PBI36

Review and Comparison of Overall Survival Extrapolation in Health Technology Assessments CAR-T Therapies

Adam Kasle, Tingting Qu, Yang Meng

BresMed America Inc, Las Vegas, NV, USA

Background and objectives

Chimeric antigen receptor T-cell (CAR-T) therapy is a transformative therapy that involves patients' own immune cells being collected, engineered, and infused back to attack cancer cells. In 2017, two CAR-T therapies were approved by the US Food and Drug Administration (FDA): axicabtagene ciloleucel for the treatment of adults with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)[1] and tisagenlecleucel for the treatment of pediatric B-cell acute lymphoblastic leukemia (B-ALL).[2]

These therapies have recently undergone cost-effectiveness evaluations by the US Institute for Clinical and Economic Review (ICER) and the UK National Institute for Health and Care Excellence (NICE). We reviewed and compared these assessments, focusing on extrapolation of overall survival (OS), to explore which method was most suitable and accurate in predicting long-term OS.

Methods

We identified one ICER evaluation that included two populations and three NICE technology appraisals (TAs) of the cost-effectiveness of CAR-T therapies in B-ALL and R/R DLBCL, which are presented in Table 1. Following review of OS methods in each evaluation, we performed a targeted search of updated trial data cuts and compared the original OS extrapolation to the latest trial data available.

Table 1: Overview of NICE and ICER CAR-T therapy valuations

Evaluation	NICE TA554[3]	NICE TA559[4]	NICE TA567[5]	ICER DLBCL[6]	ICER B-ALL[6]
Population	R/R B-ALL in people aged up to 25 years	R/R DLBCL or primary mediastinal large B-cell lymphoma in adults after two or more systemic therapies	R/R DLBCL in adults after two or more systemic therapies	R/R DLBCL in adults after two or more systemic therapies	R/R B-ALL in people aged up to 25 years
Trial	ELIANA, ENSIGN, B2101J	ZUMA-1	JULIET	ZUMA-1	ELIANA, ENSIGN, B2101J
Intervention	Tisagenlecleucel	Axicabtagene ciloleucel	Tisagenlecleucel	Axicabtagene ciloleucel	Tisagenlecleucel
Comparators	Blinatumomab and salvage chemotherapy	Salvage chemotherapy excluding pixantrone	Salvage chemotherapy excluding pixantrone	Salvage chemotherapy	Clofarabine-based therapy and blinatumomab-based therapy
Final recommendations	Recommended for CDF	Recommended for CDF	Recommended for CDF	Cost effective, but highly uncertain	Cost effective, but highly uncertain

Key: R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; R/R DLBCL, relapsed/refractory diffuse large B-cell lymphoma; ICER, Institute for Clinical and Economic Review; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Results

Table 2: OS extrapolation methods used in CAR-T therapy evaluations

Evaluation	Method for extrapolation (base case)	NICE criticisms/ICER justifications	Final model approach (if applicable)
NICE TA554	Exponential mixture cure model, using a logistic regression to model probability of patients experiencing long-term remission; cure fraction was based on proportion of patients alive at 54 months; uncured patients followed parametric curve from time of infusion	Cure fraction was a key driver of results and was highly uncertain given that it varied by approximately 35% in scenario analyses due to lack of long-term data	Company's preferred extrapolation using mixture cure models; since longer-term follow up data were not available, the Committee still considered this highly uncertain
NICE TA559	Weibull mixture cure model, using a logistic regression to model probability of patients experiencing long-term remission; cure fraction for base case curve was 50%; uncured patients followed parametric curve from time of infusion	Cure fraction was a key driver of results and was highly uncertain given that it varied between 1% and 53% in scenario analyses, due to data immaturity and short follow-up in ZUMA-1; ERG preferred a hybrid approach using best fitting single OS curve (log-logistic) constrained by PFS curve, resulting in 40% cure fraction	Company's preferred extrapolation using mixture cure models; since longer-term follow-up data were not available, the Committee still considered this highly uncertain; true OS was between company's and ERG's preferred extrapolations
NICE TA567	Log-normal mixture cure model to predict a cure fraction; revised base case: one-knot spline using 2018 JULIET data	Hybrid (spline) model was easier to validate clinically and allowed experts to specify a time point at which patients were cured; cure point between 2 and 5 years was most clinically plausible	One-knot spline model, with cure point at 2 years with standard mortality ratio of 1.0 applied to general population mortality, while the Committee noted that 2 years was optimistic and ERG analysis (4–5 years) was pessimistic; further long-term data were necessary to address uncertainty
ICER DLBCL	Log-normal curve, with a cut-off at 24 months, after which patients experienced general population mortality	Log-normal curve chosen based on AIC; choice of cut-off and general population mortality after cut-off based on flattening of OS curve in publicly available trial data	N/A
ICER B-ALL	Log-normal curve, with a cut-off at 30 months, after which patients experienced general population mortality	Log-normal curve chosen based on AIC; choice of cut-off and general population mortality after cut-off based on flattening of OS curve in publicly available trial data	N/A

Key: AIC, Akaike information criterion; B-ALL, B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; ERG, Evidence Review Group; HTA, health technology assessment; ICER, Institute for Clinical and Economic Review; N/A, not available; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression free survival; TA, technology appraisal.

Discussion

We identified a newer data cut of ZUMA-1 after the NICE and ICER assessments.[7] Table 3 compares the key OS extrapolation results reported in the health technology assessments (HTAs), with the latest data cut available. Using digitized data, Figure 1 shows the overlay of original and newer Kaplan–Meier data, as well as the preferred extrapolations in the HTAs.

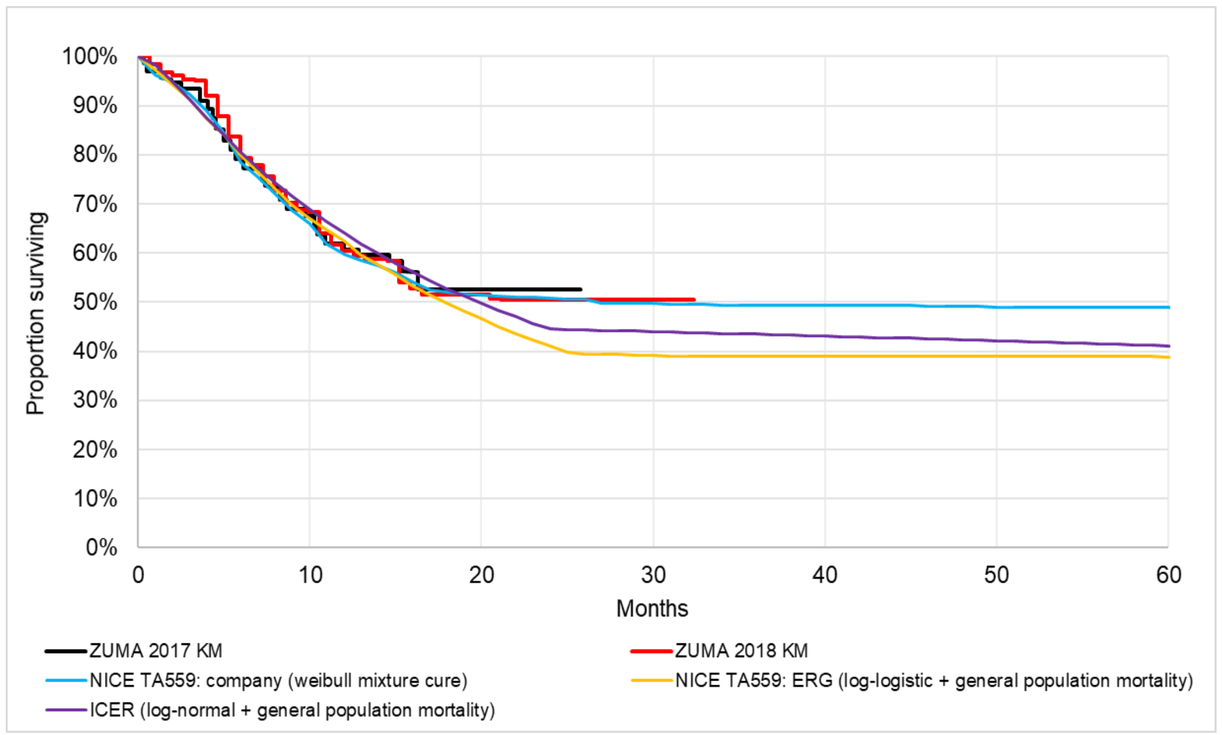
The company base case OS extrapolation approach in NICE TA559 (a log-logistic mixture cure model with an estimated cure fraction of 50%) appears to predict the latest available Kaplan–Meier data better than the ERG-preferred curve and the curves chosen by ICER.

Table 3: Comparison of OS extrapolations in CAR-T therapy evaluations vs results from newer trial data cuts

Evaluation	Trial data source (data cut date)	OS results in economic evaluation	Newer data cut date	Notable OS results in newer data cut
NICE TA559	ZUMA-1 (August 2017)[8]	Estimated 24-month survival: • Company base case: 50.6% • ERG base case: 41.0%	August 2018[7]	Estimated 24-month survival: 50.5% (95% CI: 40.2, 59.7%); median OS not reached at median follow-up of 27.1 months
ICER DLBCL		Estimated 24-month survival: • 44.19%; those alive at 2 years were considered cured, as 42.00% were alive at 5 years		

Key: B-ALL, B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; ERG, Evidence Review Group; ICER, Institute for Clinical and Economic Review; NICE, National Institute for Health and Care Excellence; OS, overall survival; TA, technology appraisal.

Figure 1: Comparison of OS extrapolations vs trial Kaplan–Meier data over 5 years for axicabtagene ciloleucel in DLBCL evaluations



Key: DLBCL, diffuse large B-cell lymphoma; ERG, evidence review group; ICER, Institute for Clinical and Economic Review; KM, Kaplan-Meier, NICE, National Institute for Health and Care Excellence; OS, overall survival; TA, technology appraisal.

Conclusions

Different approaches, including mixture cure models, spline models and the use of general population mortality after a cutoff time have been used in recent NICE TAs and US ICER assessments for extrapolation of OS for CAR-T therapies.

Mixture cure models seem to be a potentially suitable and promising method and have predicted Kaplan–Meier data available from a newer trial data cut more accurately than other methods.

In the recent ICER guidance on assessing high-impact single and short-term therapies, ICER has made cure proportion modeling (including mixture and non-mixture cure proportion models) the standard reference case when relevant and suggests addressing uncertainty by providing alternative survival modeling approaches.[9]

References

1. Gilead. YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion. 2017. Available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf. Accessed: January 13, 2020.
2. Novartis. KYMRIAH™ (tisagenlecleucel) suspension for intravenous infusion. 2017. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf. Accessed: January 13, 2020.
3. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. 2018. Available at: https://www.nice.org.uk/guidance/ta554/history. Accessed: January 13, 2020.
4. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. 2019. Available at: https://www.nice.org.uk/guidance/ta559/history. Accessed: January 13, 2020.
5. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. 2019. Available at: https://www.nice.org.uk/guidance/ta567/history. Accessed: January 13, 2020.
6. Institute for Clinical and Economic Review. CAR-T Therapies: Final Evidence Report. 2018. Available at: https://icer-review.org/material/car-t-final-report/. Accessed: January 13, 2020.
7. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019; 20(1):31-42.
8. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N. Engl. J. Med.* 2017; 377(26):2531-44.
9. Institute for Clinical and Economic Review. Adapted Value Assessment Methods for High-Impact "Single and Short-Term Therapies" (SSTs). 2019. Available at: https://icer-review.org/wp-content/uploads/2019/11/ICER_SST_FinalAdaptations_111219-1.pdf. Accessed: January 13, 2020.

Accepted for presentation at ISPOR 2020, Orlando, Florida, USA

QR CODE PLACE HOLDER