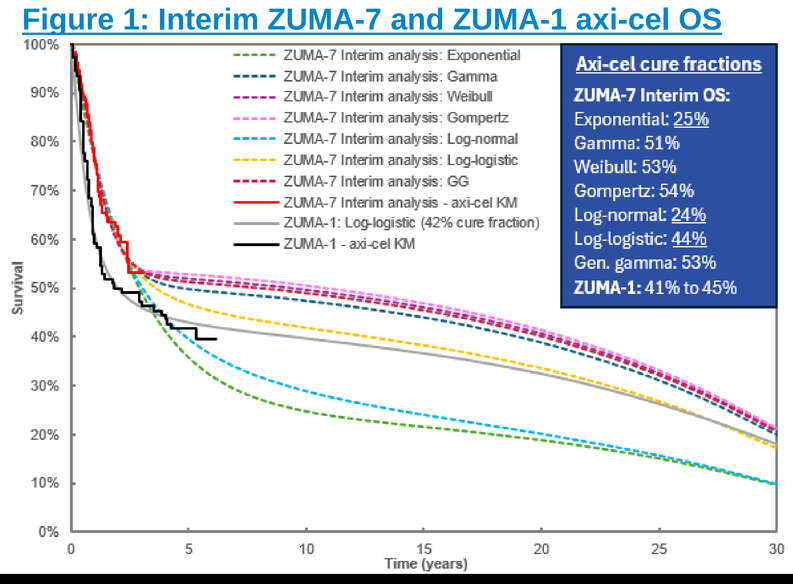

Figure 2: Primary and key Interim ZUMA-7 axi-cel OS

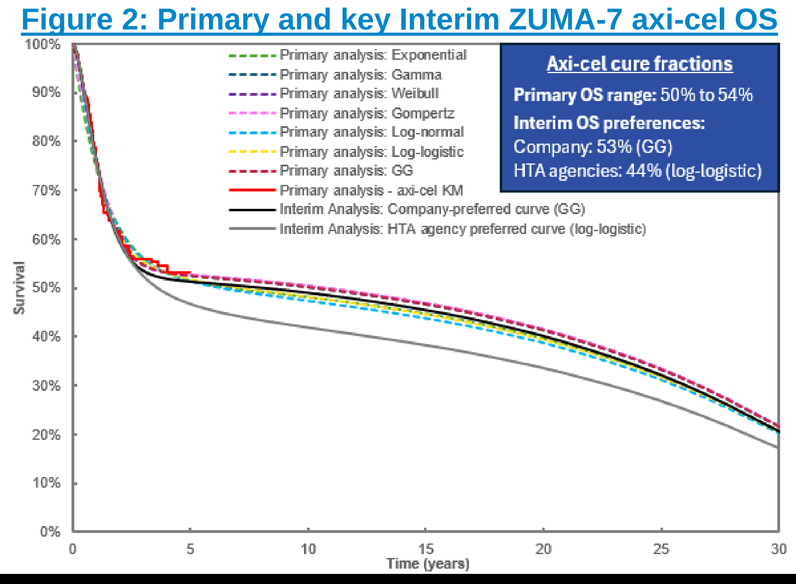

Table 1. Key elements extracted from axi-cel appraisals

	Axi-cel appraisal submission country and health technology assessment agency							
	Norway NoMA	Canada CADTH	England NICE	Australia MSAC	Sweden TLV	France HAS	Denmark DMC	The Netherlands ZIN
Data cuts used in the model at submission								
Data cuts available at submission	Interim only*	Interim only	Interim only	Interim (rejected) and then Primary	Interim** and then Primary	Primary only	Primary only	Primary only
Reported survival modelling methods for long-term outcomes								
Full cure fraction ranges	Axi-cel: 24-54%; SoC: 32-49%			Interim: axi-cel: 24-54%; SoC: 32-49% Primary: axi-cel: 50-54%; SoC: 41-45%		Axi-cel: 50-54%; SoC: 41-45%		
Submitted OS distributions (cure fractions)	Axi-cel: GG (53%) SoC: GG (42%)	Axi-cel: GG (53%) SoC: GG (42%)	Axi-cel: GG (53%) SoC: Crossover adjusted HR	Axi-cel: GG (53%) SoC: GG (42%) Axi-cel: gamma (54%) SoC: GG (41%)	Axi-cel: GG (53%) SoC: GG (42%) Axi-cel: GG (54%) SoC: GG (41%)	Axi-cel: GG (54%) SoC: GG (41%)	Axi-cel: gamma (54%) SoC: Crossover adjusted HR	Axi-cel: GG (54%) SoC: GG (41%)
Agency preferred OS distributions	Axi-cel: GG SoC: GG	Axi-cel: log-logistic SoC: GG	Axi-cel: log-logistic SoC: Crossover-adjusted HR	Interim: NR Axi-cel: gamma SoC: GG	Interim: NR Axi-cel: log-normal SoC: log-normal	Axi-cel: GG SoC: GG	Axi-cel: gamma SoC: Crossover-adjusted HR	Axi-cel: exponential SoC: GG
Agency preferred OS cure fractions	Axi-cel: 53% SoC: 42%	Axi-cel: 44% SoC: 42%	Axi-cel: 53% SoC: NR	Interim (both): NR Axi-cel: 54% SoC: 41%	Interim (both): NR Axi-cel: 50% SoC: 44%	Axi-cel: 54% SoC: 41%	Axi-cel: 54% SoC: NR	Axi-cel: 51% SoC: 41%
Rationale provided for preference	Submission base-case considered appropriate *	Clinically plausible, most conservative axi-cel OS curve	Clinically plausible, most conservative options selected	Submission base-case considered appropriate	Most conservative options selected	Submission base-case considered appropriate	To account for axi-cel not approved at 3L+	Clinically plausible, most conservative axi-cel OS curve
ZUMA-1: Agency considerations	Validate mixture cure modelling	Extrapolation selection	To excluded implausible curves	Both submissions: Not considered	Not considered	Not considered	Validate mixture cure modelling	Validate mixture cure modelling
Other considerations in assessment: Agency preferred settings and perspective								
Post-event utility data source	ZUMA-1	Clinical expert opinion	ZUMA-1	Interim: ZUMA-7 Primary: ZUMA-1	ZUMA-1	ZUMA-1	ZUMA-1	ZUMA-1
Survivor mortality	SMR: 1.09	SMR: 1.18	SMR: 1.09	SMR: 1.09	SMR: 1.09	SMR: 1.09	SMR: 1.09	SMR: 1.09
Manufacturing success	Neutral comments	Negative comments	Re-apheresis cost captured in model	No comment	No comment	No comment	Negative comments	No comment

* NoMA were only provided a description of the Primary Analysis OS to support results from Interim cost-effectiveness analysis. ** TLV did not formally assess the Interim analysis submission documents.
Abbreviations: Axi-cel – axicabtagene ciloleucel; EFS – event-free survival; GG – generalised-gamma; OS – overall survival; NR – not reported; SMR – standardised mortality ratio; SoC – standard of care.

Submissions using Interim axi-cel data only

- NICE considered exponential and log-normal clinically implausible for axi-cel OS as the cure fractions were below those in ZUMA-1 (Figure 1). CADTH and NICE preferred the log-logistic model to extrapolate axi-cel OS because it was considered the most conservative model, whilst still reflecting the survival benefit conveyed in the ZUMA-1 data.
- NoMA stated that Interim data were too immature to estimate a cure fraction. ZUMA-1 was used to validate the use of MCM extrapolations for OS and exclude the use of spline-models. Primary analysis became available during the submission process and was used to help validate the long-term survival predictions in the model based on the Interim OS data.

Submissions using Interim and Primary axi-cel data

- MSAC did not state a preferred OS distribution in the first submission based on Interim data, citing too much uncertainty. In the second submission with the Primary OS data, MSAC accepted generalised gamma for axi-cel.
- TLV did not formally assess the first submission. In a conservative approach to account for uncertainty in the Primary OS data, the TLV selected the most conservative distributions for axi-cel and SoC in the second submission.
- ZUMA-1 was not considered directly in OS modelling by either MSAC or TLV. MSAC considered ZUMA-1 too limited, as it is a single arm trial at a different line of treatment (3L+).

Submissions using Primary axi-cel data only

- Both the DMC and HAS accepted the axi-cel OS distribution proposed within the company submission.
- ZUMA-1 was used to validate the use of MCM extrapolations for OS by the DMC and ZIN, but not by HAS.
- ZIN preferred the exponential OS distribution for axi-cel to intentionally select a conservative estimate because median survival was not met in ZUMA-7.

Moving from Interim to Primary OS (Figure 2)

- Figure 2 demonstrates that the company-preferred axi-cel Interim OS distribution (generalised gamma; black line) was consistent with the Primary OS survival curve convergence.
- CADTH and NICE conservatively chose the log-logistic Interim OS distribution (solid grey line), which underestimated the axi-cel survival benefit relative to the Primary OS analysis.

Other considerations in assessment

- Crossover adjustments were used when CAR T treatment was not approved for routine use in 3L+ DLBCL (Denmark and England) as SoC in ZUMA-7 did not reflect clinical practice.
- Most agencies used ZUMA-1 post-event utility data.
- An SMR of 1.09 for was used by all agencies, except CADTH who utilised a conservative estimate of 1.18.
- Manufacturing failure results in delays to treatment and worse patient outcomes.[12] The 99% axi-cel manufacturing success was viewed in a negative or neutral framing by all agencies.

CONCLUSIONS

- This review of 2L DLBCL axi-cel HTA appraisals demonstrated that conservative approaches to extrapolation were used by HTA agencies in response to perceived uncertainties, with limited consideration of clinical plausibility or the wider evidence.
- This conservative approach led to the selection of the log-logistic axi-cel Interim OS distribution (see Figures 1 and 2), which proved to undervalue the axi-cel survival benefit (Figure 2). The Interim base-case was only considered appropriate when validated with the Primary OS data.
- Whilst ZUMA-1 analyses led to agencies accepting the plausibility of cure, formal use in anchoring or confirming Interim ZUMA-7 distributions was absent or varied.
- As most agencies took a conservative approach to OS distribution selection, without ZUMA-1 to validate the ZUMA-7 OS distributions, agencies may have selected even more pessimistic distributions.
- Inconsistencies in approaches were still evident, with most agencies preferring to use more conservative functions.
- HTA agencies selecting 'pessimistic' OS curves without considering clinically valid rationale or fully incorporating all wider evidence, risk under-valuing the technology and disincentivising future investment.
- Requiring 48-months follow-up from a comparative Phase 3 randomised control trial, whilst not considering mature and relevant supportive evidence, is a high bar to set for pharmaceutical companies, and may be prohibitive, can result in delays to access to treatment and loss of life.
- When CAR T is not in routine use at 3L+ DLBCL, there is increased reliance on crossover adjustment analyses.

RECOMMENDATIONS

- Greater consideration of the evolving evidence base when selecting appropriate survival and post-event utility settings, particularly where more mature data is available in later lines.
- Encourage more formal approaches to incorporating relevant external evidence to address uncertainties, rather than employing conservative assumptions

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DISCLOSURES

- BD, SV and JTS are employees of Kite, a Gilead Company and hold stock in Gilead.

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