Cost effectiveness of axicabtagene ciloleucel versus tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the United States

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Aims: To assess from a US payer perspective the cost-effectiveness of the chimeric antigen receptor T (CAR T)-cell therapies axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) to treat relapsed or refractory (r/r) large B-cell lymphoma (LBCL) following ≥2 systemic therapy lines.

Methods: A three-state (i.e. pre-progression, post-progression, and death) partitioned survival model was used to estimate the quality-adjusted life-years (QALYs) and costs for patients on each treatment over a lifetime horizon. Progression-free survival (PFS) and overall survival (OS) were based on a matching-adjusted indirect treatment comparison (MAIC) that accounted for differences in trial population baseline characteristics. Mixture cure models (MCMs) were used to account for long-term survivors. Costs included drug acquisition and administration for the CAR T-cell therapies and conditioning chemotherapy, apheresis, CAR T-specific monitoring, transplant, hospitalization, adverse events, routine care, and terminal care. Health state utilities were derived from trial and published data. Sensitivity analyses included probabilistic sensitivity analyses (PSAs) and an analysis of extremes that assessed the results across a vast array of combinations of parametric OS and PFS curves across the two therapies.

Results: Compared to tisa-cel, axi-cel resulted in 2.31 QALYs gained and a cost reduction of $1,407 in the base case. In the PSA, the cost per QALY gained was ≤$31,500 in 95% of the 1,000 simulations. In the analysis of extremes, the cost per QALY gained was ≤$7,500 in 99% of the 1,296 combinations of MCMs and ≤$40,000 in 95% of the 1,296 combinations of standard models.

Limitations: In absence of head-to-head comparative data, we relied on a MAIC, which cannot account for all possible confounders. Moreover, some outcomes (i.e. transplantations, hospitalizations, adverse events (AEs)) were not adjusted in the MAIC.

Conclusions: In this simulation, axi-cel was a superior treatment option as it is predicted to achieve better outcomes at lower or minimal incremental costs versus tisa-cel.

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies characterized by an often aggressive and unpredictable course. Considered a common form of cancer, approximately 500,000 new NHL cases and 250,000 NHL-associated deaths are reported annually. In the United States (US), an estimated 77,240 new cases and 19,940 NHL-associated deaths are predicted to occur in 2020. The most common form of NHL are large B-cell lymphomas (LBCLs), which include diffuse LBCL (DLBCL), primary mediastinal B-cell lymphoma, and transformed follicular lymphoma.

First-line treatment of LBCL typically includes rituximab chemotherapy and haemopoietic stem cell transplantation. However, suboptimal outcomes persist with 30–50% of patients experiencing relapsed or refractory (r/r) disease and a 5-year survival of approximately 63% in the US and 55% in Europe. Moreover, the majority of DLBCL patients are ineligible for transplant and ultimately have no curative options.

Chimeric antigen receptor T-cell (CAR T) therapy has emerged as a new treatment paradigm with demonstrable improvements in outcomes compared to historic data from salvage chemomunotherapy (e.g. complete response rates of 58% for axi-cel in ZUMA-1, 40% for tisa-cel in JULIET trial versus 7% for salvage chemotherapy in SCHOLAR-1). CAR T therapies target the
antigens expressed by malignant and non-malignant B-cells to degrade the volume of cancerous cells within the body. Two CAR T products currently predominate the r/r LBCL treatment landscape. Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are approved by the US Food and Drug Administration to treat r/r LBCL after ≥2 prior systemic therapies.22,23

Notwithstanding the improved outcomes and increased costs associated with CAR T therapy compared to salvage chemotherapy (with gains of approximately 2–8 years of life at increased costs of approximately $350,000–$490,000 across prior cost-effectiveness models comparing CAR T to chemotherapy24–27), limited information is available regarding comparative cost effectiveness among these CAR T therapies. The present analysis was conducted to assess from a US payer perspective the cost effectiveness of axi-cel versus tisa-cel for the treatment of r/r LBCL among patients who previously received ≥2 lines of systemic therapy.

Methods

We developed a mathematical model to estimate the cost effectiveness of axi-cel versus tisa-cel for the treatment of r/r LBCL in patients who received ≥2 lines of systemic therapy. The model was developed in accordance with established guidelines28,29 and reported according to the CHEERS guidelines30.

This analysis adopted a US payer perspective and included direct medical costs (2019 US dollars), regardless of the setting or location of care; indirect and direct non-medical costs were excluded. The primary outcome of the analysis was the incremental cost per quality-adjusted life-year (QALY) gained. All outcomes were discounted at 3.0% annually consistent with accepted guidelines for US-based pharmacoeconomic analyses31. Costs obtained from published literature or data sources reported before 2019 were inflated to 2019 US dollars using the medical care component of the US Bureau of Labor Statistics Consumer Price Index for all urban consumers12.

The model adopted a lifetime horizon to allow sufficient time for outcomes to accrue. In practice, the time horizon was set at 45 years based on the cohort’s mean age at baseline (56 years in the JULIET trial26). A cycle length of 1 month (30.4375 days) was chosen as it provides the appropriate level of detail and is consistent with previous analyses of axi-cel and tisa-cel in LBCL.25,27,33,34

The modelled target population was consistent with patient population in the ZUMA-1 trial (NCT02348216)19, adjusted in the base case analysis based on a published matching-adjusted indirect comparison (MAIC)35 in which ZUMA-1 trial population was adjusted to match the JULIET trial (NCT02445248) population using the standard matching algorithm per Signorovitch et al.16 by matching International Prognostic Index (IPI) score (<2 or 2), Eastern Cooperative Oncology Group (ECOG) score (0 or 1), disease stage (<3, 3 or 4), refractoriness to therapy (r/t), double/triple hit status (double hit or triple hit), number of prior therapies (<3, 3 or ≥4), and cell of origin (DLBCL or other types of LBCL). The patient characteristics applied in the model (i.e. mean age 56 years, 64.5% female, body surface area (BSA) of 1.92 m², and body weight of 78.7 kg) were based on the JULIET trial37. More detailed study and patient characteristics of ZUMA-1 and JULIET are provided in Supplemental Table 1.

Model structure

Consistent with previous cost-effectiveness models evaluating CAR T therapy24–27,33,34, a three-state (pre-progression, post-progression, and death) partitioned survival model (PSM) was selected to track the outcomes of two identical cohorts, one receiving axi-cel and the other receiving tisa-cel, who had relapsed or become refractory on ≥2 prior lines of systemic therapy. The model considered the patient cohorts to be distributed into these three mutually exclusive states, while accounting for their direct medical costs and QALYs.

Building on prior work for CAR T in r/r LBCL (e.g. previous economic models accepted in health technology assessments33,34 or published literature24,25,27), mixture cure models (MCMs) were employed in the base case, explicitly assuming that a portion of each cohort would achieve long-term remission. This assumption was partly driven by the observation that ZUMA-1 and JULIET may include heterogeneous populations in terms of progression-free survival (PFS) and overall survival (OS) outcomes. That is, over time, the survival curve may exhibit an “L” shape with a long tail or plateau, suggesting that a fraction of patients may achieve favourable longer-term outcomes and may not experience LBCL-related mortality. In an alternate scenario analysis, standard parametric models without mixture cure were applied.

Model inputs

Progression-free and overall survival

Base case. Building on prior research that demonstrated the possibility of cure associated with the use of CAR T therapies in this setting25,27,33,34,38, we adopted a partitioned survival mixture cure modelling (PS-MCM) approach to capture the heterogeneity of underlying patient characteristics as they relate to treatment outcomes in the PSM framework. Unlike the standard PSM approach that relies on single parametric curves (one for each OS and PFS) for the overall patient population, the PS-MCM stratified OS and PFS survival curves into one cured patient group and one non-cured group. The maximum likelihood estimation method39 was used to identify a cure fraction and all other model parameters while fitting six standard parametric functions (i.e. exponential, Weibull, log-logistic, log-normal, Gompertz, and gamma) to the non-cured group’s PFS and OS curves. It was assumed that patients in the cured group experience no disease-related events (i.e. disease progression or disease-related mortality events). The survival curves of both groups were adjusted to account for age- and gender-specific background US mortality40, assuming the mortality events observed within the trial period only captured LBCL-related deaths. The final survival curve applied for the overall population was then estimated based on the two groups’ curves
weighted by the cure fraction. This procedure was applied to the individual patient data of the ZUMA-1 trial, before and after adjusting baseline patient characteristics to match those of JULIET via MAIC, and to the JULIET data, which were recovered using the algorithm developed by Guyot et al.41. In each of these analyses, the parametric OS and PFS distributions used in the model for each treatment arm were selected based on the standard goodness of fit criterion as measure by the Akaike information criterion (AIC), second-order bias correction of AIC (AICc), log-likelihood, and evidence ratio.

Scenario analyses. Multiple additional scenario analyses were conducted, including: (1) an analysis which used standard PSM instead of the PS-MCM to fit the OS and PFS independently for both therapies (similarly to the base case, the standard statistical tests (e.g. AIC, AICc) were used to decide the choice of the parametric distribution for OS and PFS in both therapies in this scenario); (2) an analysis using unadjusted ZUMA-1 data to assess the impact of the MAIC on the results; (3) an analysis in which the best fit model for each therapy was selected based on the lowest AIC among 12 possible models (i.e. six standard PSM and six PS-MCM) each for OS and PFS; and (4) a comprehensive set of analyses testing the impact of parametric survival function selection. In the latter, we ran the model across all 1,296 possible combinations of six parametric models for the OS/PFS curves across the two CAR T therapies (i.e. 1,296=(6 functions)^2 (2 CAR T × 2 survival curves (i.e. OS and PFS))). This analysis was conducted for the PS-MCM and standard PSM separately, and the results presented via cost effectiveness acceptability curves (CEAC).

Adverse events
Grade 3/4 adverse events (AEs) occurring in ≥5% of patients in the ZUMA-1 and JULIET trials were considered for inclusion in the model. To prevent double counting, in line with Roth et al.25, it was assumed that all AEs (such as cytokine release syndrome (CRS) and neurotoxicity) occurred while patients were hospitalized for their initial treatment, with the exception of B-cell aplasia requiring treatment with intravenous immunoglobulin (IVIG) (Table 1).

Utilities
Utilities were applied to the various health states. Based on the published analysis of the EuroQol EQ-5D-5L data collected in ZUMA-142, we applied different utility values for pre-progression time while on and off treatment, with a further distinction between the first 24 months and the remainder of the model time horizon (Table 1). Post-progression utility was based on external literature43 (Table 1).

Costs
Costs associated with CAR T therapy included drug acquisition, apheresis, drug administration, conditioning chemotherapy, monitoring, and AE costs, all applied as one-time costs in the first model cycle. The drug acquisition cost for CAR T therapy, given as a one-time treatment, was set at the manufacturers’ list price of $373,000 (Table 1), based on the wholesale acquisition cost (WAC) from the RED BOOK44. CAR T therapies require an apheresis procedure in which peripheral blood mononuclear cells for CAR T production are harvested prior to administration of the CAR T therapy. Costs of apheresis ($111.72) and administration ($143.08) were obtained from the Centers for Medicare and Medicaid Services (CMS) Physician Fee Schedule (Table 1)45. Patients also received one-time conditioning chemotherapy before the infusion of the CAR T, for which drug acquisition and administration costs were estimated (Table 1). In ZUMA-1, the population received intravenous (IV) fludarabine (30 mg/m² BSA per day) and cyclophosphamide (500 mg/m² per day) on days −5, −4, and −3 as conditioning chemotherapy18. In JULIET, most of the population received both IV fludarabine (25 mg/m²) and cyclophosphamide (250 mg/m²) for three doses (Table 1)20. For all drugs, a dose intensity of 100% was assumed and the assumption was made that there was no vial sharing. All drug acquisition costs were based on WACs obtained from RED BOOK44. All costs for IV administration and monitoring procedures were obtained from the CMS Physician Fee Schedule45.

In line with Roth et al.25, it was assumed that patients received one positron emission tomography (PET)/computed tomography (CT) scan and four follow-up office visits after CAR T infusion (Table 1).

As the base case model assumed inpatient administration of CAR T, it was assumed possible AEs such as CRS and neurological events would be treated during the inpatient stay. Therefore, additional AE costs were charged only for B-cell aplasia. In ZUMA-1, 8% of patients experienced B-cell aplasia and were treated with IVIG (Table 1); the treatment for B-cell aplasia in patients treated with axi-cel in our model was assumed to be a treatment course of IVIG (500 mg/kg every 4 weeks for 12 months) in line with Roth et al.25. In JULIET, 18.3% of patients received IVIG for treatment of B-cell aplasia with 1.43 infusions on average46.

Costs of SCT and hospitalization were estimated based on trial data and applied once in the first model cycle (Table 1). Based on the 1-year ZUMA-1 follow-up data (with a median follow-up of 15.4 months), 7.9% (eight out of 101 patients) received allogeneic SCT following r/r disease after axi-cel treatment (Kite data on file as of June 2020). In JULIET, after a median follow-up of 14 months, 5.4% of patients who did not have a response received SCT (six of 111 patients, five allogeneic, one autologous followed by allogeneic). The cost of SCT ($296,545) was based on the cost of allogeneic SCT from Broder et al.32,47.

According to ZUMA-1 and JULIET trial data, many patients receiving a CAR T infusion will be hospitalized for the treatment and remain in hospital for several days. This hospitalization occurs as the immune response is initiated and AEs may occur in the first few weeks following the CAR T infusion. The hospital length of stay for axi-cel and tisa-cel in our model was based on ZUMA-1 and JULIET data, respectively,
Table 1. Base case model parameter estimates and data sources.

| Parameter | Value | Distribution for sensitivity analyses | References |
|-----------|-------|---------------------------------------|------------|
| Female proportion at baseline | 64.5% | NA | 20 |
| Mean age at baseline, years | 56.0 | NA | 37 |
| Mean body weight (kg); surface area (m²) | 78.7; 1.92 | Normal | 37 |
| Tisa-cel CAR T conditioning chemotherapy and monitoring costs (one-off) | | | |
| LOS: non-ICU days (tisa-cel) | 13.9 | Gamma | 25,a |
| LOS: ICU days (tisa-cel) | 3.7 | Gamma | 25,a |
| LOS: non-ICU days (axi-cel) | 24.8 | Gamma | 25,b,b |
| LOS: ICU days (axi-cel) | 0.9 | Gamma | 25,b,b |
| Cost per day: non-ICU | $3,642 | Gamma | 32,48 |
| Cost per day: ICU | $6,044 | Gamma | 32,49 |
| Cost of SCT (per procedure) | $1,757 | Gamma | 32,50 |
| Adverse event cost (one-off) | | | |
| Axi-cel | 7.9% | Beta | Kite data on file |
| Tisa-cel | 5.4% | Beta | 20 |
| Pre-progression, routine care costs (<24 months) | | | |
| Pre-progression: routine care costs (<24 months) | $1,757 | Gamma | 32,50 |
| Pre-progression: routine care costs (>24 months) | $351 | Gamma | Assumption |
| End of life (3 months) | $18,759 | Gamma | 32,51 |
| Utilities | | | |
| Pre-progression: on CAR T cell treatment (applied in 1st month) | 0.740 | Beta | 42 |
| Pre-progression: off treatment (<24 months since model entry) | 0.782 | Beta | 42 |
| Pre-progression: off treatment (>24 months since model entry) | 0.820 | Beta | 42 |
| Post-progression | 0.390 | Beta | 43 |

Abbreviations. AEs, Adverse events; axi-cel, Axicabtagene ciloleucel; CAR T, Chimeric antigen receptor T-cell; CPT, Current procedural terminology; CT, Computed tomography; ICU, Intensive care unit; IVIG, Intravenous immunoglobulin; LOS, Length of stay; NA, Not applicable; PET, Positron emission tomography; SCT, Stem cell transplant; tisa-cel, Tisagenlecleucel; WAC, Wholesale acquisition cost.

as reported in published literature or health technology assessments.

Costs of hospitalization were obtained from published literature and the Healthcare Cost and Utilization Project (HCUP).

All patients were assumed to have the same routine care while alive, irrespective of treatment received (Table 1). The monthly cost of routine care ($1,757) was based on the disease-related imaging procedure costs (total disease-related health care costs, excluding chemotherapy, radiation therapy, AE, and SCT costs) in relapsed LBCL population. For patients who were alive and remained progression-free for more than 2 years, an 80% reduction in monthly routine care costs (i.e. $351) was assumed.

Terminal care costs were applied upon death (Table 1) to capture the resources used at the end of life, regardless of the cause of death. It was assumed that the terminal care costs accrued for three months, in line with Roth et al. For patients who were alive and remained progression-free for more than 2 years, an 80% reduction in monthly routine care costs (i.e. $351) was assumed.
For simplicity, the monthly cost was multiplied by three and applied as a one-off cost in the model upon death.25

Other assumptions
As this cost-effectiveness analysis relied on MAIC-adjusted OS and PFS for axi-cel (ZUMA-1 population reweighted to match JULIET trial), patient characteristics were also based on the JULIET trial. However, all other clinical inputs for axi-cel, such as hospitalization rates, transplant rates, and AE rates, were based on unadjusted ZUMA-1 trial data, assuming no differences before and after MAIC.

Outcomes
We estimated average per-patient costs, survival curves, life years (LYs), and QALYs, as well as incremental costs, QALYs, and cost per QALY gained. Costs were categorized as follows: (1) CAR T therapy-related costs: drug acquisition, apheresis, drug administration, conditioning chemotherapy, treatment-specific monitoring, and AE; (2) SCT; (3) hospitalization; (4) routine care costs; and (5) end of life care.

Sensitivity analyses
Parametric uncertainty was assessed via univariate and probabilistic sensitivity analyses (PSAs) (1,000 runs). Parameters included in these assessments were assigned an appropriate uncertainty distribution whereby the mean was typically equal to the point estimate used in the deterministic analysis (Table 1). The uncertainty around the central estimate was set according to distributional information provided in the original source.52 Where distributional information was not available, the standard error was typically set at 20%. For event rates and utility values, a beta distribution was used to restrict draws to the 0–1 range. For costs and resource use estimates, a gamma distribution was fitted to restrict draws to the 0-to-positive infinity range. For survival estimates, uncertainty was captured in the variance–covariance matrix of the parameter estimates and applied using the Cholesky decomposition approach.52 For the PSA, the results are presented via the CEAC.

Finally, a set of exploratory analyses were conducted to provide insight into the impact of some of the key assumptions made on model outcomes, including but not limited to variations in discount rates, change in the analytical horizon, assumptions about SCT and hospitalization, and testing how changing the assumptions about monthly routine care costs and utility of patients who survived without progression affects the results (i.e. in the base case, after 24 months, the utility increases from 0.782 to 0.82 and monthly routine care costs decreased from $1,757 to $351; in sensitivity analysis, the 24-month cut off varies from 24 to 60 months to infinity for routine care costs and utilities, in which routine care cost drops to $351 or $0 after the cut-off point) and utility increases to 0.82.

Validation
Model validity checks were largely undertaken according to the Assessment of the Validation Status of Health-Economic models (AdVISHE) checklist, except for an independent external review, which was replaced by an internal review.

Results
Base case
In the base case analysis using the PS-MCM, which allowed for patient heterogeneity in long-term remissions and survival, the predicted long-term OS curve for axi-cel (based on the MAIC adjustment) (Figure 1) was based on the log-logistic function, a gamma model for axi-cel PFS, a log-normal model for tisa-cel OS, and a log-logistic model for tisa-cel PFS. More details on fit statistics are provided in Supplemental Table 3 and 4. As Figure 1 shows, axi-cel resulted in better OS and PFS versus tisa-cel.

As shown in Table 2, compared to tisa-cel, axi-cel was predicted to result in higher LY (+3.90 years, undiscounted; +2.74 years, discounted) and QALY (+2.31 discounted) and slightly lower costs (~$1,407). The difference in total costs was driven by hospitalization costs (~$22,499) and routine care costs among progression-free survivors (+$18,106).

Univariate sensitivity analysis
Except for CAR T drug acquisition costs, few variables had a large impact on the cost per QALY gained (Figure 2). Acquisition costs for CAR T therapies also had the greatest impact on the incremental costs (Supplemental Figure 1). Other cost drivers included number of non-intensive care unit hospital days and pre-progression routine care cost. The utility of pre-progression survival had the greatest impact on incremental QALYs (Supplemental Figure 2). Other variables had a limited impact on the results of incremental costs or incremental QALYs.

Probabilistic sensitivity analysis
The cost per QALY gained was ≤$1,500 in 50% of simulations and ≤$31,500 in 95% of simulations for comparisons between axi-cel and tisa-cel (Figure 3).

Scenario analyses
While all scenarios analyses showed that axi-cel resulted in higher LYs and QALYs compared to tisa-cel, axi-cel remained cost effective and dominant when using the standard PSM models (Supplemental Figure 3), with cost per QALY gain of $8,087 when using PS-MCM but ignoring the MAIC (Supplemental Figure 4), and axi-cel remaining dominant when relying exclusively on best fit models across both PSM and PS-MCM (Supplemental Figure 5, Supplemental Table 5).

Supplemental Table 6 shows the results of additional scenario analyses. Specifically, analyses conducted to assess
the impact of discounting showed that under various scenarios, the cost per QALY gained for axi-cel vs. tisa-cel may vary from dominant to $2,471. Varying the time horizon within the range of 5–40 years had no impact on the direction of results (i.e. axi-cel being dominant). Axi-cel remained cost-effective when we conservatively assumed that long-term progression-free survivors start to experience reduction in monthly routine care costs or improvements in utilities after 60 months or even never. Axi-cel also remained cost-effective in scenarios where either SCT or hospitalization use was the same between axi-cel and tisa-cel.

This finding also reflects the same mechanism related to routine care costs: if these costs are reduced, relatively less costs accumulate in the axi-cel arm and its cost effectiveness therefore improves commensurably.

The set of analyses testing the impact of parametric survival function selection across 1,296 possible combinations (conducted for the PS-MCM and standard PSM separately) showed that the cost per QALY gained was $7,500 in 99% of the 1,296 combinations of MCMs and $40,000 in 95% of the 1,296 combinations of standard models (Supplemental Figure 6).

### Table 2. Base case results.

|                      | Axi-cel | Tisa-cel | Difference |
|----------------------|---------|----------|------------|
| Total undiscounted LYs | 13.72   | 9.82     | 3.90       |
| Pre-progression      | 13.11   | 8.82     | 4.29       |
| Post-progression     | 0.61    | 0.99     | −0.39      |
| Total discounted LYs | 9.47    | 6.73     | 2.74       |
| Pre-progression      | 8.89    | 5.98     | 2.91       |
| Post-progression     | 0.58    | 0.75     | −0.17      |
| Total discounted QALYs | 7.47    | 5.16     | 2.31       |
| Pre-progression      | 7.24    | 4.87     | 2.37       |
| Post-progression     | 0.23    | 0.29     | −0.06      |
| Total discounted costs | $586,313 | $587,720 | $1,407    |
| CAR T treatment-related costs |          |          |           |
| Drug acquisition     | $373,000 | $373,000 | $0        |
| Apheresis            | $112     | $112     | $0        |
| Drug administration  | $143     | $143     | $0        |
| Conditioning chemotherapy | $874     | $871     | $3        |
| Monitoring           | $715     | $715     | $0        |
| Adverse event        | $4,808   | $1,311   | $3,497    |
| Stem cell transplant | $23,489  | $16,029  | $7,459    |
| Hospitalization      | $72,977  | $95,476  | $22,499   |
| Routine care costs   |          |          |           |
| Pre-progression      | $56,564  | $38,548  | $18,106   |
| Post-progression     | $12,257  | $15,761  | −3,504    |
| Terminal care costs  | $41,285  | $45,755  | −4,470    |
| Costs per QALY gained |         |          |           |
| Costs per LY gained  |          |          |           |

Abbreviations. Axi-cel, Axicabtagene ciloleucel; CAR T, Chimeric antigen receptor T-cell; LY, Life years; QALYs, Quality-adjusted life-years; tisa-cel, Tisagenlecleucel.

### Discussion

This model was developed to assess the cost-effectiveness of axi-cel versus tisa-cel for treatment of rt/r LBCL after ≥2 lines of systemic therapy. The results indicate that axi-cel is associated with an additional undiscounted 3.90 LYs (2.74 discounted), 2.31 additional discounted QALYs, and decreased discounted costs of $1,407 compared to tisa-cel over a 45-year time horizon.

The discounted estimates of life expectancy, QALY, and cost for axi-cel resulting from our analysis are consistent with prior research, as detailed in Supplemental Table 7, despite that our model was based on an MAIC, which increased the estimates of OS and QALYs. For instance, our estimate of life expectancy for axi-cel of 9.47 years (when using MCM) and 5.84 years (when using standard model), fall within the range of survival estimates in the literature (2.83–11.80 years).

Similar observations can be made for QALY estimates (7.47 and 6.47 QALYs with and without MCM, respectively, versus a range of 2.07–7.67 in the literature). However, for tisa-cel,
the life expectancy results of our analysis were consistent with the only other publication including tisa-cel (5.90–8.25 years) when we used MCM (6.73 years) but more pessimistic when we used non-mixture cure modelling (2.83 years). Results for QALYs were more optimistic when using MCM (5.16 QALYs) and non-mixture cure modelling (4.32 QALYs) than reported in Lin et al. (2.82–3.92 QALYs).

Total costs for tisa-cel were estimated to be comparable to or slightly higher than reported in the literature.

To select the parametric survival function that best fit the observed data, we relied on key metrics such as AIC and AICc, visual inspection of the parametric fits, and clinical rationale – including the possibility of long-term remission and survival in a fraction of patients. When no statistically significant difference existed between the best MCM or best standard model in survival outcomes prediction, we placed more weight on the clinical rationale (i.e. the possibility of long-term remission and survival) in the model selection. In most cases, the fit statistics indicated that the MCM better fit the survival outcomes than standard (i.e. without explicitly modelling patient heterogeneity in term of survival) models. The only exception was for axi-cel OS after MAIC adjustment, in which the difference in the quality of the fit between the best standard model and the best MCM was relatively small. This suggests that the MAIC adjustment of the ZUMA-1 data perhaps resulted in a more homogeneous population with better (progression-free) survival in which long-term progression-free survivors may have become less distinguishable than the other patients. Thus, as a result, based primarily on clinical rationale, MCMs were adopted in the base case for both axi-cel and tisa-cel to allow for the possibility of long-term remission, in line with prior work for CAR T in r/r LBCL (e.g. previous economic models accepted in health technology assessments or published literature). Overall,
this reliance on the assumption of cure in a fraction of patients provides a robust estimation of future survival for the treatments of interest compared to the previously published models. In any event, the alternative scenarios – where the standard model was used to estimate survival for either both axi-cel and tisa-cel or axi-cel only – produced similar outcomes as in the base case model, providing further evidence of the robustness of the analysis.

This analysis benefits from the application of extensive sensitivity and scenario analyses to test the impact of key assumptions on the results and the policy conclusions. Overall, these analyses demonstrated that the model results are very robust. Probabilistic sensitivity analysis also showed that the cost per QALY gained was ≤$1,500 in 50% of simulations and ≤$31,500 in 95% of simulations for comparisons between axi-cel and tisa-cel. Scenarios analyses showed that axi-cel was highly cost effective when using the standard PSM, when ignoring the MAIC, and when relying exclusively on best fit models across both PSM and PS-MCM. Likewise, the analyses testing the impact of parametric survival function selection across 1,296 possible combinations (separately with the PS-MCM and the standard PSM) showed that the incremental cost per QALY gained associated with the use of axi-cel versus tisa-cel was acceptable in most cases. Specifically, these analyses showed that the cost per QALY gained was ≤$7,500 in 99% of possible combinations of MCMs and ≤$40,000 in 95% of the possible combinations of standard models.

We assumed that routine costs of patients with long-term PFS decreased by 80% after 2 years being progression-free. We also assumed that the utility of PFS remained unchanged for up to 2 years. In scenario analyses where the time cut-off increased to 5 years or infinity, when progression-free patients were assumed to incur lower routine care costs and higher utility over time, axi-cel remained dominant or was shown to be highly cost-effective.

While this analysis produced robust results, it is important to highlight some of its limitations. First, to remain conservative in our estimates, we neglected to include the costs of bridging chemotherapy and cryopreservation of apheresis products for patients on tisa-cel. In JULIET, approximately 90% of these patients received physician’s choice of bridging chemotherapy in the interval between start of screening and the tisa-cel infusion. In addition, axi-cel is generated from fresh apheresis product, whereas tisa-cel is generated from cryopreserved apheresis products and requires extra resources for cryopreservation and storage. Had these costs been included, the cost difference would have further favoured axi-cel.

Second, when using PSM – with or without assumption of cure – the OS and PFS curves can only be fitted separately without capturing the structural relationship between OS and PFS. This naturally can lead to implausible estimates, such as PFS exceeding the projected OS, as was the case of axi-cel. To deal with this limitation, PFS was set to be equal to the OS when PFS was predicted to be higher than the OS. Future research should consider a multistate Markov model with mixture cure to model OS and PFS simultaneously as well as account for potential cure effect of CAR T therapies.

Third, due to the lack of head-to-head trials comparing axi-cel to tisa-cel, this cost-effectiveness analysis relied on MAIC-adjusted OS and PFS for axi-cel (ZUMA-1 population reweighted to match JULIET population) to compare long-term outcomes and costs of axi-cel versus tisa-cel. One general limitation of MAIC is that only commonly observed differences in patient characteristics could be adjusted. Specifically, the MAIC used in the present analysis matched only for IPI score (<2 or 2), ECOG score (0 or 1), stage (≥3, ≥3 or ≥4), refractoriness to therapy (r/r), double/triple hit status (double hit or triple hit), number of prior therapies (<3, 3 or ≥4), and cell of origin (DLBCL or other types of LBCL). Additionally, although baseline patient characteristics were based on JULIET to be consistent with the MAIC-adjusted survival, all other clinical inputs for axi-cel such as hospitalization use, SCT rates, and AE rates were based on unadjusted ZUMA-1 data, assuming no differences before and after MAIC. Therefore, the assumptions regarding hospitalizations used in the analysis were based on the clinical trial evidence. However, since the completion of ZUMA-1 and JULIET, improvement in the management of patients treated with CAR T therapies may have led to reduction in the need for hospitalizations. In addition, both these trials had specific requirements for the hospitalization of patients. As such, our estimates may not represent more recent “real-world” outcomes and may likely overestimate hospitalization costs. Our decision to retain the assumption for hospitalization based on the clinical trial evidence is driven by our preference to be consistent in the choice of data sources (i.e. to ensure both efficacy and safety outcomes are from the same data sources). Nevertheless, to further test the impact of hospitalization (and SCT) assumptions, we conducted scenario analyses in which we assumed that SCT and hospitalizations rates for patients treated with tisa-cel were the same as those for patients treated with axi-cel or even nil, leading to costs per QALY gained of $9,140 and $40,762, respectively.

Fourth, this study was conducted from a US payer perspective without accounting for the broader societal impacts of treatments on costs or quality of life, such as caregiver productivity or patient out-of-pocket costs.

Finally, Zhang et al. have argued that an indirect comparison between axi-cel and tisa-cel is not feasible due to important differences between the two trials’ designs and patient populations. In particular, as pointed out by Zhang et al., ZUMA-1 and JULIET differed substantially in terms of timing of leukapheresis and enrolment, use of bridging chemotherapy (approximately 90% in JULIET vs. 0% in ZUMA-1), and lymphodepleting regimens, among others. We acknowledge that the MAIC has important limitations, as noted above. However, a decision must be made by policy makers and prescribers alike, based inevitably on imperfect information, and MAICs provide a tried and tested way for adjusting for outcomes between trials. Importantly, we not only conducted our analysis based on the MAIC – which likely improved our ability to compare the two trials more fairly – but also via a scenario analysis without MAIC.
adjustment. In both cases, axi-cel was cost effective compared to tisa-cel. Nevertheless, Supplemental Table 5 provides the necessary evidence to assess the costs and consequences associated with each treatment without the MAIC adjustment, should anyone prefer to consider such evidence without conducting a formal comparison across arms.

Conclusions

Over a lifetime horizon of 45 years, treatment of r/r LBCL with axi-cel was estimated in the base case analysis to generate an additional 3.90 LYs (undiscounted) and 2.74 QALYs (discounted) compared to tisa-cel. Treatment with axi-cel decreased costs by $1,407 compared to tisa-cel. The robustness of base case analysis results was tested through a wide range of sensitivity analyses, all of which indicated greater LYs and QALYs and either minimal incremental costs or lower costs of axi-cel versus tisa-cel. As such, axi-cel may be considered a cost-effective treatment alternative compared to tisa-cel for patients with r/r LBCL in the US.

Transparency

Declaration of funding

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Declaration of financial/other relationships

RL, ID, and MFB are employees of Pharmerit – an OPEN Health Company that received funding from Kite, A Gilead Company to conduct the study. MB also owns shares of Pharmerit – an OPEN Health Company. JTS is an employee of Kite, A Gilead Company and holds Gilead equity. FLL has served as a compensated scientific advisor to Kite; BMS/Celgene; Novartis; Allogene; Amgen; Wugen; Calibra; GammDelta Therapeutics; lovance; and Cellular Biomedicine Group Inc. and has received research funding from Kite. OOO has served as a compensated scientific advisor to Kite, Pfizer, Spectrum, Bayer, Legend, and Curio Science. A peer reviewer on this manuscript has disclosed that they have previously participated in trials both with Novartis and with KITE. The peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

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Previous presentations

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