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Cost-effectiveness of second-line axicabtagene ciloleucel in relapsed refractory diffuse large B-cell lymphoma

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KEY POINTS

- Second-line axi-cel is provisionally cost-effective in selected primary refractory/early relapsed DLBCL patients at a WTP of $100 000 per QALY.
- The cost-effectiveness of second-line axi-cel depends on its long-term outcomes (a 5-year EFS of at least 26.4% is needed).

The ZUMA-7 (Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma) study showed that axicabtagene ciloleucel (axi-cel) improved event-free survival (EFS) compared with standard of care (SOC) salvage chemoimmunotherapy followed by autologous stem cell transplant in primary refractory/early relapsed diffuse large B-cell lymphoma (DLBCL); this led to its recent US Food and Drug Administration approval in this setting. We modeled a hypothetical cohort of US adults (mean age, 65 years) with primary refractory/early relapsed DLBCL by developing a Markov model (lifetime horizon) to model the cost-effectiveness of second-line axi-cel compared with SOC using a range of plausible long-term outcomes. EFS and OS were estimated from ZUMA-7. Outcome measures were reported in incremental cost-effectiveness ratios, with a willingness-to-pay (WTP) threshold of $150 000 per quality-adjusted life-year (QALY). Assuming a 5-year EFS of 35% with second-line axi-cel and 10% with SOC, axi-cel was cost-effective at a WTP of $150 000 per QALY ($93 547 per QALY). axi-cel was no longer cost-effective if its 5-year EFS was ≤26.4% or if it cost more than $972 061 at a WTP of $150 000. Second-line axi-cel was the cost-effective strategy in 73% of the 10 000 Monte Carlo iterations at a WTP of $150 000. If the absolute benefit in EFS is maintained over time, second-line axi-cel for aggressive relapsed/refractory DLBCL is cost-effective compared with SOC at a WTP of $150 000 per QALY. However, its cost-effectiveness is highly dependent on long-term outcomes. Routine use of second-line chimeric antigen receptor T-cell therapy would add significantly to health care expenditures in the United States (more than $1 billion each year), even when used in a high-risk subpopulation. Further reductions in the cost of chimeric antigen receptor T-cell therapy are needed to be affordable in many regions of the world.

Introduction

Diffuse large B-cell lymphoma (DLBCL) patients with primary refractory disease or early relapse within 12 months of initial chemoimmunotherapy have a poor prognosis.[1] Based on the durable responses seen with chimeric antigen receptor T-cell therapy (CAR-T) in the third-line setting,[2-4] the ZUMA-7 (Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma) study evaluated the safety and efficacy of CAR-T in the second-line setting for patients with primary refractory/early relapse DLBCL compared with standard of care (SOC) salvage chemoimmunotherapy followed by autologous stem cell transplant (auto-SCT).[5] It also reported a benefit in event-free survival (EFS) (24-month EFS 41% with axi-cel vs 16% with SOC; $P < .001$), leading to its recent US Food and Drug Administration approval. CAR-T is associated with various toxicities such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), as well as financial toxicities.[6] Although CAR-T has significantly changed the landscape of DLBCL, its high costs pose a significant barrier to access for patients and a financial strain on hospitals. Drug acquisition with prices ranging from $373 000 to $475 000 is the largest component of CAR-T costs. Other costs include procedures, supportive care, and hospitalizations.[7] A prior study evaluating the cost-effectiveness of CAR-T in the third-line setting for DLBCL found it may be cost-effective at a willingness-to pay (WTP) threshold of $150 000 per quality-adjusted life-year (QALY) (incremental cost-effectiveness ratio [ICER], $129 000 per QALY).[8]

The current study assessed the cost-effectiveness of second-line CAR-T in high-risk DLBCL modeling data from

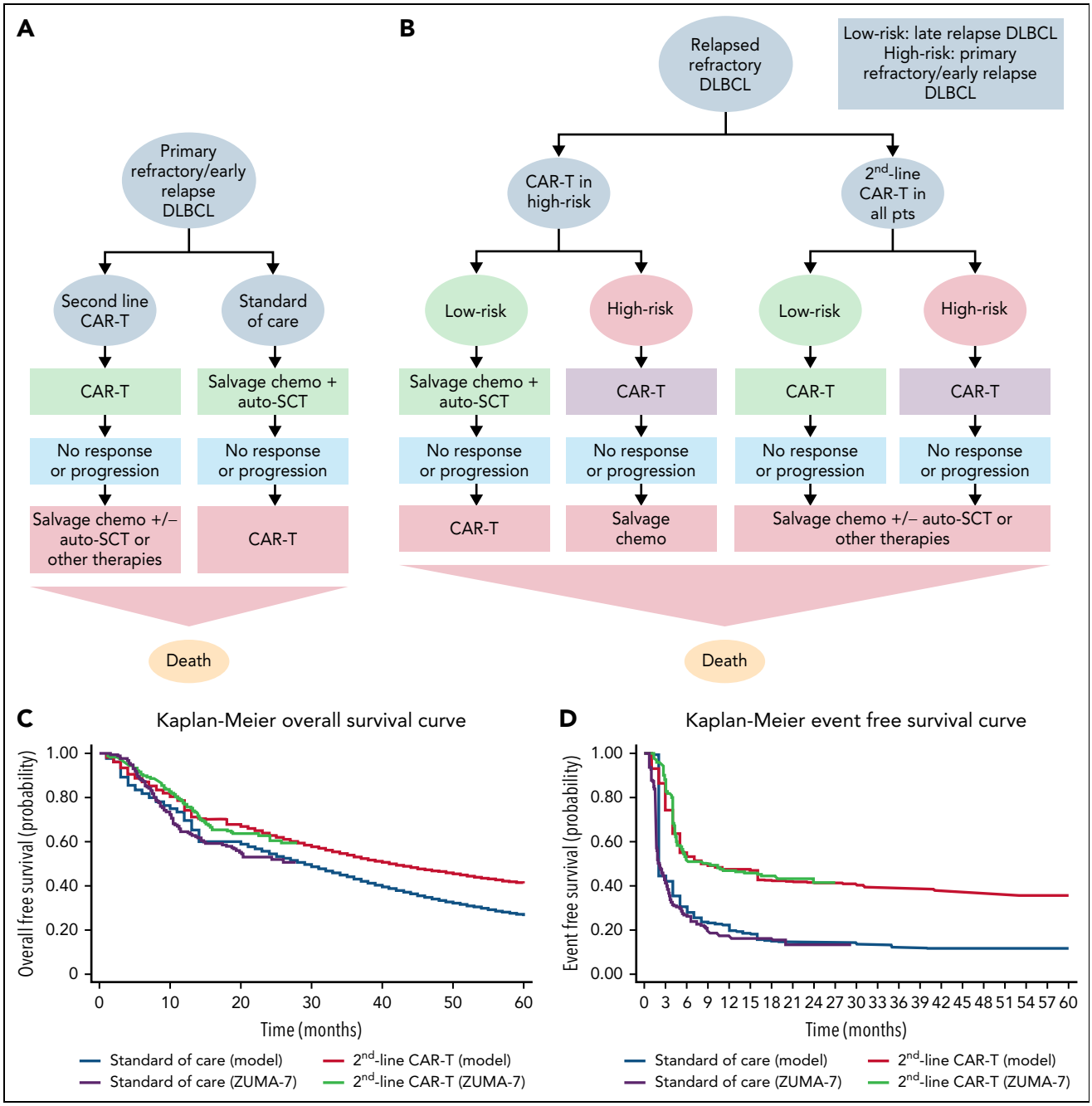

Figure 1. Model diagram for analysis comparing second-line CAR-T vs SOC therapy and modeled Kaplan-Meier curves. (A) Patients remain in the same state for all states if they are not transitioning to another state in the model. Patients in the second-line CAR-T arm receive CAR-T (axi-cel) and then enter remission if they achieve a complete response. If they do not respond or relapse, they receive salvage chemoimmunotherapy in the third-line setting. In the SOC arm, patients receive salvage chemoimmunotherapy, and if they have a complete or partial response, they proceed to auto-SCT. If they do not respond to relapse after auto-SCT, they proceed to third-line CAR-T. Patients who progress after third-line therapy are considered to have poor prognosis, low quality of life, and high costs. (B) Model diagram for analysis comparing second-line CAR-T in all patients with RR-DLBCL vs second-line CAR-T in only primary refractory/early relapse patients (with late relapse patients receiving SOC therapy). Patients who are primary refractory/early relapse are labeled high risk, and patients who have a late relapse are labeled as low risk. On the right side of this diagram, all patients receive CAR-T in the second-line setting, and if they fail to respond or relapse, they receive third-line salvage chemoimmunotherapy. On the left side, high-risk patients receive second-line CAR-T (using the ZUMA-7 outcomes), and low-risk patients receive SOC therapy (using results from CORAL). High-risk patients who do not respond or progress receive salvage chemoimmunotherapy, while low-risk patients who progress receive third-line CAR-T. Patients who progress after third-line therapy are considered to have a poor prognosis, low quality of life, and high costs. (C) Modeled OS for axi-cel and SOC in primary refractory/early relapse DLBCL. (D) Modeled EFS for axi-cel and SOC in primary refractory/early relapse DLBCL. chemo, chemoimmunotherapy; pts, patients.

ZUMA-7.[5] We also performed a threshold analysis to identify scenarios in which CAR-T would be cost-effective in the second-line setting for all patients with relapsed/refractory (RR)-DLBCL.

Methods

Model structure

We developed a state-transition Markov model using TreeAge Pro 2021 release 1.2 (TreeAge, Williamstown, MA), simulating a

Table 1. Selected model input parameters, including transition probabilities, costs, and utilities

Inputs: outcome probabilities	Base case	Sensitivity analysis range	Monte Carlo distribution	References
Therapies in the second-line setting				
axi-cel				
Overall outcomes				
EFS rate at 2 y	0.41	0.35-0.52	β	5
OS rate at 2 y	0.61	0.45-0.78	β	5
Progression-free survival rate at 2 y	0.46	0.37-0.67	β	5
Adverse events				
CRS (any grade)	0.92	0.7-1.1	β	5
CRS (grade ≥3)	0.06	0.03-0.1	β	5
SOC				
Overall outcomes				
EFS rate at 2 y	0.16	0.10-0.21	β	5
OS rate at 2 y	0.52	0.38-0.73	β	5
Progression-free survival rate at 2 y	0.27	0.12-0.42	β	5
Salvage chemoimmunotherapy				
CR after salvage	0.32	0.2-0.5	β	17
PR after salvage	0.18	0.05-0.3	β	17
Stable disease after salvage	0.18	0.05-0.3	β	17
auto-SCT				
Receipt of transplantation after CR with salvage	0.80	0.70-0.94	β	17
Receipt of transplantation after PR with salvage	0.54	0.58-0.78	β	17
OS rate after CR + SCT after 1 y	0.83	0.70-0.97	β	17
OS rate after PR + SCT after 1 y	0.59	0.45-0.72	β	17
Adverse events				
Febrile neutropenia (grade ≥3)	0.27	0.1-0.5	β	5
Anemia requiring blood transfusion (grade ≥3)	0.39	0.1-0.6	β	5
Leukopenia (grade ≥3)	0.22	0.05-0.9	β	5
Therapies in the third-line setting				
axi-cel				
CR after CAR-T	0.58	0.49-0.67	β	2
PR after CAR-T	0.24	0.17-0.33	β	2
OS rate after 4 y	0.44	0.34-0.54	β	2
EFS after 2 y	0.38	0.31-0.41	β	2
Salvage chemoimmunotherapy + auto-SCT (after second-line CAR-T)				
Overall response rate	0.30	0.1 – 0.5	β	1,20
Receipt of transplantation after CR with salvage	0.30	0.2-0.6	β	Expert opinion
Receipt of transplantation after PR with salvage	0.10	0.05-0.3	β	Expert opinion
Costs				
Inputs: Costs, 2021 US dollars				
Pharmaceutical				
Salvage chemoimmunotherapy	20 762	20 000-100 000	γ	21
axi-cel	393 104	200 000-700 000	γ	22
Administration and adverse events				
Salvage chemoimmunotherapy	14 649	14 000-44 000	γ	21,23
axi-cel	59 124	35 000-70 000	γ	21,23
auto-SCT	139 194	70 000-190 000	γ	23,24

CR, complete response; PR, partial response.

Table 1 (continued)

Inputs: outcome probabilities	Base case	Sensitivity analysis range	Monte Carlo distribution	References
Utilities				
Inputs: utilities, QALYs				
RR-DLBCL	0.63	0.3-0.8	β	25
auto-SCT therapy (2 mo)	0.43	0.2-0.6	β	26
CAR-T (2 mo)	0.50	0.3-0.7	β	26
Remission after CAR-T	0.70	0.6-0.9	β	26
Progression after CAR-T	0.45	0.1-0.6	β	26

CR, complete response; PR, partial response.

cohort of US adults (mean age, 65 years) with RR-DLBCL who either had primary refractory disease or early relapse (<12 months from initial therapy).[9] We used this model to examine the impact of the 2 treatment regimens studied in the ZUMA-7 trial: (1) SOC, defined as 2 cycles of salvage chemoimmunotherapy followed by high-dose chemotherapy and auto-SCT (if the patient responds to salvage chemoimmunotherapy) and CAR-T in the third-line setting for nonresponders and patients who relapse (2) second-line CAR-T, which consisted of conditioning chemotherapy of cyclophosphamide and fludarabine before a single infusion of axi-cel. For each treatment strategy, persons in the model transition between the following health states after completing initial therapy for RR-DLBCL: nonresponse/relapse, remission after auto-SCT, remission after CAR-T, and death (Figure 1A). One-month cycles and a lifetime horizon were used. Age-specific probability of all-cause mortality was estimated from the 2018 Centers for Disease Control and Prevention US Life Tables.[10] We estimated the effects of grade 3 to 4 adverse events associated with therapy, including febrile neutropenia, anemia requiring blood transfusion, peripheral neuropathy, ICANS, and CRS.

In the SOC arm, patients with RR-DLBCL first received salvage chemoimmunotherapy. Patients who achieved a complete or partial response after salvage chemoimmunotherapy proceeded to auto-SCT in the next month. For patients without a response, they proceeded with CAR-T. CAR-T was modeled by using a similar model as that of a previously published cost-effectiveness analysis by Lin et al.[8] We modeled third-line CAR-T as axi-cel using the ZUMA-1 (A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma) trial and used the 4-year outcomes from the ZUMA-1 study.[2,11,12] Patients who relapsed or were refractory to third-line CAR-T were modeled as having poor survival with low quality of life and high monthly costs, as they have poor clinical outcomes with widely disparate treatment strategies.[13]

In the second-line CAR-T arm, patients who relapsed or had nonresponse proceeded to salvage chemoimmunotherapy and potentially transplant, as was allowed in the ZUMA-7 protocol. Given that there are limited real-world data in this setting, we modeled different long-term responses and survival scenarios. Patients who failed 3 lines of therapy in this arm were modeled as having poor survival and outcomes[14] and high costs as described earlier.

We also modeled patients who achieved remission for >5 years as having a very low risk of subsequent progression with a slightly higher risk of all-cause mortality.[15,16] We also modeled that even after patients were assigned to a certain therapy, they may be unable to receive it or discontinue it due to worsening performance status or other reasons reflecting real-world practice.

Modeling without long-term outcomes data

With respect to modeling long-term outcomes of the SOC arm, prior studies, including CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) and SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research), have shown low rates of relapse in patients who responded to salvage chemotherapy + auto-SCT and were disease-free at 24 months.[1,17] Thus, we modeled a 5-year EFS in the SOC arm to be 10%, which is slightly lower than the 2-year EFS of 16% reported in the SOC arm in ZUMA-7.[5] In our study, to inform the long-term outcomes of CAR-T, we used 4-year data from axi-cel showing excellent survival (92%) at 4 years in patients with remission at 2 years, and another study reporting 5-year outcomes of patients treated with tisagenlecleucel (tisa-cel) in the JULIET (A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma [DLBCL]) trial showing a low rate of relapse after 24 months.[11,18] However, in the ZUMA-7 trial, the median follow-up was 24.9 months, and thus we had only 2-year overall survival (OS) and EFS for second-line CAR-T. We addressed the uncertainty in long-term outcomes with second-line CAR-T by modeling several different scenarios. For the base case scenario, we modeled that 6% of patients who received second-line CAR-T progressed or needed additional lymphoma therapy between 2 and 5 years, which is a similar rate of relapse reported for CAR-T in the third-line setting.[11,12,18,19] Based on expert opinion, we also varied the 5-year EFS from 20% to 40% with second-line CAR-T. We also modeled a scenario in which fewer patients progressed with second-line CAR-T between 2 and 5 years (corresponding to a 5-year EFS of 40%) and another scenario in which the patients

Table 2. Selected model input parameters for the analysis of second-line CAR-T in late relapse patients

Inputs: outcome probabilities	Base case	Sensitivity analysis range	Monte Carlo distribution	References
Proportion of RR-DLBCL patients with primary refractory/early relapsed disease	0.65	0.50-0.80	β	[1,32,33]
Salvage chemoimmunotherapy as a bridge to auto-SCT in second-line setting in late relapse patients				
Clinical outcomes				
EFS rate at 3 y	0.45	0.35-0.70	β	[1]
OS rate at 3 y	0.52	0.32-0.75	β	[1]
Overall response rate	0.88	0.70-0.95	β	[1]

who avoided progression with second-line CAR-T in the first 2 years progress after 2 years (5-year EFS of 20%).

Model inputs

Transition probabilities, utilities, and costs were identified from published literature and public data sources, as detailed in Table 1[2,5,17,20-26] and supplemental Table 1 (available on the *Blood* Web site). Rates of remission, survival, and relapse for SOC and second-line CAR-T were obtained from the ZUMA-7 trial.[5] We included costs related to drugs, administration costs, costs related to adverse events, transplant and cellular therapy costs, and follow-up costs. Costs were inflation-adjusted to 2021 US dollars by using the medical care component of the Consumer Price Index. Base case point estimates of cost were varied by at least ±50% for the sensitivity analysis.

Assumptions

The first assumption was that the effectiveness of third-line salvage chemoimmunotherapy in patients with nonresponse or relapse after second-line CAR-T is the same as when used in the third-line setting. Historically, patients with primary refractory or early relapse DLBCL who undergo salvage chemoimmunotherapy and auto-SCT have exhibited poor outcomes,[1,17] and we assumed that these poor outcomes remain when they are used after second-line CAR-T. For base case analysis, we modeled response rates for therapies post–second-line CAR-T to be 30%,[20] but in a sensitivity analysis, we varied it to range from 10% to 50%.[20,27] We also assumed that patients receiving second-line CAR-T would receive only steroids and no other bridging therapy, similar to the eligible population in ZUMA-7. We also assumed that patients who fail salvage chemotherapy and/or auto-SCT in the SOC arm proceed to third-line CAR-T. Finally, we assumed that patients who achieved at least 5 years of remission after auto-SCT had increased mortality compared with the general population (standardized mortality ratio [SMR], 2.2)[15,28] as did patients who received CAR-T and achieved at least 5 years of remission (SMR, 1.4).[29] For auto-SCT, primary nonrelapse reasons for mortality after 5 years were pulmonary toxicity (associated with carmustine), cardiac toxicity (related to high-dose chemotherapy), and infections, as well as secondary cancers.[15,28] CAR-T is also associated with some late effects, including hypogammaglobulinemia, prolonged cytopenias, late infections, immune-related late effects, cardiac toxicities, and subsequent malignancies.[10] It is not necessarily related to the pulmonary or cardiac toxicity that drove 46% of the long-term nondisease-related deaths after auto-SCT.[29] This is why we modeled a higher SMR for auto-SCT than for CAR-T.

Model calibration

We calibrated our model using a previously validated, limited-memory BFGS-B optimization algorithm, defining goodness of fit as the sum of the squared distance between the published survival curves and simulated ones from our model.[30] The OS, progression-free survival, and EFS were calibrated at different time points for both the SOC and second-line CAR-T arms as well as for different treatment strategies after nonresponse/relapse, such as third-line CAR-T in the SOC arm (Figure 1C-D; supplemental Sections II and III).

Analysis

As described earlier, the cost-effectiveness of each of the treatment strategies was reported from a health care perspective. Outcome measures were reported as ICERs (2021 US dollars per QALY) with a WTP threshold of $150 000 per QALY and the OS and EFS at 2 and 5 years.[31] Costs and utilities were discounted by 3% annually.

Sensitivity analyses

Extensive one-way sensitivity analyses were performed to evaluate the effect of all defined variables according to each of the strategies, including age, life expectancy after long-term remission, and costs and outcomes with cellular therapy for RR DLBCL. For the Monte Carlo probabilistic sensitivity analysis, 10 000 iterations were performed using γ distributions for cost and β distributions for transition probabilities.

CAR-T as second-line therapy in all RR-DLBCL

To assess the threshold efficacy for CAR-T in all patients with RR-DLBCL, an alternative scenario was modeled in which second-line CAR-T is not only used for primary refractory/early relapse patients (as we modeled earlier) but also for late relapse patients (>12 months). We compared this alternative model in which second-line CAR-T is used for both late relapse and primary refractory/early relapse patients vs a model in which second-line CAR-T is used only for primary refractory/early relapse patients and salvage chemoimmunotherapy followed by auto-SCT is used for late relapse patients (Figure 1B). The outcomes of salvage chemoimmunotherapy and auto-SCT in

late relapse patients were modeled by using the CORAL study[1] (Table 2). We modeled that 65% of the RR-DLBCL cases were primary refractory/early relapse, and 35% were late relapse.[32,33] As part of a pragmatic approach, late relapse patients who failed salvage chemoimmunotherapy or relapsed after SCT could proceed to third-line CAR-T, which was modeled by using the ZUMA-1 study.[2] The primary purpose of this comparison was to determine the threshold efficacy for second-line CAR-T in late relapse patients for it to be cost-effective (as CAR-T has substantial costs), and these late relapse patients have excellent outcomes with the SOC salvage chemoimmunotherapy. Similar to the primary analysis, we modeled durable responses with CAR-T in those patients who remain in remission at 2 years.

Results

Modeling second-line CAR-T in primary refractory/early relapse DLBCL patients

Base case analysis (scenario 1: 6% rate of relapse after 24-month EFS is achieved with second-line CAR-T) In the base case analysis, we assumed that 6% of patients progressed or required additional lymphoma therapy after 24 months in the second-line CAR-T arm. Assuming a 5-year EFS of 35% with second-line CAR-T and a 5-year EFS of 10% with SOC, second-line CAR-T resulted in an additional 3.29 life-years and an incremental 2.82 QALYs (Figure 2). However, second-line CAR-T cost $771 838 compared with $508 034 for SOC (incremental cost of $263 804). Based on this, second-line CAR-T was cost-effective ($93 547 per QALY) at WTPs of $100 000 per QALY and $150 000 per QALY (Table 3).

Sensitivity analyses

One-way sensitivity analyses were performed on all model inputs for this model. At a WTP of $150 000 per QALY, the model was sensitive to the cost of CAR-T and the 5-year EFS for second-line CAR-T (supplemental Section V). At a WTP of $100 000 per QALY, the model was also sensitive to the cost of salvage chemoimmunotherapy and the probability of progression after third-line CAR-T (supplemental Section VI).

Sensitivity analyses of 5-year EFS

Scenario 2: second-line CAR-T has a low rate of relapse between 2 and 5 years In this scenario, second-line CAR-T has a low rate of relapse after 2 years, which corresponds to a 5-year EFS of 40%. In this scenario, second-line CAR-T was cost-effective at WTPs of $100 000 per QALY and $150 000 per QALY (ICER $73 968 per QALY) (Tables 3 and 4).

Scenario 3: second-line CAR-T has a high rate of relapse between 2 and 5 years In this scenario, 21% of patients who did not progress or require additional therapy with second-line CAR-T at 2 years progress or require additional therapy between 2 and 5 years (potentially due to T-cell exhaustion or CD19-antigen escape). This leads to an EFS of 20% with second-line CAR-T at 5 years. In this scenario, second-line CAR-T was not cost-effective at a WTP of $150 000 per QALY (ICER $233 967 per QALY) (Table 3).

One-way and two-way sensitivity analyses

Cost of CAR-T A one-way sensitivity threshold analysis identified that if CAR-T therapy costs less than $972 061, it is cost-effective at a WTP of $150 000 per QALY (Figure 3A). Two-way sensitivity analyses of the costs of CAR-T and the 5-year EFS with second-line CAR-T are shown in Figure 3B. They show that if, for example, the cost of CAR-T is $500 000,

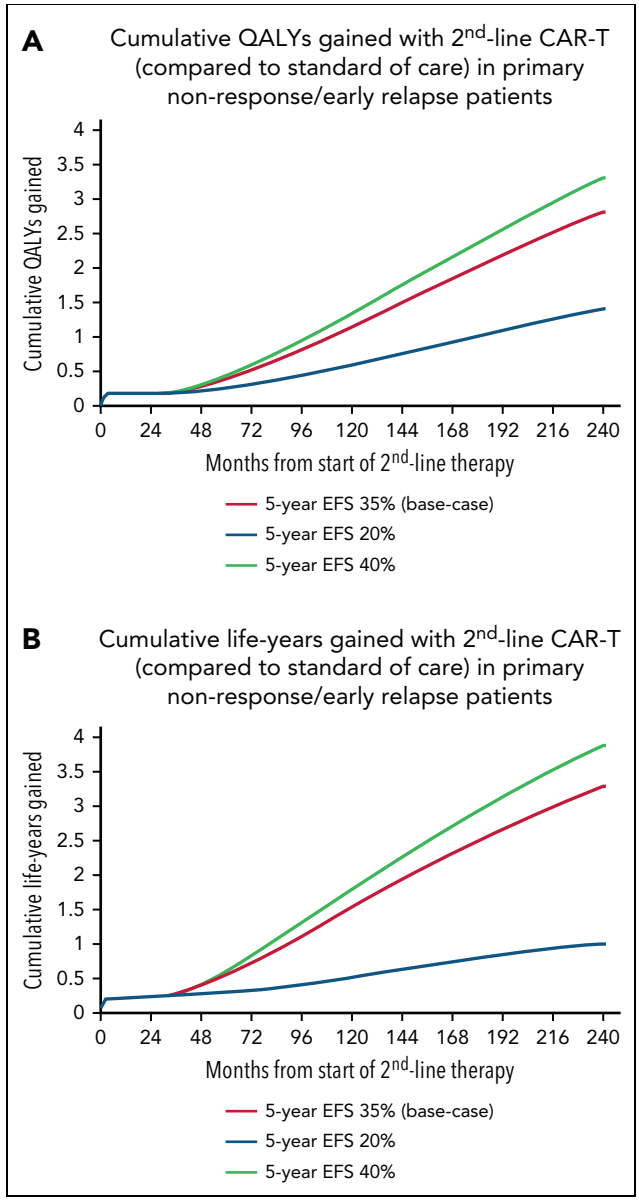

Figure 2. Graphs of cumulative QALYs gained and life-years gained. (A) A graph of cumulative QALYs gained over a lifetime horizon in second-line CAR-T compared with SOC in primary refractory/early relapse patients. The red curve represents the base case scenario in which patients who received second-line CAR-T and are event-free at 2 years have a 6% rate of relapse from 2 to 5 years, and additional QALYs are gained throughout the cohort's lifetime. The green curve represents the optimistic scenario in which second-line CAR-T has a low rate of relapse between 2 and 5 years, and the blue curve represents the pessimistic scenario in which second-line CAR-T has a high rate of relapse between 2 and 5 years. (B) A graph of cumulative life-years gained over a lifetime horizon in second-line CAR-T compared with SOC in primary refractory/early relapse patients. The orange curve represents the base case scenario in which patients who received second-line CAR-T and are event-free at 2 years have a 6% rate of relapse from 2 to 5 years, and additional life-years are gained, or that second-line CAR-T patients have lower mortality. The green curve represents the optimistic scenario in which second-line CAR-T has a low rate of relapse between 2 and 5 years, and the blue curve the pessimistic scenario in which second-line CAR-T has a high rate of relapse between 2 and 5 years.

Table 3. Detailed analysis of outcomes and cost-effectiveness of SOC and second-line CAR-T in primary refractory/early relapse patients

Treatment	2- and 5-Year outcomes				Cost-effectiveness				ICER
	2-Year OS	2-Year EFS	5-Year OS	5-Year EFS	Life-years	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Cost (2021 USD)	Incremental cost	
SOC	53%	16%	26%	10%	3.67	2.60	–	508 034	–	–
Base case (6% rate of relapse after 24-mo EFS with second-line CAR-T)										
Second-line CAR-T	62%	41%	41%	35%	6.96	5.42	2.82	771 838	263 804	93 547
Scenario 2 (second-line CAR-T has a low rate of relapse after 2 y)										
Second-line CAR-T	62%	41%	49%	40%	7.55	5.90	3.29	751 602	243 568	73 968
Scenario 3: (second-line CAR-T has a high rate of relapse after 2 y)										
Second-line CAR-T	62%	41%	32%	20%	4.69	3.99	1.39	832 497	324 463	233 967

First, the clinical outcomes (2- and 5-year OS and progression-free survival) are displayed. Effectiveness is then shown as life-years as well as QALYs. The costs displayed are the total lifetime costs related to RR-DLBCL treatment for each strategy. USD, US dollars.

second-line CAR-T has to have an EFS of at least 26.2% at 5 years to be cost-effective at a WTP of $150 000 per QALY.

5-Year EFS As shown in Figure 3C, we performed a one-way sensitivity analysis varying the 5-year EFS with second-line CAR-T from 20% to 40%. We identified that to be cost-effective at WTPs of $150 000 per QALY and $100 000 per QALY, second-line CAR-T has to at least have an EFS of 26.4% and 33.8%, respectively, at 5 years. Next, in a two-way sensitivity analysis varying the 5-year EFS with second-line CAR-T (from 20% to 40%) and the 5-year EFS with SOC (from 10% to 14%), we showed that as long as second-line CAR-T had a 5-year EFS of at least 14% higher than that of SOC, it was cost-effective at $150 000 per QALY (Figure 3D).

Other sensitivity analyses

Probability sensitivity analyses Probabilistic sensitivity analysis was derived from performing 10 000 Monte Carlo model iterations for each strategy. Cost-effectiveness acceptability curves were generated for the model (Figure 4). Second-line CAR-T was the cost-effective strategy in 57% and 73% of iterations at a WTP of $100 000 and $150 000, respectively.

Modeling second-line CAR-T in all patients with RR-DLBCL Because the use of second-line CAR-T may broaden in the future to include patients with late relapse, we performed a sensitivity analysis to identify the threshold effectiveness for CAR-T in late relapsed DLBCL to be cost-effective in all patients with RR-DLBCL. Two arms were modeled: in the first, both primary refractory/early relapse and late relapse patients receive second-line CAR-T, whereas in the second arm, only primary refractory/early relapse patients receive second-line CAR-T while late relapse patients receive salvage chemoimmunotherapy as a bridge to auto-SCT. We informed the inputs for salvage chemoimmunotherapy/auto-SCT in late relapse patients from the CORAL study[1] (Table 2). Second-line CAR-T was cost-effective in all patients if it had a 2-year EFS of at least 58.6% and 64.4% in late relapse patients at WTPs of $150 000 and $100 000, respectively (Figure 5A). To maintain the cost-effectiveness of second-line CAR-T in all patients, 5-year EFS had to be at least 47.2% in late relapse patients at a WTP of $150 000 (Figure 5B).

Discussion

This study is the first, to our knowledge, to evaluate the cost-effectiveness of second-line CAR-T in patients with RR-DLBCL. This analysis is particularly timely and relevant given the recent US Food and Drug Administration approval of axi-cel in the second-line setting for primary refractory or early relapsed DLBCL. In the primary analysis, assuming a 5-year EFS of 35% for second-line CAR-T in primary refractory/early relapse DLBCL patients, we found that second-line CAR-T was highly cost-effective at a WTP of $100 000 per QALY (ICER $93 547). Its cost-effectiveness was dependent on a modeled long-term mortality benefit with second-line CAR-T compared with SOC, which has not been seen clinically due to the short follow-up of ZUMA-7. CAR-T was cost-effective up to a cost of $972 061 in the second-line setting in these patients and was the cost-effective strategy in 73% of iterations at a WTP of $150 000.

Table 4. Sensitivity analyses of the 5-y EFS with second-line CART in primary refractory/early relapse patients compared with SOC

5-y EFS with second-line CAR-T	Cost-effectiveness					Proportion of simulations that second-line CAR-T is cost-effective at various WTP thresholds		
	Life-years gained	Effectiveness (QALYs)	Incremental effectiveness	Cost (2021 USD)	Incremental cost	ICER	$50 000	$100 000	$150 000
20%	1.02	3.99	1.39	$832 497	$324 463	$233 967	4%	19%	31%
25%	2.12	4.47	1.87	$812 288	$304 254	$162 778	7%	26%	47%
30%	2.65	4.95	2.35	$792 068	$284 033	$121 024	15%	44%	61%
35%	3.29	5.42	2.82	$771 838	$263 804	$93 547	34%	57%	73%
40%	3.88	5.90	3.29	$751 602	$243 568	$73 968	41%	72%	84%

In this table, the 5-year EFS is varied from 20% to 40%, and the clinical outcomes (OS), effectiveness (life-years gained and QALY), and total cost related to RR-DLBCL are displayed. USD, US dollars.

It is important to note, however, that the cost-effectiveness of second-line CAR-T is highly sensitive to long-term outcomes. For the primary analysis, we assumed a durable response with CAR-T in the second-line setting, with only 6% of patients progressing or requiring additional lymphoma therapy between 2 and 5 years. There are reasons to suggest that this assumption is likely to be valid. Prior studies have shown that the majority of relapses post–CAR-T are within 6 months of infusion, and the long-term results from both ZUMA-1 and JULIET suggest that being event-free at 24 months was associated with a durable response.[11,18] Hence, we expect the 5-year EFS of the ZUMA-7 trial to be largely similar to the 24-month outcomes reported. We did model both best-case and worst-case scenarios to provide the range of cost-effectiveness scenarios for second-line CAR-T as it can vary widely in different settings. In the best-case scenario, second-line CAR-T has a low rate of relapse after 2 years and remains cost-effective at a WTP of $100 000. In the worst-case scenario, second-line CAR-T has a high rate of relapse after 2 years and is no longer cost-effective (ICER $233 967). As long as the 5-year EFS with second-line CAR-T is at least 26.4%, it will remain cost-effective at a WTP $150 000, highlighting the importance of long-term outcomes with cellular therapy in determining its cost-effectiveness.

Second-line CAR-T is cost-effective in primary refractory/early relapse DLBCL despite its substantial costs, given the poor efficacy of standard care salvage chemoimmunotherapy and auto-SCT in this setting, with a 24-month EFS of 16% in ZUMA-7.[5] Standard care was associated with poor survival, as 3.29 life-years and 2.82 QALYs were gained with CAR-T in the second-line setting compared with standard care. This was the main driver behind the cost-effectiveness of CAR-T. Indeed, we showed that even if CAR-T therapy cost $517 941 and $972 061 at WTPs of $100 000 and $150 000, it would remain cost-effective. This suggests that the high costs of progression and death after standard care offset the substantial initial cost of CAR-T therapy.

The ZUMA-7 trial[5] chose to focus on patients with primary refractory/early relapse DLBCL as these patients have poor outcomes with standard care and comprise a high-risk subpopulation.[1] CAR-T has not yet been studied as second-line treatment in patients with late relapse (>12 months) after initial chemoimmunotherapy. Compared with the primary refractory/early relapse population, these patients have a substantially improved outcome with salvage chemoimmunotherapy followed by auto-SCT (3-year EFS of 45% vs 20%).[1] However in the future, there may be interest in using CAR-T (particularly tisacel and lisocabtagene maraleucel [liso-cel], associated with less CRS and ICANS than axi-cel) as second-line therapy for all patients with RR-DLBCL, both primary refractory/early relapse and late relapse patients, and particularly in older and more frail patients with comorbidities who may not be eligible for auto-SCT.[34,35] Although this patient population was not included in ZUMA-7, recent data suggest efficacy and safety of CAR-T in these patients with geriatric vulnerabilities, comorbid conditions, and functional limitations.[34] We modeled second-line CAR-T for all patients with RR-DLBCL and found that only if CAR-T was highly effective in late relapse patients with a 2-year EFS of at least 58.6% would it be cost-effective for all patients with RR-DLBCL. This EFS is significantly higher than the 2-year EFS of 38% reported

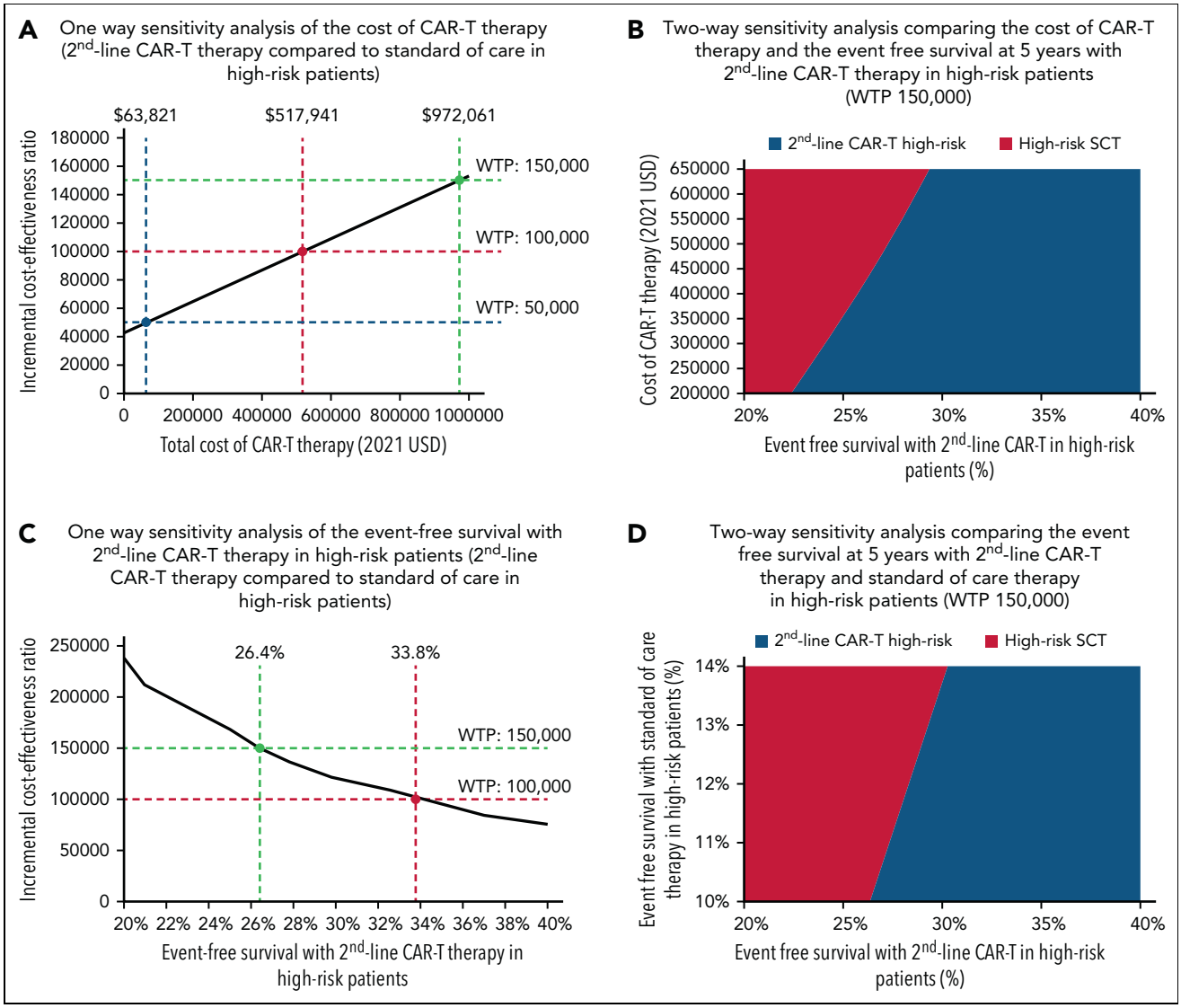

Figure 3. One- and two-way sensitivity analyses. (A) One-way sensitivity analysis of the cost of CAR-T when second-line CAR-T is compared with SOC in primary refractory/early relapse patients. In this analysis, we vary the cost-of CAR-T while keeping other parameters constant and show that second-line CAR-T is cost-effective if it costs less than $972 061 (green dotted lines) at a WTP of $150 000. (B) Two-way sensitivity analysis of the 5-year EFS of second-line CAR-T and the cost of CAR-T. In this analysis, we vary the 5-year EFS of second-line CAR-T and the cost of CAR-T simultaneously while keeping other parameters constant. The area shaded blue represents the scenarios in which second-line CAR-T is the cost-effective strategy at a WTP of $150 000. In contrast, the area shaded red represents the scenarios in which second-line CAR-T is no longer the cost-effective strategy. (C) One-way sensitivity analysis of the 5-year EFS with second-line CAR-T therapy when second-line CAR-T is compared with SOC therapy in primary refractory/early relapse patients. In this analysis, we vary the 5-year EFS with second-line CAR-T while keeping other parameters constant and show that second-line CAR-T is cost-effective if it has a 5-year EFS of 26.4% or higher (green dotted lines) at a WTP of $150 000. (D) Two-way sensitivity analysis of the 5-year EFS of second-line CAR-T and the 5-year EFS with SOC therapy. In this analysis, we simultaneously vary the 5-year EFS of second-line CAR-T and the 5-year EFS of SOC therapy while keeping other parameters constant. The area shaded blue represents the scenarios in which second-line CAR-T is the cost-effective strategy at a WTP of $150 000. In contrast, the areas shaded red represents the scenarios in which second-line CAR-T is no longer the cost-effective strategy.

with third-line CAR-T in the ZUMA-1 study[12] and the 2-year EFS of 41% observed with second-line CAR-T in primary refractory/early relapse patients in the ZUMA-7 study.[5] CAR-T theoretically may have superior outcomes in the second-line setting in late relapse patients compared with the third-line setting given fewer pre-treated patients and better T-cell function; however, it is unclear if this will be the case given the similar 2-year outcomes seen with axi-cel in ZUMA-7 and ZUMA-1.

There are ~29 108 new cases of DLBCL per year in the United States, with ~8732 patients (30%) having refractory/relapsed disease.[36] If CAR-T is adopted in the second-line setting for 65% of patients with RR-DLBCL with primary refractory/early relapse,[32,37] this would then lead to $1.5 billion of additional health care expenditures. Thus, despite being cost-effective, CAR-T in the second-line setting in high-risk patients adds a substantial amount to the direct health care costs. Different payors and different health care settings may not be able to afford this cost. This scenario highlights the need to reduce the costs of CAR-T using different reimbursement arrangements, outpatient CAR-T, and the potential use of off-the-shelf, allogeneic CAR-T products and dual-targeting CAR-T products, which may increase competition in the market and drive down the cost.

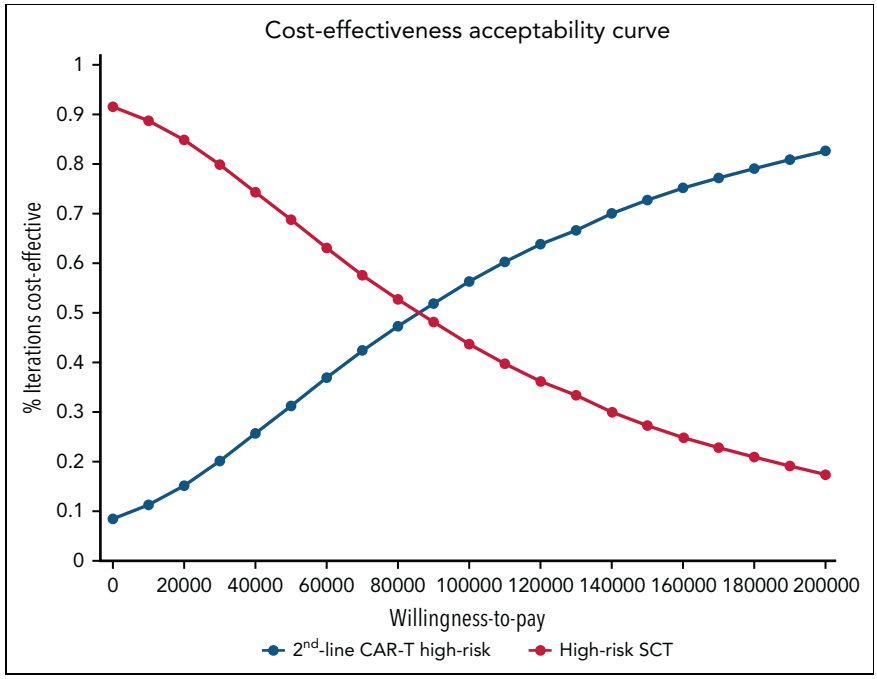

Figure 4. Cost-effectiveness acceptability curves using WTP thresholds for each strategy in patients with primary refractory/early relapsed DLBCL. The blue curve represents the percent iterations second-line CAR-T is the cost-effective strategy at each WTP threshold. In contrast, the red curve represents the percent iterations that second-line CAR-T is no longer the cost-effective strategy.

Prior cost-effective analyses have examined the impact of CAR-T in the third-line setting. Lin et al[8] found that, assuming a 5-year progression-free survival of 40%, CAR-T may be cost-effective in the third-line setting (ICER $129 000 per QALY gained) compared with salvage chemoimmunotherapy and auto-SCT. We found that CAR-T was more cost-effective in the second-line setting with an ICER of $93 547 per QALY, indicating that moving CAR-T to second-line in high-risk patients

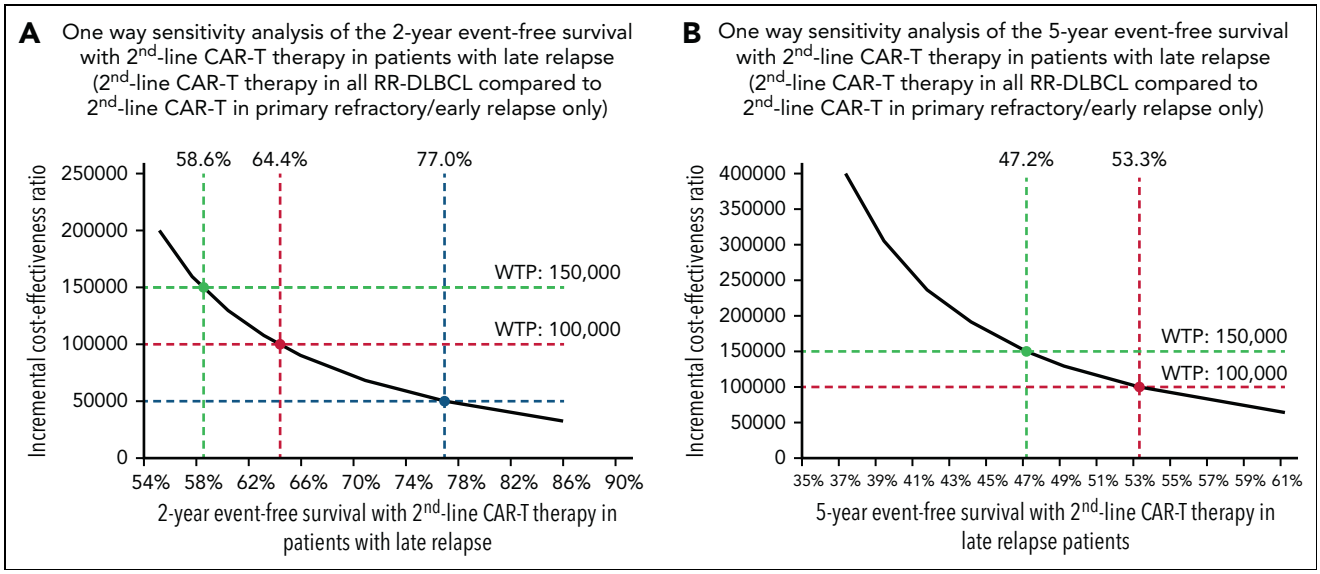

Figure 5. One-way sensitivity analyses of 2nd-line CAR-T in all patients. (A) One-way sensitivity analysis of the 2-year EFS in late-relapsed DLBCL (second-line CAR-T in all patients with RR-DLBCL compared with second-line CAR-T in primary refractory/early relapse patients and SOC in late relapse patients). In this analysis, we vary the 2-year EFS with second-line CAR-T in patients with late-relapsed DLBCL while keeping other parameters constant to identify scenarios in which CAR-T would be cost-effective for all patients with RR-DLBCL in the second-line setting. It found that second-line CAR-T is cost-effective if it has a 2-year EFS ≥58.6% (green dotted lines) at a WTP of $150 000. (B) One-way sensitivity analysis of the 5-year EFS in late-relapsed DLBCL (second-line CAR-T in all patients with RR-DLBCL compared with second-line CAR-T in primary refractory/early relapse patients and SOC in late relapse patients). In this analysis, we vary the 5-year EFS with second-line CAR-T in patients with late-relapsed DLBCL while keeping other parameters constant to identify scenarios in which CAR-T would be cost-effective for all patients with RR-DLBCL in the second-line setting. It shows that second-line CAR-T is cost-effective if it has a 5-year EFS ≥47.2% (green dotted lines) at a WTP of $150 000.

improves its cost-effectiveness. We also had 4- and 5-year outcomes of axi-cel and tisa-cel in the third-line setting, respectively, which informed us that the 2-year outcomes of CAR-T in the third-line setting remained durable long term.[11,18] Unlike the study by Lin et al,[8] we were unable to model other CAR-T products given the short-term follow-up with liso-cel in the second-line setting[38] and a lack of EFS improvement seen with tisa-cel in the second-line setting.[39]

Although cost-effectiveness analyses can help inform the cost-to-benefit ratio of different treatment strategies, they have certain limitations. As with any oncologic modeling study, the rates of response, relapse, progression, and toxicity influence the model's outcomes. One of the main limitations was that we lacked long-term follow-up data from ZUMA-7, as we only had the 2-year follow-up data to inform our model. In our primary analysis, we modeled a durable response with only 6% of patients progressing or needing additional therapy after 2 years. Recent long-term data on CAR-T in the third-line setting support this assumption.[11,18] We also modeled various scenarios to possibly reflect increased progression after 2 years, especially as CAR-T becomes used second-line in real-world practice. Another limitation is that we could only model one CAR-T product, as described earlier. An additional limitation is that we primarily modeled using the ZUMA-7 study, which had strict inclusion criteria, including not allowing any bridging therapy except for glucocorticoids and not allowing patients with impending organ-compromising disease.[5] This may mean that the results from ZUMA-7 are superior to those that will be seen in real-world practice when patients with a higher burden of disease are treated. However, the TRANSFORM (Lisocabtagene maraleucel vs standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma) study evaluating liso-cel in the second-line setting, which allowed for one cycle of bridging therapy, had a similar median EFS to ZUMA-7.[5,38] We modeled scenarios with lower EFS to account for the possibility of patients with a higher burden of disease than that included in ZUMA-7. In addition to the strict inclusion criteria in ZUMA-7, patients who achieved a complete response or partial response to salvage chemoimmunotherapy proceeded to auto-SCT. In real-world practice, patients who achieve partial response after the first salvage therapy but still have significant residual disease often are treated with CAR-T. Thus, an additional limitation is that ZUMA-7, which informed our model inputs, may not reflect the patient population or patient management in real-world practice. We also looked at the cost only from the health care perspective, and the cost of CAR-T can vary in different settings and may be transmitted to the patient. The final limitation is that we lacked data on the feasibility of stem cell collection and the efficacy of therapies, including auto-SCT after second-line CAR-T.

In conclusion, although CAR-T in the second-line setting for primary refractory/early relapse DLBCL showed a substantial improvement in EFS without a statistically significant improvement in OS compared with SOC, this modeling analysis found that it is cost-effective at a WTP of $100 000 and $150 000 if its response is durable. These analyses can help provide support for payor coverage and clinicians' utilization of CAR-T in the second-line setting. Widespread adoption of CAR-T in the second-line setting will lead to substantially increased costs even in a high-risk subgroup, highlighting the importance of alternative reimbursement models and other efforts to reduce its cost.

Authorship

Contribution: S.K. and N.R.T. designed the study and acquired the data; S.K., N.R.T., and M.S. analyzed the data; S.K., N.R.T., M.S., A.F.H., and Y.S. interpreted the data and performed the statistical analysis; S.K., N.R.T., and A.F.H. wrote the manuscript; and S.S., P.S., L.E.B., A.V.D., M.G.M., T.S., L.L.P., J.Z., S.J.F., L.W.K., and S.T.R. helped revise the manuscript. All authors discussed the data and the analysis methods and contributed to the manuscript.

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Footnotes

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