JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia

John K. Lin, Benjamin J. Lerman, James I. Barnes, Brian C. Boursiquot, Yuan Jin Tan, Alex Q.L. Robinson, Kara L. Davis, Douglas K. Owens, and Jeremy D. Goldhaber-Fiebert

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on September 13, 2018.

Corresponding author: John K. Lin, MD, Center for Primary Care and Outcomes Research, Stanford University, 117 Encina Commons, Stanford, CA 94305; e-mail: johnklin@stanford.edu.

0732-183X/18/3699-1/$20.00

A B S T R A C T

Purpose

The anti-CD19 chimeric antigen receptor T-cell therapy tisagenlecleucel was recently approved to treat relapsed or refractory pediatric acute lymphoblastic leukemia. With a one-time infusion cost of $475,000, tisagenlecleucel is currently the most expensive oncologic therapy. We aimed to determine whether tisagenlecleucel is cost effective compared with currently available treatments.

Methods

Markov modeling was used to evaluate tisagenlecleucel in pediatric relapsed or refractory acute lymphoblastic leukemia from a US health payer perspective over a lifetime horizon. The model was informed by recent multicenter, single-arm clinical trials. Tisagenlecleucel (under a range of plausible long-term effectiveness) was compared with blinatumomab, clofarabine combination therapy (clofarabine, etoposide, and cyclophosphamide), and clofarabine monotherapy. Scenario and probabilistic sensitivity analyses were used to explore uncertainty. Main outcomes were life-years, discounted lifetime costs, discounted quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (3% discount rate).

Results

With an assumption of a 40% 5-year relapse-free survival rate, tisagenlecleucel increased life expectancies by 12.1 years and cost $61,000/QALY gained. However, at a 20% 5-year relapse-free survival rate, life-expectancies were more modest (3.8 years) and expensive ($151,000/QALY gained). At a 0% 5-year relapse-free survival rate and with use as a bridge to transplant, tisagenlecleucel increased life expectancies by 5.7 years and cost $184,000/QALY gained. Reduction of the price of tisagenlecleucel to $200,000 or $350,000 would allow it to meet a $100,000/QALY or $150,000/QALY willingness-to-pay threshold in all scenarios.

Conclusion

The long-term effectiveness of tisagenlecleucel is a critical but uncertain determinant of its cost effectiveness. At its current price, tisagenlecleucel represents reasonable value if it can keep a substantial fraction of patients in remission without transplantation; however, if all patients ultimately require a transplantation to remain in remission, it will not be cost effective at generally accepted thresholds. Price reductions would favorably influence cost effectiveness even if long-term clinical outcomes are modest.

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed pediatric malignancy.[1] Although treatment advances have driven 5-year survival rates to > 90%, the prognosis of refractory or relapsed disease is poor, and ALL remains a leading cause of death as a result of childhood cancer.[2,3] Those who survive relapse typically require hematopoietic stem-cell transplantation (HSCT) to remain in remission. Chimeric antigen receptor (CAR) T cells represent a new class of cancer immunotherapies that genetically engineer patient T cells to target their disease. Unlike other currently available treatments for relapsed and refractory ALL, CAR T cells, through long-term persistence, may cure a patient's disease without transplant.

ASSOCIATED CONTENT

Data Supplement
DOI: https://doi.org/10.1200/JCO.2018.79.0642

DOI: https://doi.org/10.1200/JCO.2018.79.0642

In 2017, the US Food and Drug Administration approved tisagenlecleucel (Kymriah; Novartis, Basel, Switzerland) as the first anti-CD19 CAR T-cell therapy for relapsed or refractory pediatric ALL. Although tisagenlecleucel-induced remission rates are promising compared with those of established therapies ($> 80\%$ v $< 50\%$), only short-term follow-up data currently exist.[4-9] Whether tisagenlecleucel is sufficient to cure relapsed or refractory disease without future transplantation remains unknown. Tisagenlecleucel also costs $475,000 (wholesale acquisition), which makes it the most expensive cancer therapy to date, and has expensive and potentially life-threatening adverse effects.[10] Given the high cost and broad applicability in other malignancies of tisagenlecleucel, a pressing question for policymakers, payers, patients, and clinicians is whether the cost of therapy represents reasonable value.

This study evaluated the cost effectiveness of tisagenlecleucel for relapsed and refractory pediatric ALL. As with other novel therapies considerable uncertainty exists about long-term outcomes, which in this case is durability of remission. To explore this uncertainty, we determined price thresholds at various levels of long-term effectiveness that would make tisagenlecleucel economically attractive. These results provide a robust framework for a value-based evaluation as long-term outcomes data become available.

METHODS

Modeling Without Long-Term Outcomes Data

Durability of remission is most clinically meaningful when assessed after several years; however, the median follow-up in tisagenlecleucel's pivotal trial was 13 months.[4,11] Extrapolation of long-term outcomes from short-term data is common in oncologic modeling, but this approach can result in inaccurate assessments.[12] We addressed this uncertainty by evaluating three scenarios that cover a broad range of plausible long-term outcomes on the basis of observed variance and expert opinion (Data Supplement). The most optimistic scenario models 5-year relapse-free survival without HSCT at 40%, the intermediate scenario models 20%, and the most pessimistic scenario assumes that all patients who receive tisagenlecleucel experience a relapse within 5 years without transplant (0%; Fig 1).

Although blinatumomab and the clofarabine-containing therapies also lack long-term follow-up data, most patients who receive these therapies experience a relapse without HSCT. Therefore, for these therapies, data from the transplantation literature inform long-term overall and relapse-free survival, which leads to relatively less uncertainty about long-term outcomes than tisagenlecleucel (Data Supplement).

Treatment Strategies

For each scenario, we compared tisagenlecleucel with three currently available treatments for relapsed and refractory pediatric ALL: blinatumomab; clofarabine, cyclophosphamide, and etoposide combination therapy (clofarabine combination); and clofarabine monotherapy.

Model Structure

We modeled a hypothetical cohort of US children with relapsed or refractory B-cell ALL by developing a Markov model that followed the cohort monthly over the patients' lifetimes (Fig 2). For each treatment strategy, after receiving initial therapy, some patients achieve remission and the remainder are refractory or die. While in remission, patients may receive HSCT. Among patients with transplantations, first-time recipients and those who are minimal residual disease negative face more-favorable outcomes than those who received previous transplants or are minimal residual disease positive (Data Supplement). Patients who achieve 5 years of continuous remission are considered effectively cured and face a very low probability of relapse (and decreased lifespan compared with the general population).[11,13] Upon relapse, patients receive palliative chemotherapy until death.

Blinatumomab and the clofarabine-containing therapies are generally insufficient to ensure durable long-term remission in relapsed disease, and additional therapy (ideally transplantation) is required. Therefore, we modeled these therapies as bridges to transplantation. In the month after initial remission, a proportion of patients proceed immediately to HSCT. This proportion was derived by pooling data from blinatumomab and clofarabine studies using a meta-analysis with random effects (Data Supplement). Those for whom transplantation is unavailable instead receive a 2-year course of consolidation, intensification, continuation, and maintenance chemotherapy[14] (Data Supplement). In our main analyses, we assume the nontransplantation 5-year relapse-free survival rates are $< 10\%$ and increase to 25% in scenario analysis (Data Supplement).

The treatment course for tisagenlecleucel deviates from this model structure in two ways. First, the model reflects the pivotal trial in which approximately 18% of patients did not complete initial tisagenlecleucel infusion,[4] due to a major adverse event, manufacturing failure, or death. We considered patients who failed to complete infusion due to a major adverse event unable to tolerate additional therapy, and these patients' survival probabilities were modeled as such[15] (Data Supplement). Patients who were unable to receive tisagenlecleucel as a result of manufacturing failure instead received blinatumomab. Second, unlike the blinatumomab or clofarabine therapies, tisagenlecleucel is potentially curative.

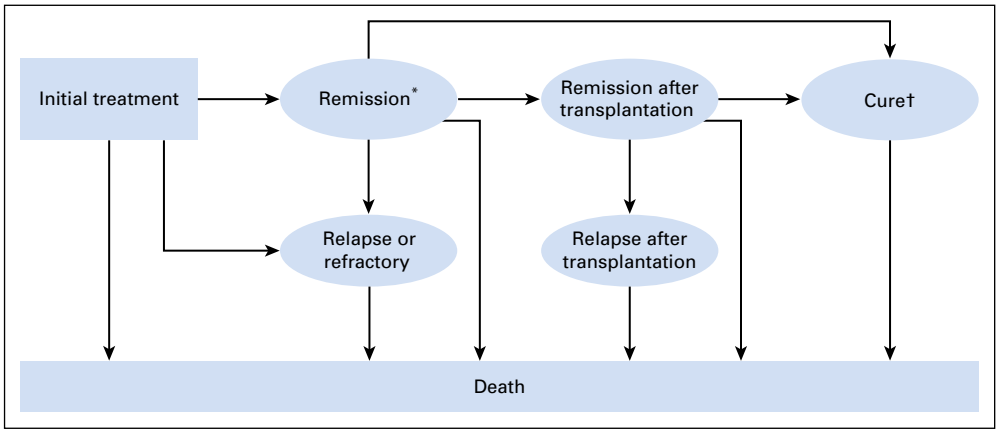

Fig 1. Simplified diagram of Markov model structure. For all states, patients remain in the same state if they are not transitioning to another state in the model. (*) Patients in nontisagenlecleucel strategies who achieve initial remission but do not undergo hematopoietic stem-cell transplantation all receive a 2-year course of postinduction chemotherapy (consolidation, continuation, maintenance) while they remain in remission, modeled as additional monthly costs. (†) Patients are considered cured if in remission or remission after receiving a transplantation for 5 years. These patients experience a low risk of relapse and higher background mortality than a person of similar age from the general population.

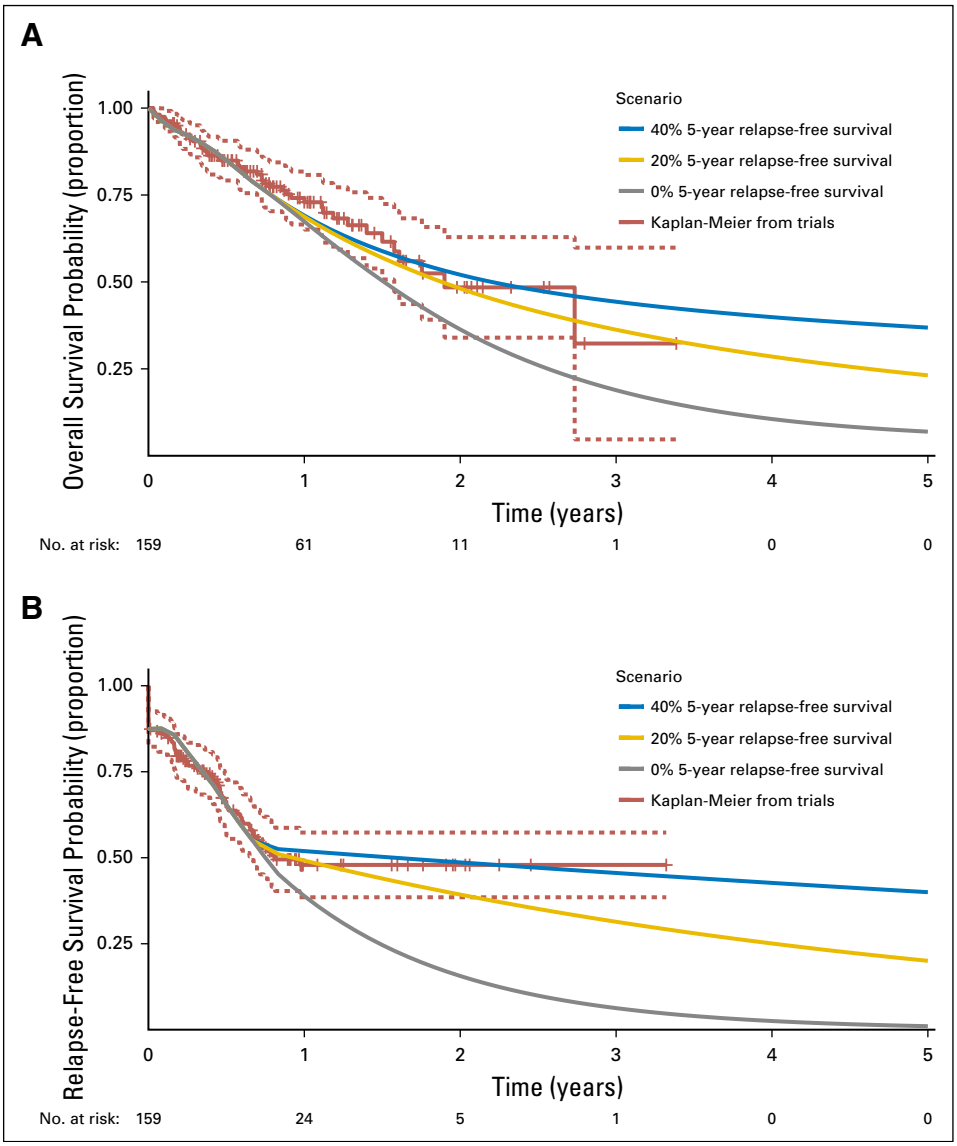

Fig 2. Modeled overall and relapse-free survival curves for three tisagenlecleucel long-term remission scenarios. Modeled (A) overall and (B) relapse-free survival curves for patients with relapsed or refractory pediatric B-cell acute lymphoblastic leukemia who receive tisagenlecleucel (time 0) superimposed on Kaplan-Meier curves that combine one pivotal and two supportive clinical trials. Dotted lines indicate combined 95% CIs. Tick marks on the Kaplan-Meier curves indicate censored events. On the basis of the Kaplan-Meier curves presented in the three tisagenlecleucel trials, patients represented by the relapse-free survival curve were censored if they received alternative treatments (including stem-cell transplantation) while in remission, whereas overall survival includes all patients. For clarity, the 95% CIs around the modeled scenarios are not shown; these can be seen in the Data Supplement.

Accordingly, after patients achieved remission with tisagenlecleucel in our model, a minority received transplantation or alternative therapy (modeled as consolidation, intensification, continuation, and maintenance chemotherapy) at rates and times that reflect those observed in the pivotal trial[4] (Data Supplement).

If tisagenlecleucel does not produce sustained remission without transplantation, its ability to induce short-term remissions may render it a clinically useful bridging therapy. Therefore, we also modeled tisagenlecleucel as a bridge to transplantation (similar to the blinatumomab and clofarabine therapies) under a 0% transplantation-free 5-year relapse-free survival scenario.

Model Inputs and Calibration

Rates of remission, survival, and relapse under each treatment strategy were informed by trial evidence using model calibration. We identified eight trials, all single arm: three tisagenlecleucel (one pivotal, two supportive), one blinatumomab, three clofarabine combination therapy, and one clofarabine monotherapy.[4-9,16] When multiple trials were available, we aggregated data to create a unified survival curve.

We calibrated the model's inputs using a constrained optimization algorithm to match the overall and relapse-free survival curves from the trials.[17] To model each of the three tisagenlecleucel 5-year relapse-free survival scenarios, we calibrated the model inputs to match the unified overall survival curve in the trials as well as a modified relapse-free survival curve that terminated at 40%, 20%, and 0% at 5 years (Fig 1). Technical details are provided in the Data Supplement. We estimated the effects of grade 3 to 4 adverse events (including cytokine release syndrome and graft-versus-host disease) and secondary malignancies by modeling their incidences, costs, and quality-of-life decrements from trials and retrospective data[13,18] (Data Supplement).

Costs and Utilities

Our analysis adopts a US health care payer perspective and accounts for direct health care costs, including drugs, therapy administration, adverse events, HSCT, and follow-up care[19-24] (Table 1; Data Supplement). Our model reflects the outcome-based payment scheme Novartis was using at the time of writing wherein the payer is responsible for tisagenlecleucel's cost only if the patient achieves initial remission.[10] Related costs, including pre-infusion chemotherapy, administration, and complications, were incurred regardless of whether the patient achieved remission. Follow-up costs after tisagenlecleucel assume 5 years of B-cell aplasia that requires monthly intravenous

Table 1. Key Input Parameters

Parameter	Base-Case Value (range for PSA)	Distribution	First Author
Patient characteristics			
Age, years	11		Maude[4]
Proportion of patients with prior transplantation	0.62 (0.54-0.69)	β	Maude[4]
Clinical outcomes			
Tisagenlecleucel			
Proportion who did not complete transfusion			
Death before infusion	0.08 (0.03-0.14)	β	Maude[4]
Severe adverse event precluded further therapy	0.03 (0.01-0.08)	β	Maude[4]
Other therapy given (manufacturing issue)	0.08 (0.03-0.14)	β	Maude[4]
Remission rate after initial therapy	0.84 (0.78-0.89)	β	Maude[4]
Proportion of initial remissions MRD−[a]	0.95 (0.89-0.99)	β	Maude[4]
Proportion of HSCT recipients MRD−[a]	0.75 (0.42-0.96)	β	Maude[4]
Overall survival rate at 1 year[b]	0.73 (0.65-0.81)	β	Maude[4]
Blinatumomab			
Remission rate after initial therapy	0.39 (0.27-0.50)	β	von Stackelberg[5]
Proportion of initial remissions MRD−	0.52 (0.70-0.33)		von Stackelberg[5]
Overall survival rate at 1 year[b]	0.39 (0.28-0.51)	β	von Stackelberg[5]
Clofarabine combination therapy			
Remission rate after initial therapy	0.47 (0.36-0.58)	β	Hijiya[7] Locatelli[8] Miano[9]
Overall survival rate at 1 year[b]	0.28 (0.14-0.41)	β	Hijiya[7] Locatelli[8] Miano[9]
Clofarabine monotherapy			
Remission rate after initial therapy	0.30 (0.19-0.41)	β	Jeha[6]
Overall survival rate at 1 year[b]	0.18 (0.06-0.29)	β	Jeha[6]
HSCT			
Receipt of HSCT after initial remission[c]	0.55 (0.42-0.67)	β	von Stackelberg[5] Hijiya[7] Locatelli[8] Miano[9]
First transplantation: overall survival at 1 year[d]	0.77 (0.75-0.79)	β	Crotta[25]
Prior transplantation: overall survival at 1 year[d]	0.43 (0.36-0.51)	β	Kato[26]
Five-year risk of relapse after 5-year relapse-free survival[e]	0.005 (0.003-0.007)	β	Pui[11]
Standardized mortality ratio after 5-year relapse-free survival[f]	1.9 (1.12-3.00)	Log-normal	Pui[13]
Costs, 2017 US $[g]			
Drug			
Tisagenlecleucel	475,000		Red Book Online[27]
Blinatumomab	44,000		CMS[19]
Clofarabine combination therapy	67,000		CMS[19]
Clofarabine monotherapy	47,000		CMS[19]
Administration and adverse events			
Tisagenlecleucel[h]	60,000 (53,000-68,000)	γ	Maude[4] CMS[20] HCUPnet[28] OSHPD[29]
Blinatumomab	23,000 (19,000-28,000)	γ	von Stackelberg[5] CMS[20] HCUPnet[28] OSHPD[29]
Clofarabine combination	72,000 (60,000-85,000)	γ	Hijiya[7] CMS[20] HCUPnet[28] OSHPD[29]
Clofarabine monotherapy	57,000 (47,000-68,000)	γ	Jeha[6] CMS[20] HCUPnet[28] OSHPD[29]
HSCTi	555,000 (471,000-638,000)	γ	Hettle[23]
Bridging and lymphodepleting chemotherapy	Data Supplement		
Postinduction chemotherapy	Data Supplement		
Long-term follow-up	Data Supplement		

(continued on following page)

Table 1. Key Input Parameters (continued)

Parameter	Base-Case Value (range for PSA)	Distribution	First Author
Utilities (quality of life)			
Treatment initiation (induction)[j]			
Tisagenlecleucel	0.78 (0.71-0.85)	β	Tengs[30]
Blinatumomab	0.78 (0.74-0.82)	β	Delea[31] van Litsenburg[32]
Clofarabine combination	0.71 (0.67-0.75)	β	Furlong[33]
Clofarabine monotherapy	0.71 (0.67-0.75)	β	Furlong[33]
Postinduction chemotherapy[j,k]			
Consolidation	0.75 (0.72-0.78)	β	Furlong[33]
Intensification	0.77 (0.74-0.80)	β	Furlong[33]
Continuation	0.79 (0.75-0.83)	β	Furlong[33]
Maintenance	0.83 (0.79-0.87)	β	Furlong[33]
Other health states			
Remission < 5 years since initial therapy (while not receiving therapy)	0.88 (0.82-0.93)	β	van Litsenburg[32] Furlong[33]
Remission > 5 years since initial therapy	0.92 (0.82-0.98)	β	Furlong[33]
Relapse (after any treatment, nontransplantation)	0.76 (0.70-0.82)	β	Delea[31] van Litsenburg[32]
Post-transplantation health states			
Month 1 after transplantation	0.64 (0.56-0.71)	β	Parsons[34] Rodgers[35]
Month 2 after transplantation (in remission)	0.62 (0.54-0.70)	β	Parsons[34] Rodgers[35]
Month 3 after transplantation (in remission)	0.63 (0.55-0.71)	β	Parsons[34] Rodgers[35]
Months 4-60 after transplantation (in remission)	0.80 (0.74-0.86)	β	Terin[36]
≥ 5 years after transplantation (in remission)	0.86 (0.80-0.91)	β	van Litsenburg[32] Furlong[33] Portwine[37]
Month 2 after transplantation (relapsed disease)	0.56 (0.48-0.64)	β	Parsons[34]
Month 3 after transplantation (relapsed disease)	0.57 (0.49-0.65)	β	Parsons[34]
> 3 months after transplantation (relapsed disease)	0.73 (0.67-0.79)	β	Parsons[34]

Abbreviations: CMS, Centers for Medicare & Medicaid Services; HCUPnet, Healthcare Cost and Utilization Project Network; HSCT, hematopoietic stem cell transplantation; MRD−, minimal residual disease negative; OSHPD, Office of Statewide Health Planning and Development; PSA, probabilistic sensitivity analysis.
[a]The proportion of MRD− patients who receive HSCT is used for the following tisagenlecleucel scenarios: 40%, 20%, and 0% 5-year relapse-free survival. The proportion of MRD− initial remissions is used for the bridge-to-transplantation tisagenlecleucel scenario.
[b]See Data Supplement for monthly relapse, prerelapse mortality, and postrelapse mortality transition probabilities.
[c]See Data Supplement for forest plot of combined proportions.
[d]See Data Supplement for post-HSCT monthly relapse, prerelapse mortality, and postrelapse mortality transition probabilities stratified by prior transplantation as well as MRD.
[e]Five-year risk of relapse is converted to monthly probabilities assuming constant risk.
[f]Standardized mortality ratios quantify the increase in mortality of patients in long-term remission with respect to the general population.
[g]See Data Supplement for detailed breakdown of individual component contributions to cost.
[h]Includes the cost of lymphodepleting and bridging chemotherapy.
[i]Cost of HSCT listed here comprises cost of transplantation, inpatient stay, outpatient follow-up, and complications for the first 12 months. Details are provided in the Data Supplement.
[j]Utilities (quality-of-life estimates) while patients receive treatment are modeled as dependent on what treatment is received (and associated toxicities) rather than whether the patient achieves remission or has refractory disease.
[k]Postinduction chemotherapy is modeled as a 2-year course of chemotherapy to the fraction of patients initially treated with blinatumomab or a clofarabine-containing therapy who achieve remission but are unable to receive a transplantation. This is divided into 2 months of consolidation, 2 months of intensification, 2 months of continuation, and 18 months of maintenance (see Data Supplement).

immunoglobulin infusions for patients in remission. Costs were inflation adjusted to 2017 US dollars.[38]

We used estimates from the leukemia and HSCT literature to assign preference-weighted utilities to each health state modeled.[30-37] When preference-weighted data did not exist, we used established methodologies to estimate utilities from oncology-specific quality-of-life scales.[35,39,40] Additional details are provided in the Data Supplement.

Main Outcomes

Outcomes were life-years, costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ie, incremental cost per QALY gained) over a lifetime horizon.[41] Costs and QALYs were discounted at 3% annually.[41,42] We defined the long-term effectiveness and prices at which tisagenlecleucel would be cost effective at three willingness-to-pay (WTP) thresholds: $50,000/QALY, $100,000/QALY, and $150,000/QALY.

Sensitivity Analyses

To assess how variations in model input altered our conclusions, we performed one-way sensitivity analyses. We also performed several scenario analyses, including alternative payment agreements varying the remission duration threshold that triggers payment for tisagenlecleucel, modeling the pivotal trial for tisagenlecleucel alone (without the two supportive trials), assuming no pre-infusion deaths in the tisagenlecleucel arm, allowing 5-year nontransplantation relapse-free survival rates for non–CAR T-cell therapies to be as high as 25%, and comparing tisagenlecleucel with palliative chemotherapy.

We performed probabilistic sensitivity analyses in which we simultaneously sampled model inputs 1,000 times from uncertainty distributions (Table 1). To test model stability, we also modeled our base-case scenario with 10,000 simulations.

Our model was built using TreeAge Pro Healthcare 2018, R1 release (TreeAge Software, Williamstown, MA). Calibration and statistical analyses

Table 2. Clinical and Economic Outcomes Over the Lifetime Analytic Horizon

Scenario	Life-Years	QALYs	Cost, 2017 US $	ICER, $/QALY	Simulation of Cost-Effectiveness at Various WTP Thresholds, %		
					$50,000	$100,000	$150,000
Tisagenlecleucel							
40% 5-year relapse-free survival rate*	20.6 (16.4-25.0)	8.74 (7.03-10.60)	599,000 (535,000-662,000)	61,000 (51,000-90,000)	1.9	98.3	99.0
20% 5-year relapse-free survival rate*	12.30 (8.28-16.10)	5.50 (3.90-7.11)	573,000 (510,000-636,000)	151,000 (92,000-dominated‡)	0	4.8	49.4
0% 5-year relapse-free survival rate*	5.95 (4.22-9.14)	2.96 (2.20-4.44)	548,000 (493,000-607,000)	Dominated‡ (422,000-dominated‡)	0	0.6	0.8
Bridge to transplantation†	14.20 (9.93-19.30)	5.92 (4.34-7.79)	713,000 (627,000-799,000)	184,000 (124,000-977,000)	0	0.6	17.5
Other therapies							
Blinatumomab	8.55 (6.33-13.90)	3.57 (2.69-5.38)	282,000 (248,000-323,000)	0 (reference)	—	—	—
Clofarabine combination	8.55 (6.34-11.00)	3.52 (2.69-4.42)	374,000 (329,000-420,000)	Dominated‡	—	—	—
Clofarabine monotherapy	7.60 (5.80-9.89)	3.12 (2.45-3.97)	314,000 (280,000-358,000)	Dominated‡	—	—	—

NOTE. The model assumed a health system perspective, a lifetime analytic horizon, and discounted future costs and QALYs at 3% per year. Life-years and QALYs are rounded to the nearest 0.01, costs and ICERs are rounded to the nearest 1,000. All reported values are means of 1,000 simulations with 95% uncertainty intervals. Additional modeling details are available in the Data Supplement.

Abbreviations: ICER, incremental cost-effectiveness ratio (incremental cost per quality-adjusted life-year); QALY, quality-adjusted life-year; WTP, willingness to pay.

*Refers to the percentage of patients infused with tisagenlecleucel modeled to survive to 5 years without relapse in the absence of hematopoietic stem-cell transplantation. Patients in the tisagenlecleucel scenarios receive a transplantation at the empirically observed low rate and times seen in the pivotal trial.

†Modeled under the assumption that in the absence of transplantation, 0% of patients survive to 5 years without relapse. In this scenario, patients who achieve remission are modeled as receiving hematopoietic stem-cell transplantation at an equivalent rate to comparator treatment arms.

‡A treatment scenario is dominated if it results in inferior outcomes and higher costs compared with the reference treatment.

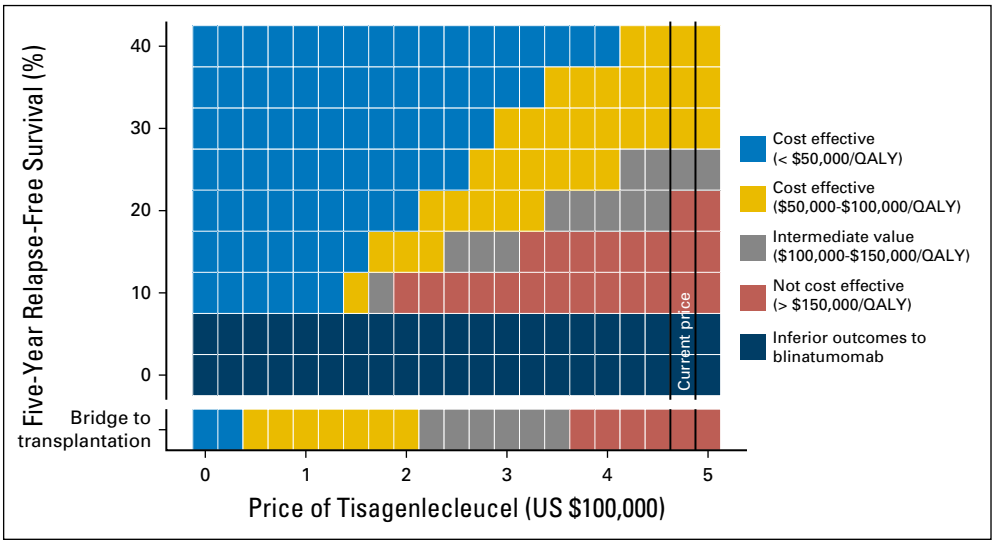

Fig 3. Two-way sensitivity analysis: cost effectiveness of tisagenlecleucel compared with blinatumomab by 5-year relapse-free survival rate and price. At 2018 US prices, tisagenlecleucel cost < $100,000/quality-adjusted life-year (QALY) down to a 5-year relapse-free survival rate of approximately 30%. If 5-year relapse-free survival rates are approximately < 20%, it is not cost effective at commonly accepted thresholds. Below 5-year relapse-free survival rates of approximately 5%, outcomes are inferior to blinatumomab. Price reductions favorably influence cost effectiveness, even if long-term clinical outcomes are modest. In the bridge-to-transplantation scenario, in the absence of transplantation, 0% of patients survive to 5 years without relapse. In this scenario, patients who achieve remission are modeled as receiving hematopoietic stem cell transplantation at an equivalent rate to comparator treatment arms.

were performed with R software, version 3.4.2. Our methods conform to Consolidated Health Economic Evaluation Reporting Standards and the Second Panel on Cost-Effectiveness[41,43] (Data Supplement).

RESULTS

Base-Case Analysis

Tisagenlecleucel resulted in longer life expectancies than other therapies at 5-year relapse-free survival rates > approximately 5%. Patients treated with tisagenlecleucel experienced life expectancies of 20.6, 12.3, and 5.95 years at 5-year relapse-free survival rates of 40%, 20%, and 0%, respectively. Blinatumomab, clofarabine combination therapy, and clofarabine monotherapy yielded average life expectancies of 8.6, 8.6, and 7.6 years, respectively. Tisagenlecleucel was the most expensive treatment strategy at $548,000 to $599,000. The comparators were less expensive at $282,000 to $374,000 (Table 2). Blinatumomab resulted in superior outcomes at lower costs than both clofarabine-containing arms.

Tisagenlecleucel's economic value was strongly influenced by its long-term outcomes. At 40% 5-year relapse-free survival, tisagenlecleucel resulted in an additional 5.07 QALYs gained at a cost of $61,000/QALY compared with blinatumomab. At 20% 5-year relapse-free survival, tisagenlecleucel resulted in an additional 1.80 QALYs gained at a cost of $151,000/QALY. At 0% 5-year relapse-free survival, blinatumomab had superior outcomes at a lower cost than tisagenlecleucel (Table 2; Data Supplement). At its current price, tisagenlecleucel cost < $100,000/QALY down to a 5-year relapse-free survival rate of approximately 30% and < $150,000/QALY down to a rate of approximately 25% (Fig 3).

Reducing tisagenlecleucel's price increases its cost effectiveness, even if long-term outcomes are modest. At a 5-year relapse-free survival rate of 20%, a price reduction to approximately $325,000 or $450,000 would meet $100,000/QALY or $150,000/QALY WTP thresholds, respectively. Tisagenlecleucel is not cost-effective compared with blinatumomab at any price below a 5-year relapse-free survival rate of approximately 5% (Fig 3).

In a worst-case scenario in which all patients who receive tisagenlecleucel eventually relapse without transplantation, use of the therapy as a bridge to transplantation resulted in an increased life expectancy (5.7 years) compared with blinatumomab (2.35 QALYs gained at $184,000/QALY). To meet a $100,000/QALY or $150,000/QALY threshold would require reductions in price to approximately $200,000 or $350,000, respectively.

Sensitivity Analyses

In one-way sensitivity analyses, two model parameters rendered tisagenlecleucel cost effective by assuming modest long-term outcomes: reductions in price and a low discount rate. In a bridge-to-transplantation scenario, increasing the proportion of patients who receive a transplantation (among those who achieve remission) from 0.55 to 0.75 improved tisagenlecleucel's economic value, but it would not make it cost effective. Tisagenlecleucel's economic value was substantially worse if costs and benefits were taken into account over 15 years rather than through each individual's lifespan. Several parameters moderately worsened tisagenlecleucel's economic value: standardized mortality ratio after long-term remission, cost of care after long-term remission, and cost of care for grade 4 cytokine release syndrome. Our assessment of tisagenlecleucel's cost effectiveness was not materially changed with variation in other short-term costs (Data Supplement; Fig 4).

In probabilistic sensitivity analyses, tisagenlecleucel at a 5-year relapse-free survival rate of 40% was cost effective in 99.3%, 98.7%, and 6.0% of simulations at WTP thresholds of $150,000, $100,000, and $50,000, respectively. Tisagenlecleucel at a 5-year relapse-free survival rate of 20% was cost effective in 53.1%, 6.5%, and 0% of simulations at equivalent thresholds. At a 5-year relapse-free survival rate of 0% and in the absence of transplantation, tisagenlecleucel consistently produced inferior outcomes to blinatumomab at a higher cost (Table 2; Data Supplement).

Scenario Analyses

The current outcomes-based payment agreement did not materially affect tisagenlecleucel's economic value compared with

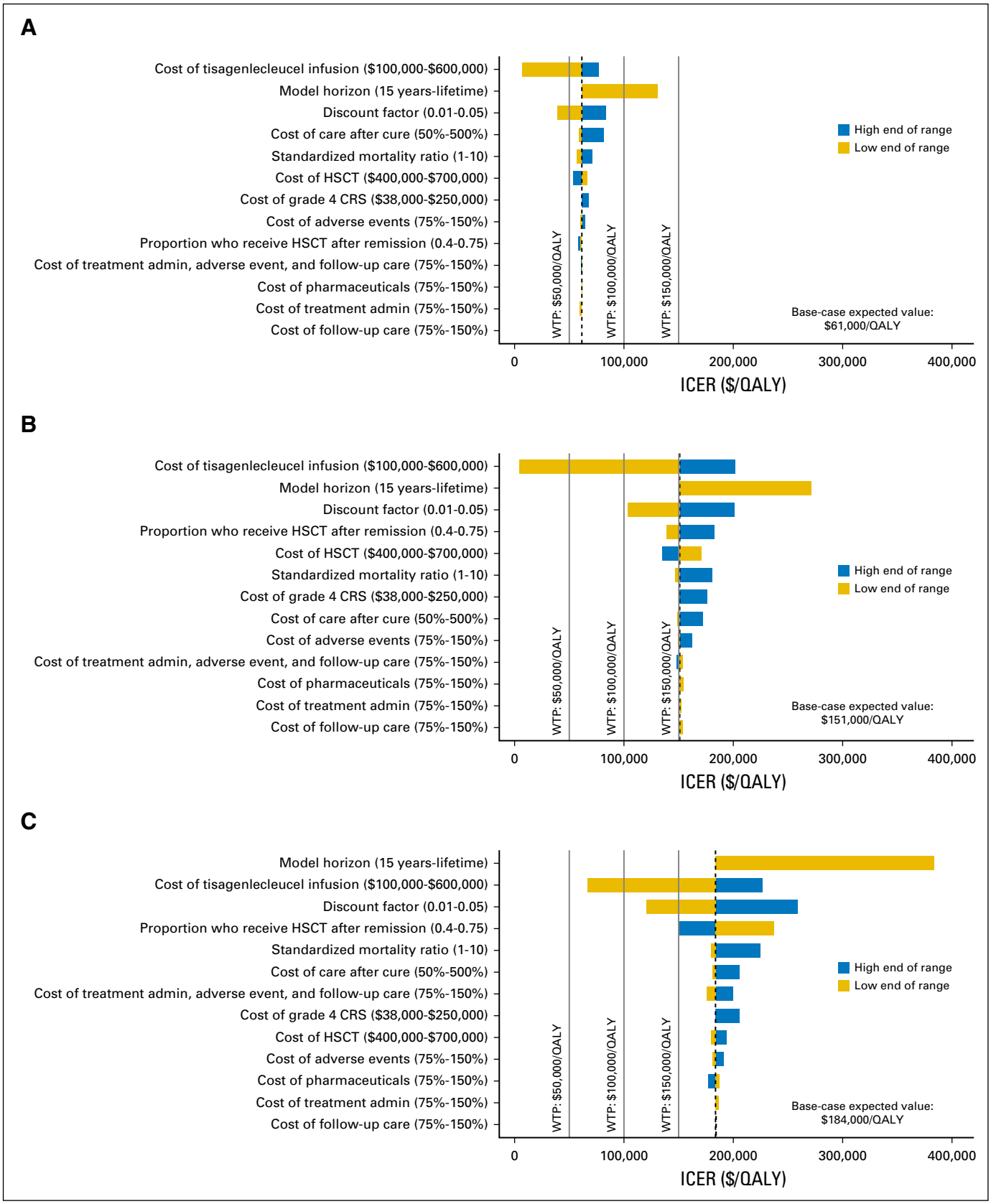

Fig 4. One-way sensitivity analyses (tornado diagrams) of tisagenlecleucel versus blinatumomab that show how variations in individual inputs alter tisagenlecleucel's cost effectiveness. Three effectiveness scenarios of tisagenlecleucel are shown: (A) 40% 5-year relapse-free survival versus blinatumomab, (B) 20% 5-year relapse-free survival versus blinatumomab, and (C) bridge to transplantation versus blinatumomab. In the bridge-to-transplantation scenario, patients who do (continued on next page)

a traditional agreement that requires all patients to pay. However, alternative payment agreements resulted in the therapy becoming more economically attractive. Increasing the remission duration threshold that triggers payer responsibility from any initial remission to 7 months of remission allowed tisagenlecleucel to meet a $100,000/QALY WTP threshold at 40% and 20% 5-year relapse-free survival rates and a $150,000/QALY WTP threshold in a bridge-to-transplantation scenario (Data Supplement).

The following scenarios did not change our assessment of tisagenlecleucel's economic value: assuming no infusion failure as a result of death or manufacturing, comparing tisagenlecleucel directly with palliative chemotherapy, using only tisagenlecleucel's pivotal trial to inform outcomes, or allowing 5-year non-transplantation relapse-free survival rates for non–CAR T-cell therapies to be as high as 25%. The results were robust to analyses with 10,000 simulations (Data Supplement).

DISCUSSION

We find that tisagenlecleucel may provide substantial survival gains for children with relapsed or refractory ALL compared with currently available therapies. However, we also show that at its current price and payment structure, the long-term effectiveness of tisagenlecleucel (ie, the ability to keep a substantial fraction of patients in remission without transplantation) is an important but uncertain determinant of its cost effectiveness.

At our most optimistic assumptions (40% 5-year relapse-free survival), tisagenlecleucel would result in considerable survival gains (12.1 life-years) while representing good economic value (< $100,000/QALY). In a field where developments often are incremental, these results would represent an important advance. However, as we modeled progressively lower long-term effectiveness (20% to 0% 5-year relapse-free survival), its economic value diminished. If tisagenlecleucel fails to meet the goal of transplantation-free cure, clinicians may use it as a bridge to transplantation. This worst-case scenario would lead to an increased life expectancy (5.7 years), but at a cost of $184,000/QALY, it would not meet commonly accepted thresholds for cost effectiveness.

Tisagenlecleucel's robust short-term outcomes make it a critical therapy for children with relapsed or refractory ALL. However, our results suggest that at tisagenlecleucel's current price and payment structure, its economic value is uncertain. This uncertainty may lead payers to choose not to cover tisagenlecleucel or to only cover it for certain patient populations. Our analysis indicates two potential ways payers may be more willing to assume the risk of suboptimal long-term clinical outcomes. The first is a lower price. At a price of $200,000 or $350,000, tisagenlecleucel would meet a < $100,000/QALY or < 150,000/QALY threshold, even in a worst-case scenario in which all patients experience relapse and tisagenlecleucel is used as a bridge to transplantation. As additional outcomes data are reported, this price could be adjusted to reflect increased certainty about tisagenlecleucel's long-term effectiveness.

Some payers, patient advocates, and pharmaceutical companies support outcomes-based pricing for tisagenlecleucel, which ties reimbursement to clinical outcomes. This theoretically allows all stakeholders to share in the financial risk of a therapy with uncertain outcomes and therefore increases its economic attractiveness (and the likelihood that the payer will cover the therapy). In Novartis'currently proposed arrangement, the payer is responsible for the price of tisagenlecleucel only if the patient achieves initial remission.[10] However, because of tisagenlecleucel's high initial remission rates, this does not materially mitigate risk compared with a traditional payment model. If the arrangement is changed such that payment occurs only if the patient achieves 7 months of remission, tisagenlecleucel would meet a < $100,000/QALY threshold at a 40% and 20% 5-year relapse-free survival rate and a < $150,000/QALY threshold in a worst-case, bridge-to-transplantation scenario (Data Supplement).

To our knowledge, this cost-effectiveness analysis is the first to explore the uncertainty of tisagenlecleucel's long-term effects in pediatric patients with ALL. The results are consistent with two non–peer-reviewed analyses, and our conclusions provide stakeholders with a deeper understanding of the determinants of tisagenlecleucel's cost effectiveness.[44,45] We conclude from two other analyses that tisagenlecleucel would be cost effective at a WTP threshold of $100,000/QALY. However, the analyses followed the current standard oncologic modeling approach with the evaluation of only one long-term effectiveness scenario by extrapolating short-term data to predict future outcomes. This approach yielded a 5-year relapse-free survival rate estimate for tisagenlecleucel of approximately 42%.[44] Although this outcome is possible and produces similar economic results to our 40% relapse-free survival scenario, this assumption may be overly optimistic given the pivotal trial's short follow-up.[4]

Although there will always be uncertainty assessing the economic value of a novel therapy in its early stages given the rapid rise of next-generation cancer therapies (and their prices), it is arguably more important than ever that patients, payers, and clinicians have access to reliable and robust cost-effectiveness data early on to inform their understanding of the therapy's economic value. We show that by modeling multiple plausible long-term outcome scenarios, including a worst-case scenario of zero transplantation-free long-term remissions, we can provide an account of the range of tisagenlecleucel's likely economic value. Moreover, we demonstrate the effect of changes in price or payment structure on its economic value if long-term clinical outcomes are modest.

This study has several limitations. No high-quality long-term clinical outcomes data exist for tisagenlecleucel. We addressed this limitation by modeling multiple long-term effectiveness scenarios, including one where all patients eventually experience relapse. All trials for relapsed or refractory pediatric ALL were single-arm studies, which limited a direct comparison between treatment

(Continued) not receive a transplantation eventually experience relapse. Among patients who achieve initial remission, the fraction who receive a transplantation is identical in all arms. The dotted line depicts the incremental cost-effectiveness ratio of the base-case. The gray lines depict the three willingness-to-pay (WTP) thresholds evaluated: $50,000/quality-adjusted life-year (QALY), $100,000/QALY, and $150,000/QALY. Incremental cost-effectiveness ratios (ICERs) lower than a given threshold can be interpreted as the intervention being cost effective at that threshold. admin, administration; CRS, cytokine release syndrome; HSCT, hematopoietic stem-cell transplantation.

arms. We compared tisagenlecleucel with the next most optimal therapy in a conservative manner because patients enrolled in tisagenlecleucel trials had poorer baseline prognostic characteristics than those in comparator trials (Data Supplement). Although we evaluated two extremes of using tisagenlecleucel—with minimal transplantation, and as a bridge to transplantation—both treatment strategies as well as intermediates likely will coexist eventually, which may change tisagenlecleucel's cost effectiveness. As strategies are developed that incorporate alternative timing of transplantation, these can be evaluated in future cost-effectiveness analyses. As with all modeling studies, data availability limited our analysis. Several uncertain inputs would worsen tisagenlecleucel's economic value if more pessimistic than modeled, including cost of cytokine release syndrome and costs and outcomes after cure. Other variations in cost did not materially influence tisagenlecleucel's cost effectiveness. We did not account for tisagenlecleucel's non–health care benefits in this analysis, such as future productivity, which may be substantial given the young age at which patients may be cured.

At tisagenlecleucel's current price and payment structure, its long-term clinical effectiveness is a critical determinant of its cost-effectiveness. If tisagenlecleucel results in a substantial fraction of patients who achieve durable remission without transplantation, it would represent good economic value. However, its value diminishes under scenarios of lower long-term effectiveness. Price reductions of tisagenlecleucel or payment only for longer-term remissions would favorably influence cost-effectiveness, even if long-term clinical outcomes are modest.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: John K. Lin, Benjamin J. Lerman, Brian C. Boursiquot, Yuan Jin Tan
Data analysis and interpretation: John K. Lin, Benjamin J. Lerman, Jeremy D. Goldhaber-Fiebert
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. WHO: Incidence of Childhood Leukaemia: Fact Sheet 4.1, 2009. http://www.euro.who.int/__data/assets/pdf_file/0005/97016/4.1.-Incidence-of-childhood-leukaemia-EDITED_layouted.pdf
2. Smith MA, Seibel NL, Altekruse SF, et al: Outcomes for children and adolescents with cancer: Challenges for the twenty-first century. J Clin Oncol 28:2625-2634, 2010
3. Bhojwani D, Pui C-H: Relapsed childhood acute lymphoblastic leukaemia. Lancet Oncol 14: e205-e217, 2013
4. Maude SL, Laetsch TW, Buechner J, et al: Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 378:439-448, 2018
5. von Stackelberg A, Locatelli F, Zugmaier G, et al: Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 34:4381-4389, 2016
6. Jeha S, Gaynon PS, Razzouk BI, et al: Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 24:1917-1923, 2006
7. Hijiya N, Gaynon P, Barry E, et al: A multicenter phase I study of clofarabine, etoposide and cyclophosphamide in combination in pediatric patients with refractory or relapsed acute leukemia. Leukemia 23:2259-2264, 2009
8. Locatelli F, Testi AM, Bernardo ME, et al: Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. Br J Haematol 147:371-378, 2009
9. Miano M, Pistorio A, Putti MC, et al: Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. Leuk Lymphoma 53:1693-1698, 2012
10. Bach PB, Giralt SA, Saltz LB: FDA approval of tisagenlecleucel: Promise and complexities of a $475000 cancer drug. JAMA 318:1861-1862, 2017 .
11. Pui CH, Pei D, Campana D, et al: A revised definition for cure of childhood acute lymphoblastic leukemia. Leukemia 28:2336-2343, 2014
12. Prasad V, Mailankody S: How should we assess the value of innovative drugs in oncology? Lessons from cost-effectiveness analyses. Blood 126:1860-1861, 2015
13. Pui C-H, Cheng C, Leung W, et al: Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med 349:640-649, 2003
14. Parker C, Waters R, Leighton C, et al: Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): An open-label randomised trial. Lancet 376:2009-2017, 2010
15. von Stackelberg A, Völzke E, Kühl J-S, et al: Outcome of children and adolescents with relapsed acute lymphoblastic leukaemia and non-response to salvage protocol therapy: A retrospective analysis of the ALL-REZ BFM Study Group. Eur J Cancer 47: 90-97, 2011
16. Novartis: Tisagenlecleucel (CTL019) for the treatment of pediatric and young adult patients with relapsed/refractory B-Cell acute lymphoblastic leukemia. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf
17. Byrd RH, Lu P, Nocedal J, et al: A limited memory algorithm for bound constrained optimization. SIAM J Sci Comput 16:1190-1208, 1995
18. Schmiegelow K, Levinsen MF, Attarbaschi A, et al: Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. J Clin Oncol 31:2469-2476, 2013
19. Centers for Medicare & Medicaid Services: 2018 ASP drug pricing. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html
20. Centers for Medicare & Medicaid Services: Physician fee schedule, 2017 .https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx
21. Centers for Medicare & Medicaid Services: Clinical laboratory fee schedule. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files.html
22. Majhail NS, Mau LW, Denzen EM, et al: Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: A study using a large national private claims database. Bone Marrow Transplant 48:294-300, 2013
23. Hettle R, Corbett M, Hinde S, et al: The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. Health Technol Assess 21:1-204, 2017
24. de Waure C, Capri S, Veneziano MA, et al: Extracorporeal photopheresis for second-line treatment of chronic graft-versus-host diseases: Results from a health technology assessment in Italy. Value Health 18:457-466, 2015
25. Crotta A, Zhang J, Keir C: Survival after stem-cell transplant in pediatric and young-adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Curr Med Res Opin 34:435-440, 2018
26. Kato M, Horikoshi Y, Okamoto Y, et al: Second allogeneic hematopoietic SCT for relapsed ALL in children. Bone Marrow Transplant 47:1307-1311, 2012
27. IBM Watson Health: Micromedex Red Book. Greenwood Village, CO, IBM Watson Health. http://www.micromedexsolutions.com
28. Healthcare Cost and Utilization Project: Nationwide HCUP databases. http://www.hcup-us.ahrq.gov/databases.jsp
29. California Office of Statewide Health Planning and Development: Hospital Annual Financial Data. Sacramento, CA, Office of Statewide Health Planning and Development. https://oshpd.ca.gov/data-and-reports/cost-transparency/hospital-financials/
30. Tengs TO, Wallace A: One thousand health-related quality-of-life estimates. Med Care 38:583-637, 2000

31. Delea TE, Amdahl J, Boyko D, et al: Cost-effectiveness of blinatumomab versus salvage chemotherapy in relapsed or refractory Philadelphia-chromosome-negative B-precursor acute lymphoblastic leukemia from a US payer perspective. J Med Econ 20:911-922, 2017

32. van Litsenburg RL, Huisman J, Raat H, et al: Health-related quality of life and utility scores in short-term survivors of pediatric acute lymphoblastic leukemia. Qual Life Res 22:677-681, 2013

33. Furlong W, Rae C, Feeny D, et al: Health-related quality of life among children with acute lymphoblastic leukemia. Pediatr Blood Cancer 59: 717-724, 2012

34. Parsons SK, Tighiouart H, Terrin N: Assessment of health-related quality of life in pediatric hematopoietic stem cell transplant recipients: Progress, challenges and future directions. Expert Rev Pharmacoecon Outcomes Res 13:217-225, 2013

35. Rodgers C, Wills-Bagnato P, Sloane R, et al: Health-related quality of life among children and adolescents during hematopoietic stem cell transplant recovery. J Pediatr Oncol Nurs 32:329-336, 2015

36. Terrin N, Rodday AM, Parsons SK: Joint models for predicting transplant-related mortality from quality of life data. Qual Life Res 24:31-39, 2015

37. Portwine C, Rae C, Davis J, et al: Health-related quality of life in survivors of high-risk neuroblastoma after stem cell transplant: A national population-based perspective. Pediatr Blood Cancer 63:1615-1621, 2016 .

38. US Bureau of Economic Analysis: Personal consumption expenditures: Services: Health care (chain-type price index). https://fred.stlouisfed.org/series/DHLCRG3A086NBEA

39. Lawitschka A, Güclü ED, Varni JW, et al: Health-related quality of life in pediatric patients after allogeneic SCT: Development of the PedsQL Stem Cell Transplant module and results of a pilot study. Bone Marrow Transplant 49:1093-1097, 2014

40. Parsons SK, Shih MC, Mayer DK, et al: Preliminary psychometric evaluation of the Child Health Ratings Inventory (CHRIs) and Disease-Specific Impairment Inventory-Hematopoietic Stem Cell Transplantation (DSII-HSCT) in parents and children. Qual Life Res 14:1613-1625, 2005

41. Sanders GD, Neumann PJ, Basu A, et al: Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 316:1093-1103, 2016

42. Weinstein MC, Siegel JE, Gold MR, et al: Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. JAMA 276:1253-1258, 1996

43. Husereau D, Drummond M, Petrou S, et al: Consolidated Health Economic Evaluation Reporting Standards (CHEERS)–explanation and elaboration: A report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 16:231-250, 2013

44. Tice JA, Walsh JM, Otuonye I, et al: Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value: Evidence Report. Boston, MA, Institute for Clinical and Economic Review 2018

45. Hao Y, Eldjerou L, Yang H, et al: Cost-effectiveness analysis of CTL019 for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia in the United States. Blood 130, 2017 [suppl 1; abstr 609]

Affiliations

John K. Lin, **James I. Barnes**, and **Douglas K. Owens**, Veterans Affairs Palo Alto Health Care System, Palo Alto; **John K. Lin**, **James I. Barnes**, **Alex Q.L. Robinson, Douglas K. Owens**, and **Jeremy D. Goldhaber-Fiebert**, Stanford University; and **Benjamin J. Lerman**, **Brian C. Boursiquot**, **Yuan Jin Tan**, and **Kara L. Davis**, Stanford University School of Medicine, Stanford, CA.

Support

Supported in part by a Veterans Affairs Office of Academic Affiliations advanced fellowship in health service and research development (J.K.L. and J.I.B.). All views expressed herein are those of the authors and do not necessarily reflect the views of the Department of Veterans Affairs. B.J.L. and B.C.B were supported by a National Center for Advancing Translational Science Clinical and Translational Science Award (TL1TR001084 and UL1TR001085).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

John K. Lin
No relationship to disclose

Benjamin J. Lerman
No relationship to disclose

James I. Barnes
No relationship to disclose

Brian C. Boursiquot
No relationship to disclose

Yuan Jin Tan
No relationship to disclose

Alex Q.L. Robinson
No relationship to disclose

Kara L. Davis
Consulting or Advisory Role: Novartis
Research Funding: Novartis
Travel, Accommodations, Expenses: Novartis

Douglas K. Owens
No relationship to disclose

Jeremy D. Goldhaber-Fiebert
No relationship to disclose