Importance  Tisagenlecleucel, a chimeric antigen receptor T-cell therapy for relapsed or refractory pediatric acute lymphoblastic leukemia, has been approved for use in multiple jurisdictions. The public list price is US $475,000, or more than CaD $600,000. Assessing the cost-effectiveness of tisagenlecleucel is necessary to inform policy makers on the economic value of this treatment.

Objective  To assess the value for money of tisagenlecleucel compared with current standard care for tisagenlecleucel-eligible pediatric patients with acute lymphoblastic leukemia under unknown long-term effectiveness.

Design, Setting, and Participants  A cost-utility analysis of tisagenlecleucel compared with current standard care using a Canadian population-based registry of pediatric patients with acute lymphoblastic leukemia was performed. Results from 3 pooled single-arm tisagenlecleucel clinical trials and a provincial pediatric cancer registry were combined to create treatment and control arms, respectively. The population-based control arm consisted of patients meeting clinical trial inclusion and exclusion criteria, starting at second relapse. Multistate and individual-level simulation modeling were combined to predict patient lifetime health trajectories by treatment strategy. Tisagenlecleucel efficacy was modeled across long-term cure rates, from 10% to 40%, to account for limited information on its long-term effectiveness. Uncertainty was tested with 1-way and probabilistic sensitivity analysis. Data were collected in September 2017, and analysis began in December 2017.

Exposures  Tisagenlecleucel compared with current standard care for tisagenlecleucel-eligible patients.

Main Outcomes and Measures  Relative health care costs, survival gains, and quality-adjusted life-years (QALYs) between tisagenlecleucel and current standard care.

Results  The treatment and control arms were modeled on 192 and 118 patients, respectively. The mean (SD) age of control individuals was 10 (4.25) years, and the mean (SD) age of the pooled clinical trial sample was 11 (6) years. The control individuals had 78 boys (66%), and the pooled clinical trial sample had 102 boys (53%). Treatment with tisagenlecleucel was associated with an additional 2.14 to 9.85 life years or 1.68 to 6.61 QALYs, compared with current care. The average additional cost of tisagenlecleucel was CaD $470,013 (US $357,031). Accounting for the total discounted cost over the patient lifetime resulted in an incremental cost of CaD $71,000 (US $53,933) to CaD $281,000 (US $213,453) per QALY gain.

Conclusions and Relevance  To our knowledge, this study offers the first cost-effectiveness analysis of tisagenlecleucel compared with current standard care for pediatric patients with acute lymphoblastic leukemia using a constructed population-based control arm. At a willingness-to-pay threshold of $150,000/QALY, tisagenlecleucel had a 32% likelihood of being cost-effective. Tisagenlecleucel cost-effectiveness would fall below $50,000/QALY with a long-term cure rate of over 0.40 or a price discount of 49% at its currently known effectiveness.
Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for 1 in 5 diagnoses. Developments in ALL treatment have dramatically improved survival rates throughout the last 20 years. Relapsed ALL has not seen the same advances, with 5-year survival rates of 20% to 60%, depending on relapse site and timing. Treatment for high-risk, relapsed pediatric ALL has involved hematopoietic stem cell transplant (HSCT). Outside of HSCT, salvage regimens generally consist of adapted combinations of front-line therapies. While HSCT was considered the only curative option in these high-risk situations, not all patients with relapsed ALL will be eligible for HSCT. Furthermore, HSCT is associated with significant morbidity and treatment-related mortality. Both graft vs host disease (GVHD) and relapses after HSCT are common. Hematopoietic stem cell transplant is also costly, with a first-year inpatient cost of almost CA$230 000 (US$174 712) in Canada.

As an alternative, the US Food and Drug Administration and other national health authorities have approved tisagenlecleucel, a chimeric antigen receptor (CAR) T-cell therapy, as a potentially curative treatment for pediatric ALL. This technique involves modifying a patient’s own harvested T-cells to target CD19, a protein almost universally expressed on the surface of ALL cells. The CAR T-cells are expanded ex vivo and reintroduced into the patient after minimal preparatory chemotherapy. Early trials showed complete remission rates in the first 3 months postinfusion for 90% to 100% of patients. A multicenter trial with tisagenlecleucel showed complete response rates of 81%, with 50% of patients leukemia-free 1 year postinfusion. Longer-term effectiveness of tisagenlecleucel and other CAR T-cell therapies is uncertain, yet the public list price for 1 course of tisagenlecleucel was set by the manufacturer at CA$625 000 (in 2018) (US$475 000). While this price will likely face some downward pressure in a public insurance setting, it nonetheless attracted considerable concern from the medical community.

For tisagenlecleucel to be formally reimbursed and provided to eligible patients in Canada, an assessment of whether the outcomes of tisagenlecleucel justify the treatment cost must be determined. We estimate the cost utility of tisagenlecleucel vs standard care through an evaluation of their comparative cost and efficacy throughout the lifetime for patients diagnosed with pediatric ALL starting at second relapse. Two previous cost-effectiveness studies have assessed this question, with conflicting conclusions on tisagenlecleucel value for money. Both studies were conducted within the US context and relied on data from published clinical trials. In contrast, our Canadian study harnessed real-world, population-level registry data to estimate long-term and quality of life-adjusted survival, along with lifetime costs for tisagenlecleucel-eligible patients receiving current standard care or tisagenlecleucel.

Methods

To understand the value for money of tisagenlecleucel compared with standard care, we used a cost-utility analysis to estimate lifetime costs and quality-adjusted life-years (QALY) for tisagenlecleucel-eligible patients undergoing treatment via tisagenlecleucel or standard care and modeled from a public insurer perspective. While tisagenlecleucel’s indication does allow for treatment in some refractory or first-relapse patients, based on the available evidence and to provide a conservative estimate to comparators, our analysis began at second relapse. We included costs associated with in-hospital treatment and follow-up care for both treatment strategies and applied a 1.5% annual discounting on costs and QALYs. Health outcomes of interest were after tisagenlecleucel and standard care-associated life expectancy and QALYs. Cost utility was determined by an incremental cost-utility ratio (ICUR): the incremental costs of tisagenlecleucel over standard care, divided by their QALY differential. This study was approved by the Hospital for Sick Children Research Ethics Board (REB #1000058063). Informed consent was not required for use of registry data. Data were collected in September 2017.

We used a microsimulation model to estimate the mean costs and QALYs over a patient’s lifetime for each strategy. The model simulated 100 000 patients with twice-relapsed ALL and tracked them as they transitioned through clinical and health states. At simulation start, all patients were assumed to be 10 years old, aligning with the median age from our matched Ontario pediatric registry cohort (eTable 1 in the Supplement). Patients could transition between health and treatment states in monthly cycles up to a maximum age of 60 years. A multistate model was used to estimate transition likelihood for each strategy using the registry and published clinical trial data. State-specific health care resource utilization and quality of life was informed by provincial formularies and literature sources. See eMethods in the Supplement for model fitting procedures (eFigure 1 and eTable 2 in the Supplement).

Current Standard Care Strategy

To inform transitions for patients in the standard care strategy, we used individual-level patient data from the Pediatric Oncology Group of Ontario’s Networked Information System...
(POGONIS) provincial pediatric cancer registry, which prospectively captured detailed disease, treatment, and outcome data. Standard care encompassed any treatment a tisagenlecleucel-eligible patient received at the discretion of their treating physician, including intensive combination chemotherapy and HSCT. We included any patient with ALL who would have been eligible for a tisagenlecleucel clinical trial. This included patients with 2 or more relapses, older than 2 years, and younger than 21 years.26 POGONIS patient demographics compared with trial patient information are detailed in the online supplement (eTable 1 in the Supplement), along with exclusion and inclusion criteria.

The standard care strategy involved a 3-state model of second (or higher) relapse, HSCT, and death (eFigure 2 in the Supplement). Individual patients started and could remain in the relapse state where they underwent treatments such as chemotherapy or palliative care. These treatments were not explicitly modeled but were accounted for in cost and utility adjustments. Alternatively, patients transitioned to HSCT or died. Hemato poetic stem cell transplant was modeled separately owing to its unique cost and survival impact. Most HSCT treatment costs occurred in the first cycle of the HSCT state after a cycle of conditioning (Table 1).29,31,35,38

On receiving HSCT, each patient was at risk of acute GVHD for the first 100 days and chronic GVHD thereafter.11,12 Tunnel states incorporated these adverse event risks. Acute and chronic GVHD were assumed to occur in 35% and 47% of patients, respectively.33 In the modeled states of relapse or HSCT, patients remained in either state if they achieved stable disease or if they had a subsequent relapse. Patients transitioned out of relapse or HSCT states only on death. Long-term HSCT survival began 2 years after treatment. All-cause mortality was calculated based on Canadian 2011 sex-stratified life tables, adjusted by a standardized mortality ratio for Canadian survivors of ALL (20.8; 95% CI, 14.8-28.4).39 A competing risk death state was not included during treatment.
ment cycles as nontreatment or cancer-related deaths occurred in only 2% of cases in POGONIS.

**Tisagenlecleucel Strategy**

To model patient survival trajectories for tisagenlecleucel, we pooled data from 3 clinical trials. Treatment trajectories covered 5 health or treatment states starting at a tisagenlecleucel treatment when T-cell harvesting occurred (eFigure 2 in the Supplement). A cycle length of 1 month coincided with manufacturing time for tisagenlecleucel, which was estimated to take approximately 22 days. Based on clinical trial outcomes, some patients did not receive infusion of their manufactured cells but instead died or moved directly to standard care while awaiting manufacturing. If manufacturing was successful and the patient remained stable, they moved to infusion. After infusion, movements to either posttreatment HSCT, cure, or death were possible (eFigure 2 in the Supplement). The HSCT state was modeled as in the standard care strategy. We did not include a bridge-to-HSCT component as evidence for tisagenlecleucel as a bridging therapy is currently lacking. A cure state was included to account for the limited long-term survival information currently available for tisagenlecleucel. Our base case estimates used a range of cure rates from 10% to 40% for those offered treatment, based on expert opinion.

After tisagenlecleucel infusion, patients were at risk for adverse events, including cytokine release syndrome and encephalopathy during the first 3 cycles. In every health or treatment state, a patient was at risk of death. Probability of dying in the short term was based on clinical trial outcomes. For extrapolations past any trial data periods, we used the greater of either the all-cause ALL-adjusted mortality or predicted mortality based on extrapolated survival curves.

**Model Input Data**

**Costs**

Cost comprised tisagenlecleucel and standard care–related health care costs within the public payer’s budget, with all costs adjusted to 2018 Canadian dollars. Related expenses included hospitalizations, physician services and outpatient visits, and treatment and treatment-related complications. Table 1 outlines all costs, utilities, and assumptions. As both strategies began with patients after second relapse, we incorporated an average monthly cost of postrelapse, non-HSCT treatment that included salvage chemotherapy and palliative care based on direct billing data in cycle one. For patients moving to HSCT, we used a cost of HSCT from the Ontario Case Costing Initiative for the first 30 days of stay. This cost included all physician, hospital, medical, and procedure fees. If a patient received HSCT, we included conditioning costs for 4 weeks and acute GVHD costs for 35%. Long-term costs included first-year follow-up costs, where we differentiated between the first 100 days and post–100-day follow-up. We included a weighted cost of chronicGVHD during this time interval. Long-term annual follow-up costs were applied from 1-year posttreatment onwards.

For those who received tisagenlecleucel, the most significant cost component was the product itself. This cost was applied only for patients who had undergone infusion and who went into remission within 1 month of treatment, per the manufacturer-proposed value-based pricing policy. In the most recent clinical trial, 81% of the infused patient cohort achieved remission. Patients who were not infused still incurred preparatory costs of bridging chemotherapy and leukapheresis. For those infused, additional nonproduct costs applied for cell infusion, monitoring and management of adverse events, and associated hospitalizations.

Tisagenlecleucel-related adverse events included cytokine release syndrome, B-cell aplasia, and encephalopathy. All other adverse events costs, including cytopenia–related transfusions, were assumed to occur with other adverse events. Cytokine release syndrome represented a significant cost, with almost all patients experiencing cytokine release syndrome in clinical trials. Cytokine release syndrome of grade 3, occurring in 47% of patients, resulted in an intensive care unit stay and receipt of anticytokine drugs. Costs were weighted by the probability of each adverse event occurring. Those experiencing B-cell aplasia incurred a monthly cost for intravenous immunoglobulin treatment, continuing for 5 years or until relapse or death. If a patient did not die, after 3 months, only long-term follow-up costs applied. Drug unit costs for harvesting, adverse events, and intravenous immunoglobulin treatment are found in eTable 3 in the Supplement.

**Utilities**

We obtained utility weights for ALL stages and treatments from the literature (Table 1). We used preference-based Pediatric Quality of Life inventory for most utility measures. When Pediatric Quality of Life inventory was not available, we used EuroQol’s 5-dimensional utility rating. As there are currently no utility estimates for tisagenlecleucel treatment to our knowledge, we assumed utility was equal to that of HSCT without GVHD for the first cycle and equal to post–100-day HSCT ALL survivor utility subsequently. All patients began at a utility level of 0.75, corresponding with a second relapse state.

**Sensitivity Analysis**

We performed 1-way sensitivity analyses to alter components such as HSCT cost, the proportion of patients infused and entering remission, and B-cell aplasia and cytokine release syndrome risk duration. We tested structural assumptions around assumed age at treatment, time horizon, and standardized mortality ratio. We also tested the association of tisagenlecleucel price discounting with payment structure, which may occur on negotiation in a public insurance setting. With a probabilistic sensitivity analysis, we explored the association of input parameter uncertainty with model outcomes. Literature-derived parameters were varied based on underlying distributions and reported means and variances. Time-to-event outcome uncertainty was extracted from our fitted multistate model. A Monte Carlo simulation was then used to propagate input parameter uncertainty to the cost–utility analysis outcomes. Results of the probabilistic sensitivity analysis were used to demonstrate a cost-effectiveness plane with 95% confidence bands and a cost-effectiveness acceptability curve. Analysis began in December 2017 and ended in January 2019.
Cost-effectiveness of Tisagenlecleucel vs Standard Care in Acute Lymphoblastic Leukemia

Results

Of 118 patients in the control arm, 78 were boys (66%). The median (range) age was 10 (3-20) years, and all had previously relapsed. The pooled clinical trial data used to inform the treatment arm consisted of 192 patients, 102 (53%) of which were boys. The median age (range) was 11 (1-25) years, and 176 (92%) had previously relapsed (eTable 1 in the Supplement).

In the standard care strategy, we estimated a 24-month survival rate of 0.23. For the 38 patients (32%) who received HSCT, survival was 0.38 (eTable 4 in the Supplement). In the tisagenlecleucel strategy, 24-month survival was 0.44.17 Figure 1 presents survival curves. Posttreatment life expectancy in the standard care group was 5.05 years (Table 2). Life expectancy after tisagenlecleucel was 7.19 to 14.90 years, depending on the assumed cure rate (10%-40%).

Patients under standard care had a mean (95% CI) of 3.46 (2.12-5.14) QALYs gained from tisagenlecleucel and standard care.17

Discussion

Understanding the value for money of tisagenlecleucel is crucial to informing funding decisions made by public health insurance plans, where cost-utility analysis provides a basis for whether new drug products will be reimbursed. However, assessing the cost-effectiveness of any CAR T-cell therapy is hindered by the single-arm nature of current clinical trials and limited short-term and long-term information for both tisagenlecleucel and standard care.17

Our results showed cost-effectiveness to be highly dependent on cure rate assumptions, with ICUR values ranging from CaD $71 000 (US $53 933) to CaD $281 000 (US $213 453) for cure rates of 40% to 10%, respectively. At a cure rate of 20% (intention-to-treat population), the estimated ICUR value was CaD $141 000 (US $107 258), which is above common thresholds in most countries.
We evaluated cost utility over a range of product discounts, knowing price negotiations are likely in some jurisdictions. Using a 20% cure rate, the ICUR fell below willingness-to-pay thresholds of CAD $100 000 (US $76 069) and CAD $50 000 (US $38 035) assuming product discounts of 23% and 49%, respectively (eFigure 5 in the Supplement).

This study found the cost-effectiveness of tisagenlecleucel to be similar to that in a recent US study using a hypothetical blinatumomab control arm but less cost-effective than found by a study using clofarabine monotherapy as the comparator. Both studies relied on Markov modeling based on clinical trial data to estimate the effectiveness of both treatment and control arms. This approach does not factor in the effects of time on transition probabilities and may be more prone to bias and uncertainty in estimating long-term outcomes than the multistate and simulation modeling techniques used in our study. Our methodological approach additionally addressed a noted limitation of these 2 studies by providing comparator-arm estimates based on long-term real-world population-level survival data to more precisely inform comparator efficacy. This population-level data provided a broader definition of standard care that included all current treatment options available to tisagenlecleucel-eligible patients, rather than narrowly defined comparator treatment arms informed from past clinical trials.

These methodological differences translated to lower life expectancy for tisagenlecleucel and standard care than previous estimates. Our estimation of standard care efficacy nonetheless represented a conservative calculation, given that we included only patients with at least 2 relapses. We also used different time-discounting rates and a significantly higher standardized mortality ratio, which have conflicting influences on the overall ICUR. The different cost structures in the United States vs Canada also make it difficult to compare the exact relationship between the methods we used and costs. Taken together, our estimates of overall cost-effectiveness should be considered lower-bound estimates.

To our knowledge, this study also provides the first investigation of the cost-effectiveness of tisagenlecleucel in a public insurer setting, with differing underlying cost structures and where funding decisions and price negotiations are made at the aggregate level. This perspective renders the opportunity costs of paying for expensive treatments more salient and cost-effectiveness calculations more consequential. Our results bolster recommendations by the Canadian Agency for Drugs and Technology in Health, which advised implementation of tisagenlecleucel in Canada on the condition of a price decrease. Other health authorities within publicly insured health care systems have also pushed for price decreases, including the United Kingdom. These results expand the evidence base for these decisions and underscore the allocative ethics that must be considered within a public insurer context. In the United States, while the Centers for Medicaid & Medicare and private insurers may place greater emphasis on efficacy over cost, the issue of drug affordability is nonetheless relevant as more expensive drug products like CAR T-cells are brought to market.

### Table 2. Mean Life Expectancy, QALYs, Total Cost per Patient Receiving Standard Care vs Tisagenlecleucela

<table>
<thead>
<tr>
<th>Factor</th>
<th>Current standard care</th>
<th>Tisagenlecleucel 0.10</th>
<th>Tisagenlecleucel 0.20</th>
<th>Tisagenlecleucel 0.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-y Overall Survival</td>
<td>5.10</td>
<td>4.19</td>
<td>3.64</td>
<td>2.77</td>
</tr>
<tr>
<td>Life Expectancy, y</td>
<td>5.05 (3.17-4.13)</td>
<td>4.05 (3.43-4.67)</td>
<td>4.55 (3.63-4.47)</td>
<td>4.67 (4.47-4.87)</td>
</tr>
<tr>
<td>QALY</td>
<td>3.48 (2.12-5.14)</td>
<td>3.14 (2.94-3.77)</td>
<td>3.64 (3.43-3.67)</td>
<td>3.14 (2.94-3.77)</td>
</tr>
<tr>
<td>Mean Cost</td>
<td>114 000 (90 000-147 000)</td>
<td>585 000 (530 000-632 000)</td>
<td>584 000 (540 000-633 000)</td>
<td>582 000 (540 000-632 000)</td>
</tr>
<tr>
<td>$/QALY</td>
<td>86 597 (68 366-111 664)</td>
<td>444 377 (409 434-487 675)</td>
<td>443 617 (410 194-486 859)</td>
<td>442 098 (409 194-486 839)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; QALY, quality-adjusted life-year.

a Average costs and QALYs are time-discounted at a rate of 1.5%.

b A dominated strategy is when it results in both fewer QALYs and higher costs than the reference treatment strategy.
Table 3. Sensitivity Analysis*

<table>
<thead>
<tr>
<th>Sensitivity Component</th>
<th>%</th>
<th>Mean Cost, $</th>
<th>QALY</th>
<th>Change From Baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Adjusted</td>
<td>Tisagenlecleucel</td>
<td>Standard Care</td>
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<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B-cell aplasia</td>
<td>83</td>
<td>100</td>
<td>760 000</td>
<td>577 310</td>
</tr>
<tr>
<td>IVIG duration, y</td>
<td>5</td>
<td>2</td>
<td>580 000</td>
<td>440 579</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td>588 000</td>
<td>446 656</td>
</tr>
<tr>
<td>CRS risk duration, mo4</td>
<td>3</td>
<td>1</td>
<td>577 000</td>
<td>438 300</td>
</tr>
<tr>
<td>Structural parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time discount</td>
<td>1.5</td>
<td>3</td>
<td>623 000</td>
<td>473 242</td>
</tr>
<tr>
<td>Time horizon, y</td>
<td>60</td>
<td>40</td>
<td>585 000</td>
<td>444 377</td>
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<tr>
<td></td>
<td>80</td>
<td></td>
<td>583 000</td>
<td>442 858</td>
</tr>
<tr>
<td>Age at treatment, y</td>
<td>10</td>
<td>5</td>
<td>584 000</td>
<td>443 617</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td>583 000</td>
<td>442 858</td>
</tr>
<tr>
<td>Next best distribution*</td>
<td>Varies</td>
<td>Varies</td>
<td>589 000</td>
<td>447 415</td>
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<td>Mortality adjustmentf</td>
<td></td>
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</tr>
<tr>
<td>Lower bound SMR</td>
<td>20.8</td>
<td>14.8</td>
<td>584 000</td>
<td>443 617</td>
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<td>Upper bound SMR</td>
<td>20.8</td>
<td>28.4</td>
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<tr>
<td>High SMR scenario</td>
<td>20.8</td>
<td>57.1</td>
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<td>442 858</td>
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<td>Costing inputs</td>
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<td></td>
<td></td>
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<tr>
<td>Proportion billed, VBP</td>
<td>81</td>
<td>100</td>
<td>679 000</td>
<td>515 781</td>
</tr>
<tr>
<td>HSCT low cost, $</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaD $112 582 (US $85 519)</td>
<td>49 171</td>
<td>346 481</td>
<td>491 723</td>
<td>346 481</td>
</tr>
<tr>
<td>HSCT high cost, $</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaD $112 582 (US $85 519)</td>
<td>49 171</td>
<td>346 481</td>
<td>491 723</td>
<td>346 481</td>
</tr>
<tr>
<td>Intention to treath</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion infused</td>
<td>82</td>
<td>100</td>
<td>643 000</td>
<td>488 435</td>
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<tr>
<td>Manufacturing failures</td>
<td>11</td>
<td>0</td>
<td>596 000</td>
<td>452 733</td>
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<td>Preinfusion deaths</td>
<td>8</td>
<td>0</td>
<td>631 000</td>
<td>479 319</td>
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<td>Combined scenarios</td>
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<tr>
<td>Proportion billed, VBP</td>
<td>81</td>
<td>100</td>
<td>760 000</td>
<td>577 310</td>
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<tr>
<td>Proportion infused</td>
<td>82</td>
<td>100</td>
<td>760 000</td>
<td>577 310</td>
</tr>
<tr>
<td>Proportion billed, VBP</td>
<td>81</td>
<td>100</td>
<td>735 000</td>
<td>558 320</td>
</tr>
</tbody>
</table>

Abbreviations: CRS, cytokine release syndrome; HSCT, hematologic stem cell transplantation; ICUR, incremental cost utility ratio; IVIG, intravenous immunoglobulin treatment; QALY, quality-adjusted life-years; SMR, standardized mortality ratio; VBP, value-based pricing.

* All costs are reported in 2018 Canadian dollars and rounded to the nearest 1000. Current conversion rates were used to report US dollars. All sensitivity analyses used a baseline cure rate of 20% and a time discounting rate of 1.5%.

b The ICUR is calculated as the incremental cost of the intervention divided by the incremental QALYs.

c Percentage change from baseline calculated based on exact ICUR values.

d Per expert opinion, CRS is currently likely to occur within 2 to 3 weeks of infusion. A risk duration of 1 month assumes any CRS occurs in first cycle.

e See eFigure 1 in the Supplement for fitted distribution rankings. In our baseline model, a cubic spline distribution was the best fitting distribution for all transitions outside of the transition from multirelapse state to death in the standard care arm, where a Gompertz distribution was used.

f High-SMR scenario is sourced from a population of pediatric patients with recurrent or progressed leukemia excluding acute myeloid leukemia.45

g Baseline calculations assume use of VBP, where only those infused and achieving remission are required to pay. Under this sensitivity test, cost is applied to 100% of infused patients, regardless of remission status.

h Model is based on an intention-to-treat analysis, whereby outcomes are calculated based on intention to receive a given treatment. In the tisagenlecleucel arm patients may not reach infusion owing to either preinfusion death or manufacturing failure/loss to other treatment.

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REFERENCES

Limitations
In this cost-utility analysis, we acknowledge some limitations. The number of observable characteristics available in both published clinical trial results and POGONIS narrowed our ability to construct matched controls. To approximate matching, we opted for a conservative requirement that all patients within the sample must have at least 2 relapses. This stipulation resulted in a lower estimated survival probability in the comparator cohort because the tisagenlecleucel trial included refractory patients. For the treatment arm, limited evidence on long-term survival required modeling over a range of cure rates. The assumed rates substantially altered the cost-utility analysis results. Longer-term data will inform more precise estimates of the cost-effectiveness over a patient’s lifetime. Finally, given the novelty of tisagenlecleucel, cost components associated with implementation and adverse events may be undercounted, again making our results lower-bound estimates. Nevertheless, we incorporate significant sensitivity analysis to address these limitations and find our results to be robust.

Conclusions
To be considered cost-effective, the large upfront price of tisagenlecleucel and other novel drugs must be offset by sustained survival effects or lower long-term complications for a public payer to consider it as good value for money. However, with novelty comes uncertainty around expected long-term benefits. As demonstrated by our results, present-day cost-effectiveness of tisagenlecleucel was highly dependent on the assumed magnitude of these long-term benefits. At its current price, the ICUR for tisagenlecleucel surpassed common willingness-to-pay thresholds across most assumed cure rates. However, as this product opens to a broader patient population and clinicians continue to refine CAR T-cell protocols, comparative efficacy with standard care will likely evolve. Nonetheless, to deliver effective and cost-effective care to patients today, price negotiation of these products has and likely will continue within publicly insured health care systems. These results provide a real-world benchmark for what product discount would make tisagenlecleucel cost-effective.


