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CADTH OPTIMAL USE REPORT

Tisagenlecleucel for Acute Lymphoblastic Leukemia: Economic Review Report

Service Line:	Optimal Use Report
Version:	Vol. 8, No. 3f
Publication Date:	January 2019
Report Length:	61 pages

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Cite As: Tisagenlecleucel for Acute Lymphoblastic Leukemia: Economic Review Report. Ottawa: CADTH; 2019 Jan. (CADTH optimal use report; vol.8, no.3f).

ISSN: 1927-0127

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
ALL	acute lymphoblastic leukemia
BIA	budget impact analysis
CAR	chimeric antigen receptor
CAR T	chimeric antigen receptor modified T cell
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRS	cytokine release syndrome
CUA	cost-utility analysis
DAS	deterministic sensitivity analysis
EFS	event-free survival
FACT	Foundation for the Accreditation of Cellular Therapy
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
HUI	Health Utility Index
ICUR	incremental cost-utility ratio
IVIG	intravenous immunoglobulin
LD	lymphodepleting
MAIC	matching-adjusted indirect comparison
ORR	overall remission rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomized controlled trial
r/r	relapsed or refractory
SCT	stem cell transplantation
SD	standard deviation
SE	standard error
SMR	standardized mortality ratio
WTP	willingness to pay

Treatment	Tisagenlecleucel (Kymriah)
Indication	For the treatment of pediatric and young adult patients 3 to 25 years with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after allogenic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced a second or later relapse.
Reimbursement Request	As per indication
Dosage Form(s)	Single-dose, one-time intravenous treatment. The recommended dose is 0.2 to 5.0 x 10^6 chimeric antigen receptor (CAR)-positive viable T cells/kg body weight for patients 50 kg and below, and 0.1 to 2.5 x 10^8 CAR-positive viable T cells in patients above 50 kg.
NOC Date	September 5, 2018
Manufacturer	Novartis Pharmaceuticals Canada Inc.

Executive Summary

Background

Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r ALL).[1] The recommended dose is 0.2-5.0 x 10^6 CAR-positive viable T cells/kg body weight for patients 50 kg and below and 0.1-2.5 x 10^8 CAR-positive viable T cells for patients above 50 kg as a single one-time treatment. The treatment process requires leukapheresis whereby patients' white blood cells are removed from their body. The cells are genetically altered to have receptors called chimeric antigen receptors (CAR). Prior to the infusion of the T cells back to the patient's bloodstream, the patient receives a brief course of chemotherapy, also known as lymphodepleting chemotherapy, to improve the chance that the new CAR T cells will be accepted and not attacked by the immune system when returned to the body. The confidentially submitted price of tisagenlecleucel is [redacted] for a one-time therapy.[2]

The report is based on a critical appraisal of economic information provided by the manufacturer, which consisted of an economic evaluation and a budget impact analysis. CADTH conducted reanalyses to consider alternative assumptions and inputs where relevant and possible.

Economic

The manufacturer submitted a cost-utility analysis comparing tisagenlecleucel to salvage chemotherapy. The manufacturer claimed that there is no specific treatment for pediatric and young adult patients with r/r B-cell ALL.[3] A multi-drug salvage chemotherapy including UK R3 ALL and COG-AAL 0031 was therefore assumed to be a comparator and used for the treatment cost calculation. The base-case analysis was conducted from the perspective of Canada's health care system over a 70-year time horizon with future costs and benefits discounted at 1.5%. The structure of the model was based on three health states (event free, progressive disease, and death) partitioned-survival model. Partitioned-survival models estimate event-free survival (EFS) and overall survival (OS) based on the trial data while progressive disease (PD) is derived as the difference between the OS and the EFS curves.

EFS was defined as the time from the date of treatment initiation to the earliest date of death, relapse, or treatment failure. During each cycle, patients were redistributed among the three health states, with death being the absorbing state. The cycle length was one month.

In the manufacturer's base-case analysis, OS and EFS data for tisagenlecleucel were based on pooled data from three single-arm trials: ELIANA (NCT02435849),[4] ENSIGN (NCT02228096),[5] and B2101J (NCT01626495)[6] trials. The individual patient data from each trial were combined directly without statistical adjustment. The OS data of salvage chemotherapy was based on a curative arm of the study by von Stackelberg et al.[7] that assessed outcomes of ALL patients under 19 years old with no response to second- line treatment (N = 51). In the base-case analysis, OS and EFS for tisagenlecleucel and comparators were extrapolated using parametric models estimated based on the respective trial data after the end of trial observation until year 5. From year 5 onwards, the predicted OS based on the literature of ALL long-term survivors was applied to both arms. EFS for the comparators was estimated based on the OS data assuming a constant cumulative hazard ratio (HR) between OS and EFS over time. The manufacturer did not use any statistical approaches to adjust for potential imbalance in demographic and clinical characteristics that may confound the association between the type of therapy received and clinical outcomes; i.e., OS or EFS data.

Health utilities associated with EFS and PD health states, and disutilities associated with treatments (including tisagenlecleucel, salvage chemotherapy and subsequent hematopoietic stem cell transplantation (HSCT), and adverse events) were obtained from the published literature.[8] Costs (pre-treatment, treatment, adverse event [AE], subsequent HSCT, follow-up, post-progression medical care, and terminal care) were based on Canadian sources. Resource use and patient characteristics for the tisagenlecleucel arm were obtained from ELIANA trial.[4] For the comparator arm, resource use, and costs were based on the Canada-specific literature and public databases.

The manufacturer reported that tisagenlecleucel was associated with additional 13.45 life-years, 11.74 quality-adjusted life-years (QALYs) gained and an incremental cost of $494,029 compared with salvage chemotherapy, resulting in an incremental cost-utility ratio (ICUR) of $42,093 per QALY.

CADTH identified the following key limitations relating to the manufacturer's economic model.

Firstly, the design of the manufacturer's economic model design raise concerns about the structural uncertainty of the model, particularly as it relates to the probabilistic estimates and subsequent descriptions of uncertainty around the mean ICUR estimates. Several features of the model were overly complex and masked features in the model, which made it challenging to appraise and verify the manufacturer's conclusions. The primary concern focuses on the use of unnecessary conditional functions and tiered macros to reset changes in the model to match the baseline assumptions in ways that were not expressly part of the model description. It appears that these structural features systematically limited the range of cost and effectiveness estimates toward the mean, raising doubt that the true magnitude of uncertainty is adequately reflected in the manufacturer or CADTH revised base-case analysis.

Secondly, the manufacturer's base case relied on two single-arm trials and one phase I/IIA, safety, and feasibility study (for tisagenlecleucel) and one retrospective cohort study by von

Stackelberg and colleagues (for salvage chemotherapy). CADTH believes that it is inappropriate to pool OS and EFS data from the ELIANA, ENSIGN, and B2101J trials due to difference in cell doses and study designs. Additionally, the manufacturer considered EFS and OS data that were not adjusted for potential differences in baseline characteristics or risk factors among the studies despite the lack of comparative evidence. The manufacturer indicated that matching-adjusted indirect comparison (MAIC) was not appropriate because: 1) the OS definitions was different between the trial and cohort studies; and 2) the study by von Stackelberg et al[7] reported limited baseline characteristics. The manufacturer's claim suggested that patients included in this study may not be an appropriate control group for tisagenlecleucel. The estimated ICURs may be confounded by several unobserved characteristics and therefore should be viewed as highly uncertain.

Thirdly, CADTH noted potential concerns with the generalizability of OS data observed from a retrospective cohort study by von Stackelberg et al[7] given that the specific chemotherapy regimens were not reported. As such, it is unclear whether OS data reported in this study is generalizable to Canadian patients with r/r B-cell ALL.

Moreover, the manufacturer's economic model did not include the cost of chemotherapy administered as a bridge to tisagenlecleucel thereby underestimating the total cost of tisagenlecleucel. According to ELIANA trial, 84% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. The most commonly used concomitant antineoplastic medications before lymphodepletion therapy (in ≥ 50% of patients) included methotrexate (64.1%), cytarabine (58.7%), and vincristine (50.0%). CADTH's revised base case added the cost of bridging therapy ($19,816.24 converted to C$) to the cost of tisagenlecleucel.[9]

Additionally, several outcomes are only partially incorporated into the overall effectiveness estimate. For instance, the impact of subsequent HSCT on progression and survival was not captured in the model. The manufacturer's economic model only accounted for the additional costs and disutilities associated with subsequent SCT. According to clinical experts consulted by CADTH, subsequent HSCT is expected to delay progression and improve patient survival. None of these clinical benefits was however considered in the submitted model. The omission of the benefits of HSCT may underestimate the ICUR because the greater proportion of patients in the salvage chemotherapy group received subsequent HSCT. There patients were therefore expected to have higher costs and worse health utility. CADTH also concern with a data source for health utility data for EFS and PD health states. The manufacturer's base case used health utility data from the published literature as opposed to health utility values derived from ELIANA trial.

Finally, uncertainty in parameter estimates may not be adequately captured as the manufacturer assumed a fixed 25% value variance from the mean for most parameters. No justification was provided for the selection of 25% or why such a percentage difference from the mean would be uniformly applied to all parameter values regardless of data type or quality of the source.

CADTH reanalysis based on efficacy and health utility data obtained from ELIANA trial comes to slightly higher ICUR but comparable conclusions about the cost-effectiveness of tisagenlecleucel compared salvage chemotherapy. Tisagenlecleucel was associated with additional 10.60 QALYs gained and an incremental cost of $565,624 compared with salvage chemotherapy, resulting in an ICUR of $53,269 per QALY. The probability that tisagenlecleucel was cost-effective was 44.2% and 99.1% at a willingness-to-pay threshold of $50,000 and $100,000 per QALY, respectively. In addition, CADTH conducted a number

of exploratory analyses to assess the uncertainty associated with a number of the parameters.

Budget Impact

The manufacturer submitted a budget impact analysis (BIA) which assessed the financial impact of the potential reimbursement of tisagenlecleucel for patients aged 3 to 25 with relapsed/refractory r/r ALL in Canada.[10] A national level analysis considering reimbursement across all provinces and territories was conducted over a three-year time horizon and based on the Canadian societal perspective. The submitted BIA model was an epidemiology-based approach, which compared two budget scenarios: 1) a Reference Scenario, where only treatment with current chemotherapy regimens is available (blinatumomab, investigational therapy, salvage therapy), and 2) a New Treatment Scenario, where tisagenlecleucel joins the market and becomes available. For each scenario, the number of patients likely to receive treatment with available regimens was multiplied by the relevant per-patient costs to determine the total costs associated with each therapy. The budget impact was then calculated by subtracting the total costs of the Reference Scenario and the total costs of the New Treatment Scenario.

The total number of pediatric and young adult r/r B-cell ALL patients expected to receive tisagenlecleucel or other treatment in the Reference Scenario and the New Treatment Scenario was estimated by combing the total eligible patient population with market share data in each year of the analysis. The market shares of treatment options in the Reference Scenario and New Treatment Scenario were predicted according to Canadian expert opinion and a survey of US leukemia care providers commissioned by the manufacturer. [redacted] Annual budget costs in the analysis included the cost of main therapy (composed of drug acquisition costs and administration and hospitalization costs), routine monitoring medical costs, adverse event management costs, subsequent therapy costs (hematopoietic stem cell transplantation), and indirect costs (limited to productivity gains). The impact of reimbursement on health outcomes was not considered. Results were reported as total annual costs in 2017 Canadian dollars.

The manufacturer reported that the incremental expenditures associated with the reimbursement of tisagenlecleucel in patients aged 3 to 25 years with r/r B-cell ALL in Canada are expected to be $15,997,769 in Year 1, $5,710,309 in Year 2, and $6,163,222 in Year 3.

CADTH identified a number of key sources of uncertainty and potential limitations relating to the manufacturer's BIA. The selection for comparators was considered inappropriate, as it is unclear whether tisagenlecleucel will be used in the same manner as blinatumomab (i.e., same line of therapy) and the inclusion of investigational therapies which are currently not approved. In addition, these comparators do not align with those considered in the manufacturer's economic evaluation. The manufacturer did not consider the cost of bridging therapy for tisagenlecleucel, as observed in the clinical trials. There exists uncertainty with respect to the estimates of potential uptake of tisagenlecleucel. Potential system constraints for tisagenlecleucel were not accounted for in the analysis. In addition, potential costs associated with tisagenlecleucel were not considered in the manufacturer analysis, including costs of manufacturing failure and costs of delay of treatment (with tisagenlecleucel or other therapies). Finally, the manufacturer considered a societal perspective for their analysis but

only considered productivity gains (cost offsets) based on an estimated proportion of patients returning to work. This approach fails to consider the broader implications of parents or other caregivers caring for patients and the cost of travel and accommodation for families/caregivers that do not live near the designated treatment facilities.

CADTH attempted to account for some of the important shortcomings by: removing blinatumomab and investigational therapy as relevant comparators and adjusting the market shares accordingly; including out-of-pocket costs as a one-time cost for patients receiving tisagenlecleucel; accounting for the cost of bridging therapy associated with tisagenlecleucel; and, assuming drug wastage for comparators. CADTH found that the incremental expenditures associated with the reimbursement of tisagenlecleucel in patients aged 3 to 25 with r/r B-cell ALL in Canada are expected to be $14,464,009 in Year 1, $5,514,709 in Year 2, and $6,283,762 in Year 3; the cumulative three-year net budget impact of reimbursing tisagenlecleucel was predicted to be $26,262,480.

Conclusions

Based on manufacturer's economic analyses and CADTH reanalyses, the ICUR for tisagenlecleucel was found to be $53,269 per QALY when compared with salvage chemotherapy. While no significant differences in the quantitative findings were observed between the manufacturer's results and CADTH reanalysis, the cost-effectiveness of tisagenlecleucel is subject to important limitations pertaining to the clinical data and effect estimates and high structural uncertainty. In the absence of comparative studies to relevant salvage chemotherapy regimens in Canada, careful consideration must be taken when considered the results of the model. More importantly, CADTH reanalyses should be revisited when the real-world manufacturing and clinical experiences with tisagenlecleucel and the long-term EFS and OS data become available.

CADTH identified a number of important sources of uncertainty relating to the manufacturer's BIA and attempted to account for some of the identified uncertainty through reanalysis. CADTH estimated that the incremental expenditures associated with the reimbursement of tisagenlecleucel in patients aged 3 to 25 with r/r B-cell ALL in Canada are expected to be $14,464,009 in Year 1, $5,514,709 in Year 2, and $6,283,762 in Year 3. The cumulative three-year net budget impact of reimbursing tisagenlecleucel was predicted to be $26,262,480. In a scenario where re-treatment with tisagenlecleucel may be necessary, the cumulative three-year net budget impact of reimbursing tisagenlecleucel may be greater than $56 million. In a scenario where commercialization constraints may not permit timely treatment of all patients eligible to receive tisagenlecleucel, the cumulative three-year incremental budget impact of funding tisagenlecleucel may be almost $18 million. Where tisagenlecleucel-related production failure is accounted for in the analysis, the cumulative three-year incremental budget impact of funding tisagenlecleucel was estimated at approximately $26 million. These scenarios and estimates should be interpreted with caution as they do not account for potentially worse health outcomes and related costs in this patient population as a result of the delay to timely therapy.

Information on the Economic Submission

Manufacturer's Economic Evaluation

The manufacturer submitted a cost-utility analysis that compared costs and outcomes of tisagenlecleucel and salvage chemotherapy in pediatric and young adult patients 3 to 25 years of age with r/r B-cell ALL.[3] The modelled patients were assumed to on average to be 12 years (SD=5.2 years) at the time of entry into the model; patients were also predominantly male (53%). The average body surface area was 1.3 m^2 and the average body weight was 41.7 kg. The model was run using monthly cycles over a 70-year horizon. All costs and outcomes were discounted at an annual rate of 1.5%, and the analysis was conducted from the perspective of the Canadian publicly funded health care system.

Model Structure

A partitioned-survival model was developed in Microsoft Excel to simulate the clinical progression of r/r B-cell ALL among pediatric and young adult patients 3 to 25 years of age receiving treatment with tisagenlecleucel or salvage chemotherapy.

The manufacturer used a partitioned-survival model with three mutually exclusive health states including event-free survival (EFS), progressive disease (PD), and death (Figure 1) to simulate the health system costs and health outcomes in terms of life expectancy and QALYs over 70 years. Unlike the economic model for r/r diffuse large B-cell lymphoma, the manufacturer used EFS as opposed to progression-free survival (PFS) the economic model for r/r ALL. EFS was defined as the time from the date of treatment initiation to the earliest date of death, relapse, or treatment failure.

At the start of the model, patients were assumed to be in the EFS state and start either tisagenlecleucel or salvage chemotherapy. Patients who transitioned to the PD state were assumed to have a worsening condition, leading to poorer quality of life. The proportion of patients in the PD health state was set to be equal to the difference between the proportion of living patients (based on the OS curve) and the proportion of EFS patients. At any point, patients could transition to death. The effects of subsequent hematopoietic stem cell transplantation (HSCT) on costs and health utilities was considered in the model. The cycle length of the model was one month.

Model Inputs

Overall survival (OS) and EFS inputs for tisagenlecleucel in the manufacturer's base-case analysis were based on pooled data from the ELIANA, ENSIGN, and B2101J trials. [4-6] The manufacturer claimed that the characteristics of patients enrolled in these studies were similar. Individual patient data from these trials were therefore combined without any statistical adjustments. The efficacy of salvage chemotherapy was obtained from a post-hoc analysis of ALL-REZ BFM 90 and 95/96 trials and ALL-REZ BFM pilot protocols. The post-hoc study included 51 patients aged 19 years or younger with a first relapse of B-cell-precursor or T-cell and non-response to relapse protocol therapy who received a curative treatment approach. The manufacturer conducted sensitivity analyses and considered clofarabine monotherapy, clofarabine combination therapy, and blinatumomab as a comparator.

In the base-case analysis, for tisagenlecleucel, the manufacturer pooled the observed OS data from three single-arm trials. The OS associated with the comparator treatment arms were derived from the published Kaplan-Meier (K-M) curves of the comparator trials. At the end of the trials, parametric survival models were used to fit to the OS data and to project survival estimates until year 5. From year 5 onwards, the model assumed the same mortality risk across treatment options. The long-term ALL survival was modelled using the 2017 Canada life table, with a mortality adjustment using the standard mortality ratio (SMR) of 5-year ALL survivors published in the literature.[11] The EFS of tisagenlecleucel was based on pooled individual data from three clinical trials of tisagenlecleucel: ELIANA (data cut-off: December 31, 2017),[4] ENSIGN (data cut-off: October 06, 2017)[5] and B2101J (data cut-off: January 30, 2017)[5] trials. Similar to OS data, EFS data beyond the trial period was estimated based on parametric functions fit to observed EFS data. For salvage chemotherapy, EFS was derived from OS data assuming a constant cumulative HR (0.83, range 0.62 to 1.00) over time. The ratios were estimated based on the mitoxantrone arm in the UK ALL study.[12] The manufacturer calculated the natural log of OS probability divided by the natural log of EFS probability at yearly intervals until the end of the observed period. The overall cumulative HR between OS and EFS was then calculated as the average of cumulative HRs form all yearly intervals. For both treatment options, the manufacturer used a model averaging approach and included all plausible survival functions as part of a weighted distribution to predict OS and EFS (for tisagenlecleucel) beyond the trial. The weight was calculated based on Akaike information criterion (AIC) score whereby a survival model with the smallest AIC was given the largest weight. Parametric function considered in the model averaging approach consisted of exponential, Weibull, log-logistic, log-normal, Gompertz, generalized gamma, and cubic spline models. The goodness of fit statistics revealed that log-normal and Weibull distributions fitted best to tisagenlecleucel OS and EFS data, respectively.

Health utility values used in the base case were obtained from a decision analysis study that compared life expectancy and quality-adjusted life expectancy of three cranial radiation therapies (CRT) for pediatric T-cell ALL patients.[8] Health utility decrements due to treatment were obtained from a study by Sung et al.[13] that reported physician elicited utility estimates for acute myeloid leukemia patients who survived post transplantation without recurrent disease. To capture short-term AEs associated with treatments (except for cytokine release syndrome [CRS]); patients receiving tisagenlecleucel or salvage chemotherapy were assumed to have a disutility of 0.42. The treatment disutilities were applied for the duration of induction chemotherapy for the salvage chemotherapy arm and for the duration of the hospitalization starting from the pre-treatment lymphodepleting regimen for tisagenlecleucel. For the tisagenlecleucel arm, additional treatment disutilities were considered for grade 3 or 4 CRS and intensive care unit (ICU) stays not due to CRS. During the ICU stay, patients were assumed to have a utility of 0 (a disutility of -0.91 based on EFS utility) as reported in ELIANA trial. The additional utility decrement was applied for patients receiving subsequent HSCT. The disutility associated with HSCT was assumed to last for 365 days.

Costs included were those for pre-treatment (for tisagenlecleucel), treatment costs, AE costs, subsequent HSCT costs, follow-up costs, post-progression medical costs, and terminal care costs. Pre-treatment cost is only considered for the tisagenlecleucel arm and includes costs associated with leukapheresis, cryopreservation, and lymphodepleting regimens. Drug costs for lymphodepleting chemotherapy were calculated as a function of unit drug costs, dosing, and proportion of patients receiving each regimen (fludarabine and cyclophosphamide or bendamustine). All costs were reported in 2017 Canadian dollars.

Manufacturer's Base Case

The manufacturer's probabilistic analysis showed that tisagenlecleucel was associated with an additional $486,630, 13.45 life-years and 11.74 QALYs gained when compared with salvage chemotherapy, resulting in an incremental cost-effectiveness ratio of $42,093 per one QALY gained.

Table 1: Summary of Probabilistic Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Tisagenlecleucel ($)	Total QALYs	Total LYs	Incremental QALYs of Tisagenlecleucel	Incremental Cost per QALY
Tisagenlecleucel	$727,010	–	12.15	14.42	–	–
Salvage chemotherapy	$232,980	$494,029	0.41	0.97	11.74	$42,093
Clofarabine monotherapy	$262,687	$464,323	0.83	1.20	11.32	$41,028
Clofarabine combination	$352,236	$374,774	3.54	4.57	8.61	$43,518
Blinatumomab	$324,762	$402,248	2.79	3.65	9.36	$42,984

LY = life-year; QALY = quality-adjusted life-year.
Source: Manufacturer's economic submission.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted both deterministic (DSAs) and probabilistic sensitivity analyses (PSAs).

In the sensitivity analysis, the manufacturer compared tisagenlecleucel with clofarabine monotherapy, clofarabine combination therapy, and blinatumomab. The analyses showed that tisagenlecleucel was associated with an incremental cost per QALY gained of $41,027, $43,518 and $42,984 compared with clofarabine monotherapy, clofarabine combination therapy, and blinatumomab, respectively. CADTH noted that the results of the manufacturer's sensitivity analyses were highly uncertain and may be subject to selection bias as the manufacturer did not describe how the source of efficacy data for all comparators were identified and selected as input parameters for the model. CADTH also noticed the inconsistency in the choice of comparators being considered in the manufacturer's economic and budget impact analysis (BIA) reports.

DSAs were performed to determine the impact of individual model parameter inputs on the base-case results, where the manufacturer varied input parameters by the 95% confidence interval (CI) or the range if such information is reported in the original source. If such information was not available, the parameters were varied by ±25% from the base case.

The results were most sensitive to the alternative parametric survival functions for EFS and OS. When EFS extrapolation was based on the Gompertz, log-normal, gamma, and exponential distributions, the ICURs ranged from $39,561 to $73,036 per QALY gained. The results were also sensitive to the assumption on the progression after year 5 (assuming EFS flatten up to reach OS vs. using parametric model to predict EFS after year 5), discount rates, subsequent HSCT rates (varying from 13.5% to 32.0% for tisagenlecleucel and from 29.5% to 56.7% for salvage chemotherapy), and the alternative assumptions for IVIG

(intravenous immunoglobulin) treatment duration (replacing a base-case value of 11.4 months to over the entire duration for EFS).

The PSA results revealed that tisagenlecleucel continued to be more expensive and more effective than salvage chemotherapy (100% of the simulations). At the commonly used willingness-to-pay (WTP) threshold of $50,000 per QALY gained, the probability that tisagenlecleucel being cost-effective was 85.9%; this probability increases to 100% if the WTP value was equal to $80,000 per QALY gained.

Limitations Identified With the Manufacturer's Economic Submission

CADTH identified the following key limitations with the manufacturer's economic model.

Model design introduced significant risk of error in estimates. The manufacturer's model design was elaborate and, in many cases, unnecessarily so, leading to a higher risk of error than a more robust design would afford. Key parameters were estimated from combined primary source data and derived values using unclear and indirect methods that made validation a challenging process. While this is not a significant methodological limitation when deriving deterministic values, the heavy reliance on tiered macros for probabilistic analysis introduces significant model uncertainty into the probabilistic output of the model.

As an example, CADTH attempted to produce a basic treatment cost estimate for each treatment comparator using the deterministic approach and found no obvious errors in the calculation. However, when deriving the same cost estimate through the probabilistic sensitivity analysis (with a standard error of 0 for all parameters relevant to this cost estimate) found the same level of variation in the cost estimate as was in the base-case PSA. Upon closer inspection, this was due to a combination of: (1) conditional formula cells distributed across the model that would re-assert a fixed value on a given parameter should it not match a pre-set value written in a table that was not identified as the adjustable parameter source, and (2) the macro itself referenced parameter values or derived deterministic values that were not indicated as adjustable parameters in the model. Significant restructuring and recoding was necessary to generate reliable outputs that were based on actually identified parameter values, however, due to time limitations not all structural limitations could be addressed to allow for a complete evaluation of the model.

The complexity of the model is not reflective of what is required to answer the decision questions. In the case of a probabilistic analysis, even changing variance estimates to extreme values led to relatively tight probabilistic outputs that were closely comparable to the manufacturer's base-case estimations – which would not be expected. Unreliable and non-intuitive results from the probabilistic analysis of this model raises significant concern on whether the model truthfully reflects the nature and magnitude of uncertainty surrounding the base-case results. This, in combination with other structural oversights identified in this section, all point to a common feature of this model to regress second-order uncertainty estimates toward the mean estimate. This systematic skew toward the mean in the probabilistic analysis is, in large part, the result of structural errors and over-complicated parameter estimates throughout the model.

The cost-effectiveness of tisagenlecleucel is highly uncertain due to the lack of head-to-head comparative efficacy and safety of tisagenlecleucel and salvage chemotherapy. EFS and OS data for each treatment arm were obtained from separate data

sources. EFS and OS data for tisagenlecleucel were pooled from two single-arm trials and one phase I/IIA, safety and feasibility study, while OS data for salvage chemotherapy were based on a post-hoc study by von Stackelberg et al., which included 51 patients aged 19 years or younger with a first relapse of B-cell-precursor or T-cell and non-response to relapse protocol therapy who received a curative treatment approach. Due to the variation in reporting of baseline characteristics in the tisagenlecleucel trials and the post-hoc study, CADTH was unable to assess whether clinical and prognostic parameters of patients enrolled in both data sources were comparable. CADTH noted that a small proportion of patients in the post-hoc study had B-cell ALL compared with those enrolled in the pooled trials (63% vs. 99%). Patients enrolled in the post-hoc study were slightly younger (median age: eight versus 11 years). Moreover, the OS was defined differently between the two data sources. OS was measured from the time of non-response to prior therapy in the post-hoc study, while OS was measured from initiation of the treatment in the tisagenlecleucel trials.

The difference in trial design, setting patient characteristics, and outcome definitions between the trials increases the uncertainty in the cost-effectiveness results. As such, it is unclear whether OS data reported in this study is generalizable to Canadian patients with r/r B-cell ALL.

It is inappropriate to pool OS and EFS data from the ELIANA, ENSIGN, and B2101J trials due to difference in cell doses and study designs. The B2101J is a phase I/IIA, single-arm, open-label, single-centre trial aimed to test the safety and feasibility of administering tisagenlecleucel to pediatric and young adult patients up to 24 years of age with r/r CD19+ B-cell leukemia and lymphoma.[6] The trial allowed multiple infusions of with doses up to a total dose range of 1.5×10^7 to 5×10^9 total T cells, while in ELIANA[4] and ENSIGN trials,[5] tisagenlecleucel was administered as single intravenous infusion, at a dose range of 0.2 to 5.0×10^6 CAR-positive (CAR+) viable T cells/kilogram (kg) body weight for patients who weigh 50 kg or less, and 0.1 to 2.5×10^8 CAR+ viable T cells for those who weigh more than 50 kg. CADTH believes that the economic model based on EFS and OR obtained from each individual trial or pooled ELIANA and ENSIGN is more appropriate.

The salvage chemotherapy regimens used in a study by von Stackelberg et al. was unknown. von Stackelberg et al. categorized chemotherapy to single-agent and polychemotherapy, but the names of these chemotherapy regimens were not reported. It is unclear whether EFS and OS data derived from this study are applicable to pediatric and young patients with r/r B-cell ALL in Canada.

The total costs of tisagenlecleucel were underestimated. The manufacturer's model did not include the cost of chemotherapy used as a bridge to tisagenlecleucel (also known as bridging therapy). According to ELIANA trial, 84% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. The most commonly used concomitant antineoplastic medications before lymphodepletion therapy (in ≥ 50% of patients) included methotrexate (64.1%), cytarabine (58.7%), and vincristine (50.0%). CADTH assessed the impact of this limitation by increasing the pre-treatment cost by 25% in one of the scenario analysis. CADTH believed that it would be more appropriate to include the cost of bridging therapy in a base case, as obtained from Lin et al.[9]

Several outcomes were only partially incorporated into the model. The impact of subsequent SCT on progression and survival was not accounted in the model. Although the manufacturer claimed that the efficacy benefit of subsequent HSCT were captured in the EFS and OS estimations, the manufacturer only accounted for the additional costs and disutilities associated with SCT. According to clinical experts consulted by CADTH,

subsequent HSCT is expected to delay progression and improve patient survival. Although the potential benefit of subsequent HSCT after tisagenlecleucel was unknown, the omission of the benefits of HSCT may in turn underestimate the ICUR because the greater proportion of patients in the salvage chemotherapy arm received subsequent HSCT (associated with additional costs and health utility decrements). CADTH also concern with a data source for health utility data for EFS and PD health states. The manufacturer's base case used health utility data from the published literature as opposed to health utility values derived from ELIANA trial.

Uncertainty analysis of most input parameters was based on unjustified assumptions of variation. Nearly all parameter values utilized variance estimates that were not based on source material. Instead, they were based on standard error estimates that assumed a 25% value variance from the mean. No justification was provided for why 25% variance from the mean was selected, or why such a percentage difference from the mean would be uniformly applied to all parameter values regardless of data type or quality of the source. Since this was uniformly applied to most parameters, it would seem reasonable to include the scale of variance as a parameter to be tested to determine the marginal impact of changing this assumption on the probabilistic analysis results. Doing so would not dramatically impact the base-case results but would offer opportunity to better characterize and interpret the probabilistic results. Applying a fixed and small value on the variance may underestimate the uncertainty in the cost-effectiveness results given that most input parameters of the model, such as cost and utility data, are highly-skewed.

Other limitations and issues related to structural uncertainty identified with the submitted evaluation include the following:

Parameters were assumed to be independent. The manufacturer assumed independence of treatment effects from secondary outcomes, including HSCT rate, adverse event (AE), post-treatment management, and terminal care. It is reasonable to expect that in the real-world there is the association between the primary measure of clinical effectiveness of a given treatment and secondary patient outcomes. However, the current construction of the model treats the primary effectiveness outcomes independent to the probability and severity of secondary outcomes. As an extreme illustration, if we alter any of the treatment's parameters to make it functionally curative (according to EFS and OS), the model will still assume the same percentage of patients receive subsequent SCTs.

The manufacturer's base-case deterministic model applies the expected mean values for their primary effect of interest, EFS, and the other secondary features of the model, including HSCT rate, AEs, etc. The model's probabilistic analysis tests the expected cost-effectiveness of tisagenlecleucel using a Monte Carlo approach wherein the expected parameter values are varied according to their probabilistic distribution. However, the model lacks any mechanical relationship the effectiveness of the treatment and secondary outcomes such as HSCT rate, AEs, intensity of management, or terminal care. Consequentially, the resulting probabilistic analysis (and DSA) dilutes a likely correlation between primary and secondary effects into random error. We expect this results in an over-estimate of first-order random error; regressing the probabilistic interpretation of the results toward the mean estimate. This will, in effect, result in an over-fit of the model to tightly match the base-case estimate, and underestimate the true uncertainty in the ICUR calculation.

CADTH is aware that the available data may not allow for an evidence-based variance-covariance matrix to address this limitation completely. However, since these secondary patient outcomes are contributing significantly to the cost-effectiveness calculations, there should be at a minimum a mechanical relationship built into the model that will allow for scenario testing. This may take the form of a Cholesky decomposition matrix with the baseline values of all relevant parameters to be 1 (independent), allowing for new analysis to be done to determine if and to what degree unadjusted correlation may be confounding the expected difference in patient outcomes and costs across treatments. Due to time-constraint, CADTH was unable to assess the impact of this limitation on the cost-effectiveness of tisagenlecleucel.

Heterogeneity of patient characteristics impacting treatment effectiveness was not considered. Based on consultation with clinical experts, there are three major patient characteristics that significantly impact the clinical effectiveness of treatment as well as the duration and intensity of management: (1) age at time of treatment, (2) time since initial diagnosis, and (3) the number of previous therapies. The heterogeneity issue is particularly important given that patients receiving salvage chemotherapy were younger age, had fewer previous regimen and longer OS (and PD) duration in compared with those receiving tisagenlecleucel. While age is partially accounted for in the model, the latter two factors are missing from the model structure completely. The primary limitation this introduces to the model is to the reliability of the data to be generalized for a cost-effectiveness study, without a model mechanism that allows stratified analysis. The input parameters are based on efficacy estimates from disparate trials that would have accounted for and reported on these patient characteristics to different degrees of completeness. It is unclear to what extent it is appropriate to compare one treatment to another when we are not accounting for differences in when and to whom each treatment would have been provided.

CADTH was unable to assess the impact of this limitation as it requires a structural addition to the model to allow for stratification of the populations according to these three characteristics, which is beyond the scope of the review. It would also require further review of data sources to obtain more detailed patient data. Given the likely small number of patients, this is an analytic limitation that will have to be addressed by the manufacturer qualitatively so that decision-makers can understand the nature of the limitation and what impact it has on the interpretation of the results.

Reference case is not probabilistic: The reference case results of the manufacturer's model used effectiveness and cost calculations based on the estimated deterministic base-case value. CADTH guidelines recommend the reference case be derived from the probabilistic analysis in order to adjust the estimated ICUR for any skew in the cost-effectiveness plane that would arise from non-normally distributed variance in the costs or effectiveness estimates. Importantly, the other limitations we identified all directly contribute to the degree of non-normally distributed variability we would expect to see in a probabilistic cost-effectiveness plane. Without addressing the previous limitations, we would expect changing the base case to be derived from the probabilistic results will have a small impact on the final ICUR measurement. CADTH used probabilistic analysis as a revised base case.

CADTH Reanalyses

As noted in the limitations, CADTH identified important limitations in the manufacturer's economic model. Several of the limitations would require significant structural revisions to the model and additional primary data analysis that is beyond the scope of this review. CADTH's revised base case incorporated the following alterations to the model:

- probabilistic analyses based on a run of 5,000 iterations
- OS and EFS data for tisagenlecleucel based on ELIANA trial
- health utility values derived from ELIANA trial
- inclusion of the cost of bridging therapy ($19,816.24 converted in CDN$).

CADTH reanalysis showed that tisagenlecleucel was associated with additional 10.60 QALYs gained and an incremental cost of $545,624 compared with salvage chemotherapy, resulting in an ICUR of $53,269 per QALY. The probability that tisagenlecleucel was cost-effective was 44.2% and 99.1% at a willingness-to-pay threshold of $50,000 and $100,000 per QALY, respectively.

Table 2: CADTH Revised Base Case

	Total Costs ($)	Incremental Cost of Tisagenlecleucel ($)	Total QALYs	Total LYs	Incremental QALYs of Tisagenlecleucel	Incremental Cost per QALY
Tisagenlecleucel	798,967	565,624	10.95	14.40	10.60	$53,269
Salvage chemotherapy	233,343		0.35	0.97		

LY = life-year; QALY = quality-adjusted life-year.

Several scenario analyses were performed to observe the magnitude of change in results by altering structural and/or data assumptions in the base-case model design. All scenarios were tested using the CADTH revised base case model. Results of scenario analyses conducted by CADTH were summarized in Table 3.

Given the significant variation in estimated EFS and OS curves over time, CADTH randomly selected the predicted EFS and OS of tisagenlecleucel estimated from any parametric survival models including exponential, Weibull, log-logistic, log-normal, Gompertz, generalized gamma, and cubic spline models (Scenario A). The high variation in curve estimates and non-normal distributions of the expected EFS and OS outputs over time led to a significant range in estimated ICURs. The mean ICUR estimate rose to $89,234. The probability of tisagenlecleucel being cost-effective compared salvage chemotherapy was nearly 0% using a $50,000 per QALY gained threshold, and a 90% chance of it being cost-effective when the threshold was raised to $150,000.

Two scenarios were run examining changes in utility calculations; the duration of tisagenlecleucel disutility was extended for up to one year rather than just for the period of index hospital admission (Scenario B), and febrile neutropenia disutility was considered (Scenario C). Each of these scenarios had relatively small effects on the estimated ICURs.

CADTH tested increasing the pre-treatment cost of tisagenlecleucel by 25% to account for bridging therapy (Scenario D) and found that only a moderate increase in the ICUR. Additionally, the per cent of tisagenlecleucel patients receiving care in hospital was varied from 100% to 0% (Scenarios E and F). 100% of patients receiving treatment in hospital had a minor impact on the estimated ICUR, which is unsurprising given the vast majority of patients in the base case were treated in hospital. Making all patients outpatients reduced the estimated cost of providing care; however, had no impact on the estimated QALYs, making the scenario more cost-effective. This highlights that the model only adjusts for changes in cost according to treatment location but did not extend this to changes in patient outcomes.

CADTH assessed the impact of a time horizon on the cost-effectiveness of tisagenlecleucel. Reducing an analytical time horizon from 70 to 20, 10, 5, and 1 years led to a substantial increase in ICUR (Scenario G to J).

CADTH tested the effect of including patient out-of-pocket costs (e.g., travel and accommodation time for patients and one caregiver, medical coinsurance amounts, copayments, and deductibles) in order to determine how a societal perspective impacts the ICUR estimate. A literature search returned a mean estimate of $16,544 over three years for patients.[14,15] Costs were incorporated as a discounted lump sum addition to tisagenlecleucel costs. Including these costs resulted in a slight increase in the estimated ICUR.

Table 3: CADTH Scenario Analyses

		Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICUR
Scenario A: Randomized OS and EFS	Tisagenlecleucel	$920,293	$694,240	7.84	12.58	7.78	$89,234
	Salvage chemotherapy	$226,053		0.06	0.62		
Scenario B: Extended AEs	Tisagenlecleucel	$798,460	$565,117	10.73	14.40	10.39	$54,391
	Salvage chemotherapy	$233,343		0.34	0.97		
Scenario C: Febrile Neutropenia Disutility	Tisagenlecleucel	$798,460	$565,117	10.8	14.40	10.45	$54,078
	Salvage chemotherapy	$233,343		0.35	0.97		
Scenario D 100% in hospital	Tisagenlecleucel	$802,710	$569,859	10.88	14.40	10.54	$54,066
	Salvage chemotherapy	$232,851		0.34	0.97		
Scenario E 0% in hospital	Tisagenlecleucel	$744,005	$511,154	10.88	14.40	10.54	$48,497
	Salvage chemotherapy	$232,851		0.34	0.97		
Scenario F Societal perspective	Tisagenlecleucel	$810,401	$577,551	10.88	14.40	10.54	$54,796
	Salvage chemotherapy	$232,850		0.34	0.97		
Scenario G Shorten time horizon to 20 years	Tisagenlecleucel	$798,460	$485,695	7.98	6.08	5.90	$82,321
	Salvage chemotherapy	$312,765		0.77	0.18		
Scenario H Shorten time horizon to 10 years	Tisagenlecleucel	$715,519	$488,316	3.62	4.87	3.51	$139,259
	Salvage chemotherapy	$227,203		0.12	0.68		
Scenario I	Tisagenlecleucel	$699,840	$473,947	2.18	3.07	2.11	$224,896

		Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICUR
Shorten time horizon to 5 years	Salvage chemotherapy	$225,893		0.07	0.62		
Scenario J Shorten time horizon to 1 year	Tisagenlecleucel	$669,384	$451,207	0.51	0.89	0.55	$815,413
	Salvage chemotherapy	$218,177		-0.05	0.46		

AE = adverse event; EFS = event-free survival; ICUR = incremental cost-utility ratio; OS = overall survival; LY = life-year; QALY, quality-adjusted life-year.
Note: In addition, exploratory analyses were also conducted to consider alternative forms for EFS and OS curves (Table 15) and reimbursement based on achieving outcomes as observed in the clinical trial (Table 16).

CADTH undertook a price-reduction analysis based on the manufacturer and CADTH revised base-case analyses. The price-reduction scenario based on CADTH revised base case showed that the ICURs of tisagenlecleucel were less than the willingness to pay of $50,000 per QALY at a 10% price-reduction (Table 5).

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs of Tisagenlecleucel Versus Salvage Chemotherapy		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CADTH**
Submitted	$42,093	$53,269
10% reduction	$38,259	$48,755
15% reduction	$36,342	$47,123
20% reduction	$34,425	$44,917
25% reduction	$32,508	$42,711
30% reduction	$30,591	$40,506
40% reduction	$26,757	$36,095
50% reduction	$22,922	$31,684
60% reduction	$19,088	$27,272
70% reduction	$15,254	$22,861

ICUR = incremental cost-utility ratio.

Information on the Budget Impact Analysis

Manufacturer's Budget Impact Analysis

The manufacturer submitted a BIA that assessed the financial impact of the potential reimbursement of tisagenlecleucel for patients aged 3 to 25 with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) in Canada.[16] A national level analysis considering reimbursement across all provinces and territories was conducted over a three-year time horizon and based on the Canadian societal perspective. Full details are provided in Appendix 3.

The submitted BIA model was built in Microsoft Excel using an epidemiology-based approach and compared two budget scenarios: 1) a Reference Scenario, where only treatment with current chemotherapy regimens is available, and 2) a New Treatment Scenario, where tisagenlecleucel joins the market and also becomes available. For each scenario, the number of patients likely to receive treatment with available regimens was multiplied by the relevant per-patient costs to determine the total costs associated with each therapy. The budget impact was then calculated by subtracting the total costs of the Reference Scenario and the total costs of the New Treatment Scenario. Figure 4 in Appendix 3 presents a schematic of the manufacturer's BIA modelling approach.

The total number of patients eligible for treatment with tisagenlecleucel in each reimbursement year was estimated using a funnel-down approach (Figure 5 in Appendix 3).To arrive at the size of the modelled population for a given reimbursement year, the total projected population of Canada for each reimbursement year was filtered to include the proportion of persons aged 3 to 25 who are diagnosed with B-cell ALL using estimates of disease prevalence in the first reimbursement year (Year 1) or annual incidence in the second and subsequent reimbursement years (years 2+). The manufacturer's analysis considered the pediatric (ages 3 to 17) and young adult (ages 18 to 25) populations separately, constituting 16.04% and 10.54% of the total population, respectively. These two populations were further narrowed down to include only persons eligible to receive tisagenlecleucel; specifically, this included the following patient groups:

- refractory following first-line therapy
- relapse/refractory after second-line therapy.

The sources of data and assumptions made to arrive at the size of the total eligible population are reported in Appendix 3.

The total number of pediatric and young adult r/r B-cell ALL patients expected to receive tisagenlecleucel or other treatment in the Reference Scenario and the New Treatment Scenario was estimated by combing the total eligible patient population with market share data in each year of the analysis. The market shares of treatment options in the Reference Scenario and New Treatment Scenario were predicted according to Canadian expert opinion and a survey of US leukemia care providers commissioned by the manufacturer. [redacted] The projected market shares of regimens and the total number of patients expected to receive tisagenlecleucel versus salvage chemotherapy, blinatumomab, and investigational therapy in the two budget scenarios is presented in Table 18, Table 19, Table 20, and Table 21 (Appendix 3).

Annual budget costs in the analysis included the cost of main therapy (composed of drug acquisition costs and administration and hospitalization costs), routine monitoring medical costs, AE management costs, subsequent therapy costs (hematopoietic stem cell transplantation), and indirect costs (limited to productivity gains); the impact of reimbursement on health outcomes was not considered. The manufacturer's analysis assumed that each patient receiving tisagenlecleucel or one of the approved chemotherapy regimens would incur the same total therapy costs.

Table 22 in Appendix 3 presents the total costs for each comparator by cost category. Results were reported as total annual costs in 2017 Canadian dollars.

Manufacturer's Base Case

Results of the manufacturer's BIA base case (Table 5) revealed that the incremental expenditures associated with the reimbursement of tisagenlecleucel in patients aged 3 to 25 years with r/r B-cell ALL in Canada are expected to be $15,997,769 in Year 1, $5,710,309 in Year 2, and $6,163,222 in Year 3. Since tisagenlecleucel is a one-time treatment, decreased expenditures after Year 1 of the analysis are observed due to the assumption that an incident population would be treated in the second and subsequent years of funding. Table 26 in Appendix 3 presents the total costs in each reimbursement year by cost category for each comparator in the two budget scenarios compared in this analysis.

Base-case results were most sensitive to the number of patients with r/r B-cell ALL (budget impact between $25,084,170 and $30,658,431 when estimates of prevalence/incidence varied +/- 10% of base-case values), the proportions of patients with relapsed/refractory disease (budget impact between $22,952,836 and $29,838,686 for values tested) and the market share of tisagenlecleucel (budget impact between $25,239,198 and $30,503,403 when varied +/- 10% of base-case values). Detailed results of the manufacturer's sensitivity analyses are presented in Table 27 of Appendix 3.

Table 5: Summary of Results of the Manufacturer's Budget Impact Analysis Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	3-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	$0	$0	$0	$0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 15,997,769**	**$ 5,710,309**	**$ 6,163,222**	**$ 27,871,300**

BIA = budget impact analysis.
Source: Manufacturer's BIA submission.[16]

Sources of Uncertainty With the Manufacturer's Budget Impact Analysis

CADTH identified a number of key sources of uncertainty and potential limitations relating to the manufacturer's BIA:

- **Inappropriate selection of comparators in the base-case analysis.** The inclusion of blinatumomab and investigational therapy as relevant comparators in the manufacturer's BIA is questionable. Despite the recent pCODR Expert Review Committee recommendation for public reimbursement of blinatumomab, it is unclear whether this treatment would be administered in the same line of therapy as tisagenlecleucel in Canadian clinical practice. The inclusion of investigational therapy (i.e., patients entering clinical trials) in the base-case analysis may be problematic as these patients are not receiving approved regimens in the treatment of r/r B-cell ALL, and allocating a proportion of market shares to non-approved therapies may bias the predictive accuracy of the budget impact estimates. In particular, blinatumomab and investigational therapy were not included in the manufacturer's pharmacoeconomic analysis base case,[3] which brings into question their relevance for the assessment of budget impact.
- **Consideration for bridging therapy associated with tisagenlecleucel pre-treatment.** The budget impact model accounted for a number of pre-treatment costs for patients receiving tisagenlecleucel in the New Treatment Scenario, including the cost of leukapheresis, cryopreservation, and the costs of lymphodepleting chemotherapy regimens. According to the ELIANA trial, approximately 84% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. [4] However, the costs associated with bridging chemotherapy were not accounted for in the manufacturer's analysis, which have led to an underestimation of the total costs associated with tisagenlecleucel.
- **Potential uptake of tisagenlecleucel.** The market penetration rates for tisagenlecleucel in the New Treatment Scenario (where tisagenlecleucel joins the market) were estimated based on a survey of US leukemia care providers commissioned by the manufacturer.[16] The applicability of estimates sourced from clinical experts in the US may be limited in the context of Canadian clinical practice. More importantly, these estimates cannot be validated as they are based on the manufacturer's internal estimates.
- **Potential "commercialization" constraints not accounted for in the analysis**. [redacted][17] [redacted][17] This has implications for the total number of patients per year eligible for treatment with tisagenlecleucel based on the manufacturer's estimates (see Table 20 in Appendix 3), which exceeds the site-specific annual capacity of these transplant programs. These commercialization constraints have the potential to delay access to timely therapy and contribute to other condition-related resource use and costs in the health system. The impact of limited capacity at available treatment sites is unclear as it was not assessed in the manufacturer's BIA.

- **Cost of product-related manufacturing issues not considered in the analysis.** The manufacturer's BIA assumed that all patients eligible for tisagenlecleucel would receive timely treatment. While the cost of AEs and other condition-related costs were appropriately used to estimate the net budget impact of reimbursing tisagenlecleucel, the potential for product-related manufacturing issues occurring at FACT-accredited pediatric sites, such as the cost associated with failed samples, was not addressed by the manufacturer. As a result, the magnitude of the impact of manufacturing issues, and associated delays to therapy, is unclear.
- **Consideration for productivity loss and other indirect costs.** Given the societal perspective adopted in this BIA, the manufacturer attempted to account for productivity gains (cost offsets) based on a proportion of patients assumed to work while receiving each treatment; productivity gain was calculated by multiplying an average annual wage by an average employment rate for pediatric and young adult patients with ALL and by the estimated proportion of patients in EFS.[16] While this approach may be acceptable, it does not consider productivity loss associated with parents or other caregivers caring for this specific patient population. In addition, the cost of travel and accommodation for families who do not live near the designated treatment facilities was not addressed. Therefore, indirect costs accounted for by the manufacturer provide an incomplete portrait of the expected out-of-pocket costs associated with the potential reimbursement of tisagenlecleucel.

CADTH Reanalyses

CADTH attempted to account for some of the important shortcomings regarding the manufacturer's budget impact model.

Table 6 presents a revised base-case analysis (CADTH base case) based on the following modifications made to the manufacturer's model:

- Blinatumomab and investigational therapy were removed as relevant comparators, with market shares adjusted accordingly.
- A total cost of C$19,816.24 for bridging therapy was sourced from Lin et al. (US$15,200) and added to pre-treatment costs associated with tisagenlecleucel.[9]
- Drug wastage was accounted for by assuming 0% vial sharing for comparators.
- Additional out-of-pocket costs relating to informal care and transportation were included for patients receiving tisagenlecleucel. These out-of-pocket costs were derived from published studies relating to stem cell transplantation and calculated as the sum of transportation and accommodation costs reported by Perez et al.[14] and the medical coinsurance amounts, copayments, and deductible costs reported by Maziarz et al.[15] The total out-of-pocket costs were added a one-time cost for patients receiving tisagenlecleucel.

Based on the revisions made to the manufacturer's BIA, CADTH found that the incremental expenditures associated with the reimbursement of tisagenlecleucel in patients aged 3 to 25 with r/r B-cell ALL in Canada are expected to be $14,464,009 in Year 1, $5,514,709 in Year 2, and $6,283,762 in Year 3; the cumulative three-year net budget impact of reimbursing tisagenlecleucel was predicted to be $26,262,480.

Table 6 presents the total costs in each reimbursement year by cost category for each comparator in the Reference Scenario (current treatment only) and the New Treatment Scenario (where tisagenlecleucel joins the market) from the Canadian societal perspective.

Results of the CADTH base case from the public payer perspective are presented in Table 7.

Table 6: Summary of Results of the CADTH Budget Impact Analysis Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 14,464,009**	**$ 5,514,709**	**$ 6,283,762**	**$ 26,262,480**

AE = adverse event; BIA = budget impact analysis.

Table 7: Summary of Results of the CADTH Budget Impact Analysis Base Case — Public Payer Perspective

Annual Cost Outcomes	Year 1	Year 2	Year 3	3-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 14,096,490**	**$ 5,374,584**	**$ 6,124,097**	**$ 25,595,171**

AE = adverse event; BIA = budget impact analysis.

CADTH also attempted to account for other sources of uncertainty relating to the manufacturer's BIA through several scenario analyses of the CADTH base case. In the first scenario analysis (Table 28), whereby a 100% increase in tisagenlecleucel usage and costs was assumed for all patients to account for the need for potential re-treatment with tisagenlecleucel, results revealed that the incremental spending required for the reimbursement of tisagenlecleucel for r/r B-cell ALL patients may increase to $31,159,485 in Year 1, $11,880,211 in Year 2, and $13,536,965 in Year 3 In a second scenario analysis (Table 29), whereby annual caps on the number of treated patients were assumed according to the manufacturer's commercialization capacity at treatment site launch, the net budget impact of reimbursing tisagenlecleucel for r/r B-cell ALL was estimated at $6,009,763 in Year 1, $5,514,709 in Year 2, and $6,283,762 in Year 3. However, the reduced budget impact in this analysis does not account for worse health outcomes (and associated health system consequences) which may result due to delays to timely treatment. A third scenario analysis was conducted focusing on the cost associated with product-related manufacturing issues (Table 30). Specifically, a proportion of patients eligible for treatment with tisagenlecleucel was assumed to incur the costs of salvage chemotherapy since they would not receive the tisagenlecleucel infusion due to a non-viable sample; the proportion of patients who would incur the costs of salvage chemotherapy was assumed from the

percentage of enrolled patients from the JULIET trial who discontinued tisagenlecleucel prior to infusion due to production failure [redacted].[4] The net budget impact of reimbursing tisagenlecleucel for r/r B-cell ALL accounting for tisagenlecleucel-related manufacturing issues was estimated at $14,499,904 in Year 1, $5,528,395 in Year 2, and $6,299,356 in Year 3.

A number of exploratory analyses of the CADTH base case were also conducted to assess the uncertainty relating to the cost of bridging therapy sourced from Lin et al.[9] (Table 31), as well as reimbursement based on achieving clinical outcomes (Table 32, Table 33, Table 38, Table 39). Specifically, where pre-treatment costs associated with tisagenlecleucel were inflated by 25% (instead of costs sourced from the published literature), the net budget impact of reimbursing tisagenlecleucel for r/r B-cell ALL was approximately $25.6 million over three years. For scenarios where reimbursement of tisagenlecleucel was assumed only for persons meeting specific performance outcomes sourced from clinical trials (e.g., ORR at 3 months, PFS over 12 months), the net expenditures associated with reimbursing tisagenlecleucel over three years ranged between $19.4 million (based on average PFS over 12 months) and $21.7 million (based on ORR at 3 months), as outcomes were defined in the trials.

Issues for Consideration

- The manufacturing process may take weeks from leukapheresis to the time tisagenlecleucel is ready to be infused back into the patient. During that time, some of the patients will die and others will experience progression of the condition becoming too sick to tolerate treatment with the CAR T cells. This has not been captured as part of the manufacturer's economic model but represent likely costs associated with the technology.
- Manufacturing failure may occur due to inadequate number of T cells in the apheresed product, poor selection of T cells on day zero of manufacturing, or irreversibly impaired T cells (i.e., no response to stimulation in culture), microbial contamination, equipment-related cell loss, high endotoxin level, and accidents. The manufacturing failure will increase ICUR because patients may require a second dose of tisagenlecleucel and/or experience disease progression that needs intensive formal and informal care.
- The availability of tisagenlecleucel is expected to cause capacity constraints and pose challenges to hospital overcrowding in Canada. This concern is supported from ELIANA trial data indicating that approximately 66% of patients were hospitalized during lymphodepleting chemotherapy, with an average duration of 14 days. The prolonged hospitalization may also impose additional financial burden, such as travel and parking costs to patients and their caregiver.
- It should be noted that the total treatment cost in the tisagenlecleucel arm did not account for potential hospital mark-up for the therapy and the bridging chemotherapy costs.
- Although tisagenlecleucel has shown very encouraging results in pediatric and young adult patients with r/r B-cell ALL, it is not yet clear whether tisagenlecleucel can be used at different stages of therapy, such as in first-line use or post HSCT.
- The limited clinical experience with tisagenlecleucel and the short follow-up of the pivotal trials causes the high uncertainty about the long-term health outcomes and side effects due to the presence of cells that have been genetically manipulated.

- If a potential curative therapy, such as tisagenlecleucel, leads to a longer life expectancy in patients with r/r B-cell ALL, the patients will incur future cost to the health care system. Considering future related and unrelated health care costs in the cost-effectiveness model will increase ICUR and make tisagenlecleucel less economically attractive.

Patient Input

Patient input was received as a joint submission from the Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), with collaboration from Leukemia and Lymphoma Society of Canada (LLSC) and Ontario Parents Advocating for Children with Cancer (OPACC). The submitters noted that at the point of being diagnosed with r/r ALL, children and young adults are already often experiencing challenges to their emotional well-being, social and cognitive development, educational involvement, and abilities to be physically and socially active due to their previous cancer treatments. Caregivers, having cared for their child for potentially many years, experience emotional stress, relationship difficulties, health problems, and financial burdens. The clinical and cost-effectiveness information provided by the manufacturer did not specifically address these aspects of r/r ALL for patients or their caregivers.

Most patients travel long distances (by plane or by car) for treatment and have short-term stays away from home. Caregivers described the additional difficulties of temporary relocation, and the challenges of being away from home and their families. Some families noted many costs associated with tisagenlecleucel including automobile expenses (e.g., parking, gas, mileage, and car rental), food for parents and child when away from home, accommodations, travel, medications, and other costs.

Conclusions

The manufacturer's economic model was unnecessarily complex and lacked transparency, which made both the assessment of validity and the ability to conduct reanalysis challenging. CADTH was also concerned about the methodological quality of OS and EFS data used in the model and unjustified variation assumption used in a probabilistic analysis. Interpretation of the cost-effectiveness results is therefore subject to the identified limitations as these could not be addressed by CADTH.

CADTH reanalysis showed that compared with salvage chemotherapy tisagenlecleucel was associated with an ICUR of $53,269per QALY. The probability that tisagenlecleucel was cost-effective was 44.2% and 99.1% at the willingness-to-pay threshold of $50,000 and $100,000 per QALY, respectively. However, as noted in the report, there exist clinical uncertainties in the cost-effectiveness results in terms of: the comparative effects relative to salvage chemotherapy, the impact of potential delays to receive tisagenlecleucel, the likely rate of manufacturing failure in practice, information on the use of tisagenlecleucel in different stages of therapy, the lack of longer term clinical evidence for tisagenlecleucel**,** and the impact on capacity constraints at health care facilities (and potential opportunity costs for delay of treatment for other patients) - which have not been captured within the economic evaluation.

CADTH identified a number of important sources of uncertainty relating to the manufacturer's BIA and attempted to account for some of the identified uncertainty through reanalysis. CADTH estimated that the incremental expenditures associated with the reimbursement of tisagenlecleucel in patients aged 3 to 25 with r/r B-cell ALL in Canada are

expected to be $14,464,009 in Year 1, $5,514,709 in Year 2, and $6,283,762 in Year 3. The cumulative three-year net budget impact of reimbursing tisagenlecleucel was predicted to be $26,262,480. In a scenario where re-treatment with tisagenlecleucel may be necessary, the cumulative three-year net budget impact of reimbursing tisagenlecleucel may be greater than $56 million. In a scenario where commercialization constraints may not permit timely treatment of all patients eligible to receive tisagenlecleucel, the cumulative three-year incremental budget impact of funding tisagenlecleucel may be almost $18 million. Where tisagenlecleucel-related production failure is accounted for in the analysis, the cumulative three-year incremental budget impact of funding tisagenlecleucel was estimated at approximately $26 million. These scenarios and estimates should be interpreted with caution as they do not account for potentially worse health outcomes and related costs in this patient population as a result of the delay to timely therapy.

Appendix 1: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”	In the base-case analysis, no direct or indirect comparison was used to adjust for variables that may confound the association between the type of treatment and clinical outcomes. It is unclear how the effect of HSCT on EFS and OS was taken into account. The submitted Excel model is unnecessarily complex and non-transparent. CADTH was unable to test most structural uncertainties.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

EFS = event-free survival; HSCT = hematopoietic stem cell transplantation; OS = overall survival.

Table 9: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH

☐ Adaptation of global model/Canadian model done by the manufacturer

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis		X	

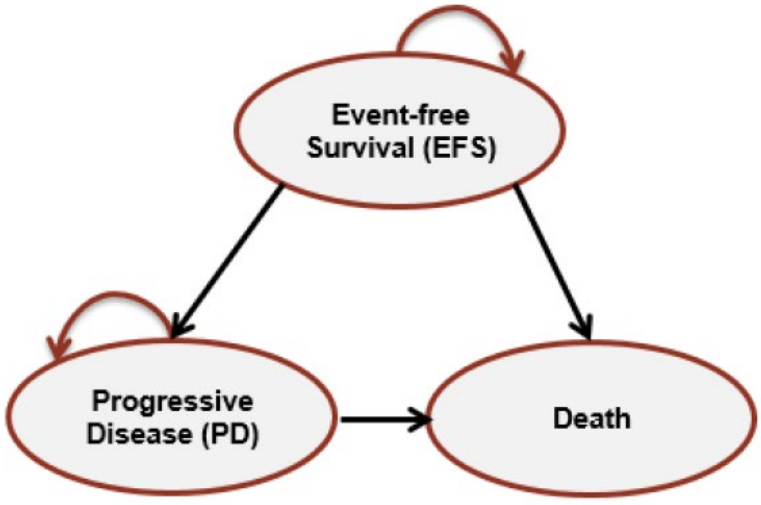
Appendix 2: Detailed Information — Economic Submission

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis comparing costs and health outcomes of tisagenlecleucel and salvage chemotherapy.[3] A partition-survival model with three health states (event free, post progression, and death) was used to forecast the costs and QALYs over a 70-year time horizon. Despite previous progression, all patients enter the model in the event-free state. The proportion of patients in the progressive disease state at each cycle was calculated as the difference between the proportion of patients who died and the proportion of patients who remain in the event-free state. The cycle length of the model was one month. The manufacturer's model structure is presented in Figure 1.

There are no head-to-head trials directly comparing efficacy between tisagenlecleucel and salvage chemotherapy. In the manufacturer's base-case analysis, clinical data from ELIANA,[4] ENSIGN[5] and B2101J[6] trials were pooled and used to inform the impact of tisagenlecleucel on OS and EFS. The pooled trials provided evidence covering 54.8 months; hence, OS and EFS values for tisagenlecleucel beyond the trial period were extrapolated parametric survival models until year 5. For salvage chemotherapy, OS data were based on observed data from the study by von Stackelberg et al.[7] until month 30 and used extrapolated data based on parametric survival models until year 5. For long-term survivors (patients who survived at the end of 5 years) in both arms, the base-case model predicted the OS based on the literature of ALL long-term survivors. The manufacturer approximated EFS for salvage chemotherapy by applying a cumulative hazard ratio between OS and PFS (0.83 for the base-case analysis) to OS data.

Figure 1: Partition-Survival Model Structure



Source: Manufacturer's economic submission.[3]

Table 10: Summary of the Manufacturer's Economic Submission

Drug Product	Tisagenlecleucel (Kymriah)
Study Question	What is the cost-effectiveness of tisagenlecleucel compared with salvage chemotherapy in pediatric and young adult patients (aged 3 to 25 years) with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r B-cell ALL) from a Canada-payer perspective?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Pediatric and young adult patients 3 to 25 years of age with r/r B-cell ALL
Treatment	Tisagenlecleucel as a single intravenous treatment
Outcome	QALYs
Comparator	Salvage chemotherapy (unspecified regimen)
Perspective	Canada payer perspective
Time Horizon	70 years
Results for Base Case	ICUR = $42,094 per QALY gained
Key Limitations	• The design of the manufacturer's economic model introduced significant risk of error in estimates as the macros used for the model were overly complex and not transparent. • The lack of head-to-head information on efficacy and safety of tisagenlecleucel and salvage chemotherapy introduces significant uncertainty in the cost-effectiveness results. • The manufacturer combined event-free and overall survival data for tisagenlecleucel from two single-arm trials and a phase I/IIA, safety and feasibility study. Dosage regimens of tisagenlecleucel used in both data sources were different. As such, the validity of cost-effectiveness results is questionable. • It is unclear whether overall survival and event-free survival data used for salvage chemotherapy were generalizable to Canadian patients with r/r B-cell ALL. • The total costs for patients receiving tisagenlecleucel was underestimated as the manufacturer's economic model did not account for the cost of chemotherapy administered as a bridge to tisagenlecleucel. • Heterogeneity of patient characteristics impacting treatment effectiveness was not considered. • Probabilistic ICURs and uncertainty analysis on most parameters were calculated based on limited variation in input parameters; for instance, variance of most input parameters was set at 25% of the mean values without justification.
CADTH Estimate(s)	• Tisagenlecleucel was associated with additional 10.60 QALYs gained and an incremental cost of $565,624 compared with salvage chemotherapy, resulting in an ICUR of $53,269 per QALY. • The probability that tisagenlecleucel was cost-effective was 44.2% and 99.1% at the willingness-to-pay threshold of $50,000 and $100,000 per QALY, respectively. • Unreliable and non-intuitive results from the probabilistic analysis of the manufacturer's economic model raises significant concern on whether the model truthfully reflects the nature and magnitude of uncertainty surrounding the base-case results. The ICUR for tisagenlecleucel is less than $50,000 per QALY with a 10% price reduction.

HSCT = hematopoietic stem cell transplantation; ICUR = incremental cost-utility ratio; r/r B-cell ALL = relapsed or refractory B-cell acute lymphoblastic leukemia; QALY = quality-adjusted life-year.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	• For tisagenlecleucel, baseline patient characteristics were obtained from pooled data from three single-arm trials (ELIANA, ENSIGN, and B2101J). • For salvage chemotherapy, data were based on a curative arm of a retrospective cohort study of patients aged 19 years or younger with a first relapse of B-cell-precursor or T-cell and non-response to protocol therapy according to protocols ALL-REZ BFM 90, 95/96, P91, 92 and 94. The median age at relapse was 8 and the percentage of male patients was 71%.	There are no head-to-head trials directly comparing efficacy and safety between tisagenlecleucel and salvage chemotherapy. The manufacturer's base-case analysis was based on two data sources without adjustment for potential imbalance of baseline characteristics and risk factors. Due to the variation in the reporting of baseline characteristics data in tisagenlecleucel trials and a study by von Stackelberg, it is difficult to assess whether baseline characteristics and clinical/prognostic parameters were comparable between studies.
Efficacy	• For tisagenlecleucel, the manufacturer combined data observed from ELIANA, ENSIGN, and B2101J trials and estimated OS and EFS up to month 54.8. At the end of the trial follow-up until year 5, the manufacturer extrapolated OS and EFS data using parametric survival models. For long-term survivors (patients who survived at the end of 5 years), the base-case model predicted the OS based on the literature of ALL long-term survivors.[11] • For salvage chemotherapy, OS was based on observed data from a study by von Stackelberg up to month 30. A weighted parametric survival models were used to extrapolate the long-term survival from month 30 to year 5. • Because von Stackelberg did not report EFS data, the manufacturer derived the EFS curve was from the OS curve assuming a constant cumulative HR over time, i.e., the cumulative hazard function for EFS would be proportional to cumulative hazard function for OS.	• There is a lack of comparative efficacy of tisagenlecleucel and salvage chemotherapy. In the base-case analysis, the manufacturer did not perform an indirect comparison or adjust for confounding. As such, the observed benefits of tisagenlecleucel may be influenced by measured and unmeasured confounders. • Patients enrolled in von Stackelberg received various salvage chemotherapy regimens; the name of drugs used was however not reported. It is unclear whether salvage chemotherapy regimens included in Stackelberg reflect standard of care in Canada. • The manufacturer derived EFS of salvage chemotherapy from OS, assuming that the cumulative hazard function for EFS would be proportional to cumulative hazard function for OS. The ratio was based on OS and EFS observed in the mitoxantrone arm in the UK ALL study.[12] This ratio may vary by the type of salvage chemotherapy. CADTH was unable to test whether the manufacturer's assumption was appropriate. • The manufacturer claimed that the efficacy of subsequent HSCT was captured in the EFS and OS estimations; however, the submitted model only incorporated costs and health utility decrements due to HSCT. The omission of benefit of HSCT on patient survival and progress may underestimate the ICUR given that the greater proportion in the salvage chemotherapy group received HSCT.
Natural history	A partition-survival model with three health states (progression-free, post-progression, and death) was used. Transition probabilities between health states were derived from the OS and EFS curves.	A partition-survival model assumes that the modelled survival end points are structurally independent. This structural assumption is potentially problematic because several survival end points are dependent. EFS and OS curves,

Data Input	Description of Data Source	Comment
		for example, have the same pre-progression death. In addition, progression can be considered as prognostic for mortality.
Utilities	• Utility values associated with health states were obtained from a published decision study[8] that compared health outcomes of cranial radiation therapy (CRT) for pediatric patients with T-cell ALL. • Treatment disutility values were based on a study that elicited utility estimates from physician for acute myeloid leukemia patients who survived post transplantation without recurrent disease.[13] • Utility decrement (–0.42) was assumed to apply for the duration of induction chemotherapy for the salvage chemotherapy arm and for the duration of the hospitalization starting from the pre-treatment lymphodepleting regimen for tisagenlecleucel. • For the tisagenlecleucel arm, additional treatment disutilities were considered for grade 3 or 4 CRS. The patients were assumed to have a disutility of -0.91 based on EFS utility for the duration of the CRS-related or non-CRS-related ICU stay reported by ELIANA trial. • Patients receiving subsequent HSCT were assumed to have additional SCT disutility, derived from a study by Sung.[13] The disutility associated with HSCT was assumed to last for 365 days.	• Because ELIANA trial measured health-related quality of life and health utility values, these utility values should be used in manufacturer's base-case analysis. • The manufacturer's base case may underestimate the cost and health decrements associated with CRS. • According to ELIANA, among the 58 patients with CRS, the median duration of CRS was 8.0 days (range: 1 to 36 days). Moreover, thirty-five patients (60.3%) were admitted to the intensive care unit for a median duration of 7 days (range: 1 to 34 days). A maximum ICU day, i.e., 34 days was used in one of the CADTH scenario analyses.
Adverse events	• The manufacturer considered only grades 3 or 4 AEs with greater than or equal to 5% rates in the tisagenlecleucel and the salvage chemotherapy arms. The AEs being considered in the model included anemia, CRS, fatigue, febrile neutropenia, hypokalemia, hypophosphatemia, hypotension, infection, neutropenia, neutrophil count decreased, paresthesia, platelet count decreased, pyrexia, stomatitis, thrombocytopenia, vomiting, and white blood cell count decreased.	Appropriate.
Mortality	• The age- and gender-specific mortality rates of Canada's population were used as the lower bound of the probabilities of death used in the model. • The long-term ALL survival was modelled using the 2017 Canada life table, with a mortality adjustment using the SMR of 5-year ALL survivors published in the literature.	Appropriate.
Resource Use and Costs		
Drug	• The unit cost of tisagenlecleucel was provided by the manufacturer. The one-time acquisition cost of tisagenlecleucel was [redacted]. • The treatment cost of salvage chemotherapy was estimated as the average cost for UK R3 ALL and	Appropriate.

Data Input	Description of Data Source	Comment
	COG-AALL 0031 regimens. The manufacturer claimed that the regimen was the most commonly used regimen for salvage chemotherapy in r/r settings based on clinical inputs.	
Administration	• For patients receiving tisagenlecleucel, they were expected to incur the additional costs for lymphodepleting chemotherapy, hospital and ICU admission. For patients who were managed in the outpatient setting, a unit cost of $199 was added to capture delivery of chemotherapy. • For salvage chemotherapy, the total cost of induction and consolidation salvage chemotherapy was incorporated as a lump sum cost comprised of drug acquisition cost, administration cost, and hospitalization cost for initial induction and two consolidation blocks based on the pCODR blinatumomab submission.	Appropriate.
Bridging therapy and lymphodepleting chemotherapy	• The manufacturer's economic model did not account for the cost of bridging therapy. • The cost of lymphodepleting chemotherapy considered in the model were calculated as a function of unit drug costs, dosing, and proportion of patients receiving either fludarabine and cyclophosphamide (regimen 1) or bendamustine (regimen).	• The submitted model is likely to underestimate the total treatment costs. According to ELIANA trial, 84% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. The most commonly used concomitant antineoplastic medications before lymphodepletion therapy (in ≥ 50% of patients) included methotrexate (64.1%), cytarabine (58.7%), and vincristine (50.0%). CADTH assessed the impact of this limitation by increasing the pre-treatment cost by 25% in one of the scenario analysis.
Subsequent HSCT	• The model assumed patients could receive subsequent HSCT. The rates of subsequent SCT were obtained from the same clinical trial study used for the efficacy estimation. HSCT costs consisted of: procedure cost, short-term follow-up cost up to 100 days, and follow-up cost from 100 days up to 2 years. The unit costs of HSCT were obtained from the published Canadian and American data sources.	Appropriate.
AEs	• AE costs were calculated for tisagenlecleucel and salvage chemotherapy based on rates of AE and unit costs per AE. The AE rate inputs were obtained from the ELIANA trial data for tisagenlecleucel and a published study (Raetz) for salvage chemotherapy. • The AE costs were estimated based on the OCCI from the Ontario Ministry of Health and Long-term Care.	• The AE profiles of the three blocks of reintroduction chemotherapy for pediatric and young adults with first isolated or combined marrow B-precursor and T-cell ALL (T-ALL) relapse used in a study by Raetz[18] may not be representative of AE profiles of salvage chemotherapy regimens used in Canada. • The cost of AEs associated with lymphodepleting regimens was not considered in the submitted model.
Health state	• The pre-progression follow-up costs consisted of physical check-ups and routine monitoring labs/procedures and were assumed to be different by treatment and time horizon.	Appropriate.

Data Input	Description of Data Source	Comment
	• For patients receiving salvage chemotherapy who remained in the EFS state, the frequency of follow-up was obtained from a Canada-specific lymphoma guideline from Alberta Health Services. • For patients receiving tisagenlecleucel who remain in the EFS state, the frequency of follow-up was derived from ELIANA trial. The unit costs per provider visit and per test/procedure were collected from the section of physician services in the 2016 OMHLTC report of the OHIP schedule of benefits and fees. • Post-progression and palliative care costs were obtained from the published literature.	

AE = adverse event; ALL = acute lymphoblastic leukemia; CRS = cytokine release syndrome; EFS = event-free survival; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; MOHLTC = Ministry of Health and Long-Term Care; OS = overall survival; pCODR = CADTH pan-Canadian Oncology Drug Review; SCT = stem cell transplantation.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Treatment disutility for tisagenlecleucel was considered for the duration of hospitalization These treatment disutilities included disutilities of AEs during the treatment period, except for CRS.	Appropriate.
Disutility of CRS was applied during ICU admission (both CRS and non-CRS-related admission).	The manufacturer's base case assumed that patients receiving tisagenlecleucel experienced health utility decrements over their ICU stay (a mean of 9.8 days for a CRS-related admission and a mean of 1.78 days for a non-CRS-related admission). According to ELIANA trial, among the 58 patients with CRS, the median duration of CRS was 8.0 days (range: 1 to 36 days). Thirty-five patients (60.3%) were admitted to the intensive care unit for a median duration of 7 days (range: 1 to 34 days).
Efficacy benefit of subsequent HSCT was captured in the EFS and OS estimations.	This assumption is questionable because subsequent HSCT rates were not one of primary or secondary outcomes of ELIANA trial. The benefit of subsequent SCT on EFS and OS is unknown because post-infusion HSCT was censored at time of HSCT in a full analysis test of ELIANA trial. According to clinical experts consulted by CADTH, subsequent HSCT is expected to delay progression and improve patient survival. None of these clinical benefits was however considered in the manufacturer's model.
In the base case, the observed data were used during the trial period. Afterwards, parametric survival models were used to project OS up to year 5. After year 5, the model estimated the OS of long-term survivors based on the literature reporting survival data of ALL long-term survivors and assumed there was no difference in mortality risk across treatment arms in the base case.	Appropriate.
EFS data are not reported for salvage chemotherapy in the literature and was estimated based on the OS data assuming a constant cumulative HR over time.	This assumption is questionable given that the ratio was based on OS and EFS observed the mitoxantrone arm in the UK ALL study. This ratio may vary by the type of salvage chemotherapy. CADTH

Assumption	Comment
	was unable to test whether the constant cumulative hazard assumption is appropriate.

AE = adverse event; ALL = acute lymphoblastic leukemia; CRS = cytokine release syndrome; EFS = event-free survival; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; MOHLTC = Ministry of Health and Long-Term Care; OS = overall survival; pCODR = CADTH pan-Canadian Oncology Drug Review; SCT = stem cell transplantation.

Manufacturer's Results

Table 13: Summary of Deterministic Results of the Manufacturer's Base Case

	Tisagenlecleucel	Salvage Chemotherapy	Clofarabine Monotherapy	Clofarabine Combination	Blinatumomab
Costs					
Pre-treatment	[redacted]	$0.00	$0.00	$0.00	$0.00
Drug/procedure	[redacted]	$0.00	$0.00	$0.00	$0.00
Outpatient administration	[redacted]	$0.00	$0.00	$0.00	$0.00
Hospitalization	[redacted]	$0.00	$0.00	$0.00	$0.00
Treatment	[redacted]	$13,594.72	$137,182.75	$100,900.70	$118,904.48
Drug/procedure	[redacted]	$8,737.38	$84,415.49	$43,232.30	$53,075.89
Outpatient administration	[redacted]		$0.00	$0.00	$5,321.83
Hospitalization	[redacted]		$42,728.00	$42,728.00	$41,856.00
Maintenance therapy	[redacted]	$4,857.34	$10,039.27	$14,940.40	$18,650.76
Adverse events	[redacted]	$13,370.73	$15,659.37	$28,507.89	$9,636.01
Follow-up	[redacted]	$10,374.67	$16,018.91	$40,879.07	$35,520.11
EFS	[redacted]	$723.68	$988.32	$1,641.30	$1,773.62
PD	[redacted]	$9,650.99	$15,030.59	$39,237.77	$33,746.49
Subsequent SCT	[redacted]	$163,963.92	$62,311.18	$152,039.27	$130,319.37
Rate of subsequent SCT	[redacted]	43.14%	16.39%	40.00%	34.29%
Terminal care	[redacted]	$31,676.24	$31,514.83	$29,908.70	$30,381.77
Total costs	$727,009.60	$232,980.27	$262,687.04	$352,235.63	$324,761.75
Incremental costs (vs. tisagenlecleucel)		$494,029.33	$464,322.56	$374,773.97	$402,247.85
Effectiveness					
Life-years (LYs)	14.42	0.97	1.20	4.57	3.65
EFS	12.74	0.68	0.79	3.49	2.72
PD	1.69	0.29	0.41	1.08	0.93
Quality-adjusted life-years (QALYs)	12.15	0.41	0.83	3.54	2.79
EFS	11.05	0.61	0.70	3.03	2.38
PD	1.24	0.21	0.30	0.79	0.68
Treatment and AE disutilities	–0.05	–0.16	–0.08	–0.05	–0.07
Subsequent SCT disutilities	–0.09	–0.25	–0.09	–0.23	–0.20
QALYs gained (vs. tisagenlecleucel)		**11.74**	**11.32**	**8.61**	**9.36**

AE = adverse event; EFS = event-free survival; HSCT = hematopoietic stem cell transplantation; PD = progressive disease; SCT = stem cell transplantation; vs. = versus.
Source: Manufacturer's economic submission.[3]

Additional CADTH Reanalyses

Table 14: Summary of Probabilistic Results of CADTH Revised Base Case (All Comparators)

	Total Costs ($)	Incremental Cost of Tisagenlecleucel ($)	Total QALYs	Total LYs	Incremental QALYs of Tisagenlecleucel	ICUR ($/QALY)
Tisagenlecleucel	$798,967	–	10.95	14.4	–	–
Salvage chemotherapy	$233,343	$565,624	0.35	0.97	10.60	$53,269
Clofarabine monotherapy	$264,208	$534,759	0.92	1.20	10.03	$51,295
Clofarabine combination	$346,596	$452,371	3.00	4.57	7.94	$54,393
Blinatumomab	$323,082	$475,885	2.47	3.65	8.48	$53,749

ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.

CADTH performed additional scenario analyses. The results are shown in Table 14. Varying a hazard ratio of OS and EFS used in salvage chemotherapy from 0.62 to 1.00 led to a slight change in ICUR. Changes in SCT rate (13.5 – 32.0% for tisagenlecleucel and 29.5 to 56.7% for salvage chemotherapy) caused noticeable variation in ICUR ($40,544 to $57,632). Extended IVIG duration from the manufacturer's base case (11.4 months) to the entire EFS had minimal impact on ICUR. Moreover, CADTH ran the revised base case asserting all EFS and OS curves (for all treatments) to a given curve estimate; Weibull, Gompertz, Exponential, Log-Logistic, and Cubic Splines. The results showed substantial variation due to the assumptions on OS and EFS data beyond the trial. Finally, CADTH tested the assumption on progression after year 5 by replacing the scenario with no progression after year 5 with predicted EFS from parametric models. The results showed a moderate increase in ICUR from $53,269 to $59,779 per QALY.

Table 15: Additional Scenario Analyses

Scenario	Comparator	Total Costs	Incremental Cost	Total QALYs	Total LYs	Incremental QALYs	ICUR ($/QALY)
HR EFS Lower Bound	Tisagenlecleucel	$793,909	$553,913	10.88	14.4	10.58	52,355
	Salvage chemotherapy	$239,996		0.30	0.97		
HR EFS Upper Bound	Tisagenlecleucel	$798,967	$573,698	10.88	14.4	10.49	54,690
	Salvage chemotherapy	$225,269		0.39	0.97		
SCT Rate Lower Bound	Tisagenlecleucel	$714,986	$432,200	10.93	14.40	10.66	40,544
	Salvage chemotherapy	$282,786		0.27	0.97		
SCT Rate Upper Bound	Tisagenlecleucel	$782,585	$599,944	10.83	14.40	10.41	57,632
	Salvage chemotherapy	$182,640		0.42	0.97		
Extended IVIG	Tisagenlecleucel	$814,444	$581,101	10.95	14.40	10.60	54,821
	Salvage chemotherapy	$233,343		0.35	0.97		
Weibull	Tisagenlecleucel	$797,316	$571,606	9.28	13.2	9.23	61,929
	Salvage chemotherapy	$225,710		0.05	0.58		
Gompertz	Tisagenlecleucel	$797,180	$566,620	11.41	16.93	11.16	50,772
	Salvage chemotherapy	$230,560		0.25	0.76		
Exponential	Tisagenlecleucel	$994,201	$768,281	7.94	11.97	7.89	97,374
	Salvage chemotherapy	$225,920		0.05	7.92		

Scenario	Comparator	Total Costs	Incremental Cost	Total QALYs	Total LYs	Incremental QALYs	ICUR ($/QALY)
Log-Logistic	Tisagenlecleucel	$788,511	$508,490	10.66	14.97	10.52	48,336
	Salvage chemotherapy	$280,021		0.14	0.70		
Cubic Splines	Tisagenlecleucel	$840,669	$608,785	11.63	17.05	11.33	53,732
	Salvage chemotherapy	$231,884		0.30	0.89		
EFS Assumption After Year 5	Tisagenlecleucel	$931,544	$691,888	12.00	14.40	11.57	59,779
	Salvage chemotherapy	$239,656		0.43	0.97		

HR = hazard ratio; EFS = event-free survival; ICUR = incremental cost-utility ratio; IVIG= intravenous immunoglobulin; LY = life-year; QALY = quality-adjusted life-year; SCT = stem cell transplantation.

Table 16: Additional Exploratory Analyses — Based on Achieving Trial Outcomes

Scenario	Comparator	Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICER
ORR at 3 months (ELIANA) (81.8%)	Tisagenlecleucel	$696,744	$463,401	10.95	14.40	10.60	$45,054
	Salvage chemotherapy	$233,343		0.35	0.97		
Average PFS over 12 months (72.6%)	Tisagenlecleucel	$655,281	$421,938	10.95	14.40	10.60	$40,911
	Salvage chemotherapy	$233,343		0.35	0.97		

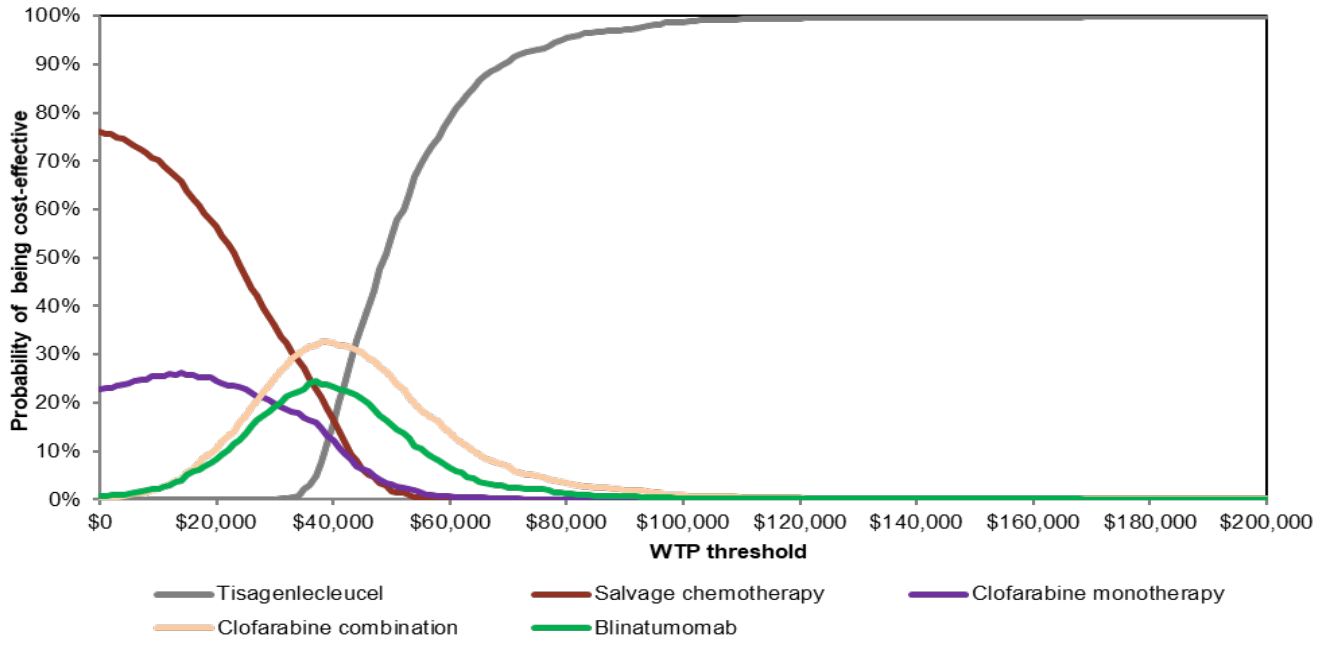
ICER = incremental cost-effectiveness ratio; LY = life-year; ORR = overall response rate; PFS = progression-free survival; QALY = quality-adjusted life-year.
Note: Exploratory analyses conducted using CADTH base case.

Table 17: Estimated the Proportion of Patients Who Survive at Each Time Interval, by Parametric Survival Models Used to Predict OS Data

		Years				
		5	10	20	50	70
Weibull	Tisagenlecleucel	0.36	0.15	0.03	0.00	0.00
	Salvage chemotherapy	0.00	0.00	0.00	0.00	0.00
Gompertz	Tisagenlecleucel	0.49	0.42	0.41	0.41	0.41
	Salvage chemotherapy	0.01	0.00	0.00	0.00	0.00
Exponential	Tisagenlecleucel	0.32	0.10	0.01	0.00	0.00
	Salvage chemotherapy	0.00	0.00	0.00	0.00	0.00
Log-Logistic	Tisagenlecleucel	0.42	0.27	0.15	0.07	0.05
	Salvage chemotherapy	0.00	0.00	0.00	0.00	0.00
Cubic Splines	Tisagenlecleucel	0.49	0.35	0.21	0.07	0.04
	Salvage chemotherapy	0.01	0.00	0.00	0.00	0.00

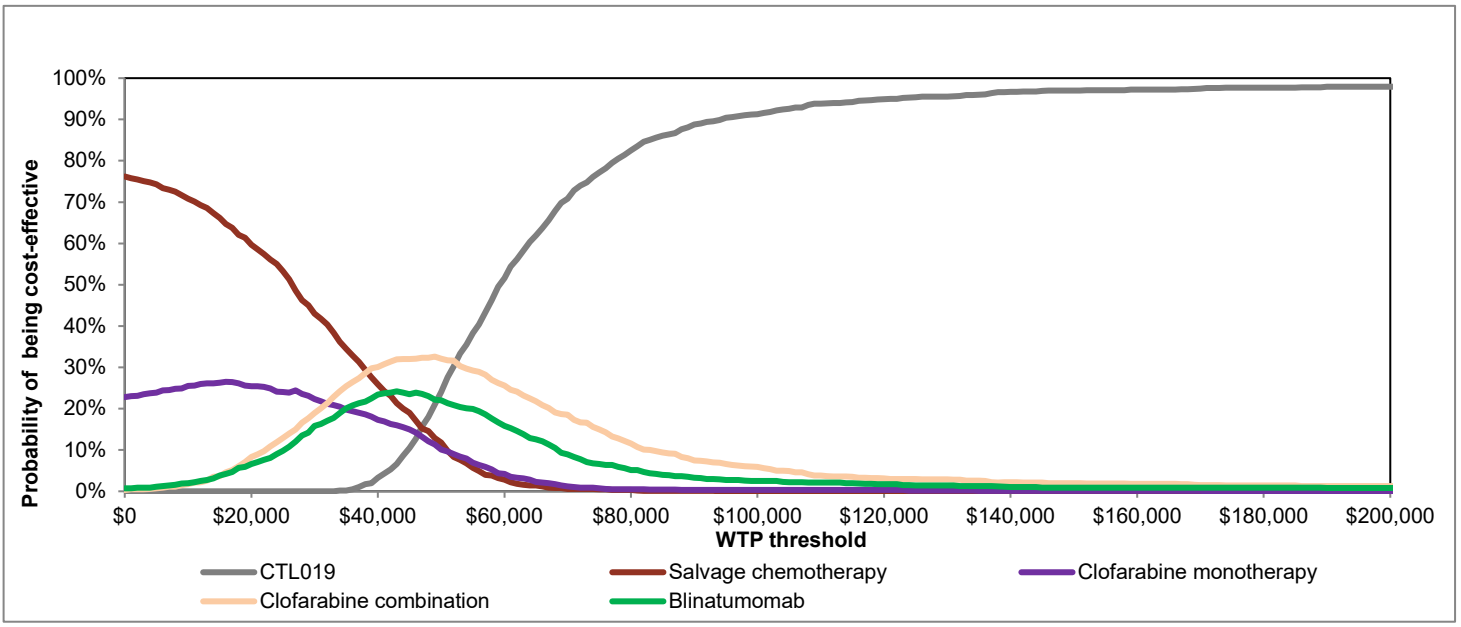
OS = overall survival.

Figure 2: Cost-Effectiveness Acceptability Curves the Manufacturer's Base Case



WTP = willingness to pay.
Source: Manufacturer's economic submission

Figure 3: Cost-effectiveness Acceptability Curves From the Revised Base Case



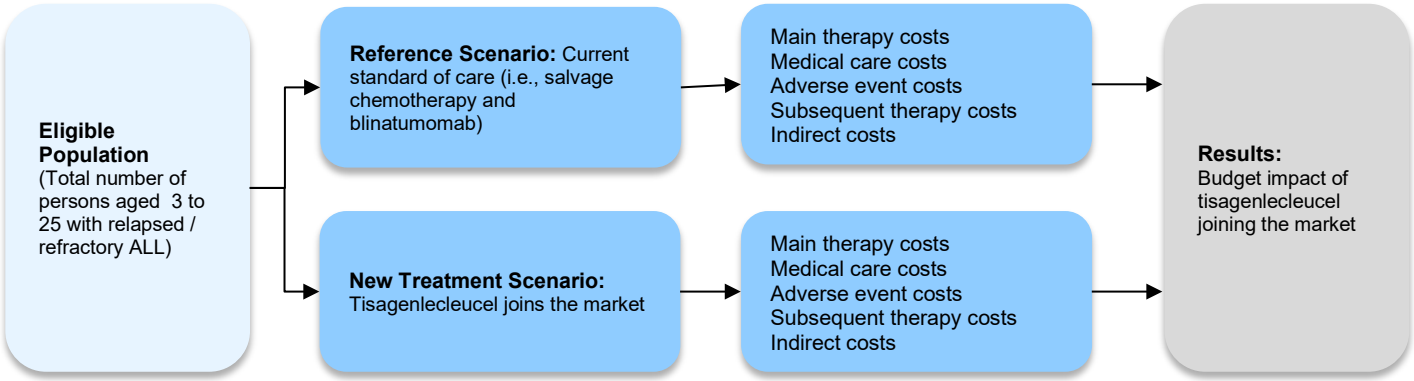
WTP = willingness to pay.

Appendix 3: Detailed Information — Budget Impact Submission

Methods

The submitted budget impact analysis (BIA) model was built in Microsoft Excel using an epidemiology-based approach and adopted a static analytic framework.[16] Two scenarios were compared in the model: 1) a Reference Scenario, where only treatment with salvage chemotherapy regimens and blinatumomab is available (i.e., current market where tisagenlecleucel is not available), and 2) a New Treatment Scenario, where tisagenlecleucel joins the market and also becomes available. For each scenario, the number of patients likely to receive treatment with available regimens was multiplied by the relevant per-patient costs to determine the total costs associated with each therapy. The budget impact was then calculated by subtracting the total costs of the Reference Scenario and the total costs of the New Treatment Scenario (Figure 4).

Figure 4: Schematic of Budget Impact Analysis Modelling Approach

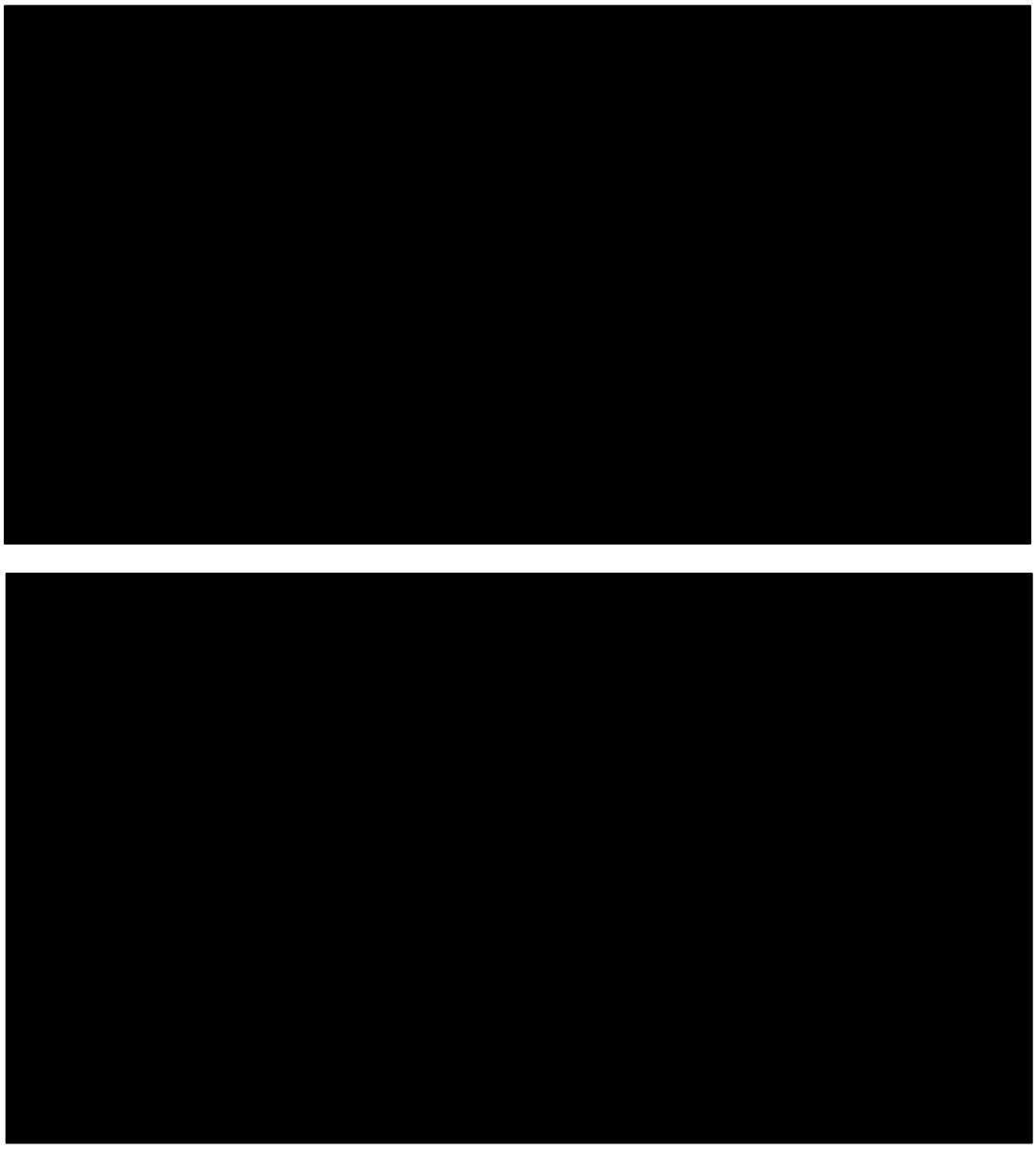


BIA = budget impact analysis.
Source: Manufacturer BIA submission.[16]

The population of patients eligible for treatment with tisagenlecleucel was estimated via a funnel-down approach (Figure 5). To arrive at the size of the modelled population for a given reimbursement year, the total projected population of Canada for each reimbursement year was filtered to include the proportion of persons three to 25 years old who are diagnosed with B-cell acute lymphoblastic leukemia (ALL) using estimates of disease prevalence (Year 1) or annual incidence (years 2+). The manufacturer's analysis considered the pediatric (ages three to 17) and young adult (ages 18 to 25) populations separately, constituting 16.04% and 10.54% of the total population, respectively. These two populations were further narrowed down to include only persons eligible to receive tisagenlecleucel; specifically, this included the following patient groups:

- refractory following first-line therapy
- relapse/refractory after second-line therapy.

Figure 5: Estimation of the Size of the Eligible Patient Population



ASCT = autologous stem cell transplantation; DLBCL = diffuse large B-cell lymphoma.
Source: Manufacturer's BIA submission.[16]

The market shares of treatment options in the Reference Scenario (Table 18) were assumed based on current availability of treatment options for B-cell ALL in pediatric and young adult age groups, with market shares estimated based on Canadian expert opinion and a survey of US leukemia are providers relating to current treatment patterns commissioned by the manufacturer.

Table 18: Market Shares in the Reference Scenario — Current Treatment Only

Comparators	Year 1	Year 2	Year 3
Tisagenlecleucel	0.0%	0.0%	0.0%
Salvage chemotherapy	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	**100.0%**	**100.0%**	**100.0%**

Source: Manufacturer's budget impact analysis submission.[16]

The potential uptake of tisagenlecleucel (Table 19) was estimated based on a survey of US leukemia care providers commissioned by the manufacturer. [redacted].

Table 19: Market Shares in the New Treatment Scenario — Tisagenlecleucel Joins the Market

Comparators	Year 1	Year 2	Year 3
Tisagenlecleucel	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	**100.0%**	**100.0%**	**100.0%**

Source: Manufacturer's budget impact analysis submission.[16]

Table 20 and Table 21 present the number of patients likely to receive tisagenlecleucel versus salvage chemotherapy, blinatumomab, and investigational therapy for the two budget scenarios according to the manufacturer's estimates and assumptions. Estimates of treated patients are the product of the total eligible patient population and the market share data in each reimbursement year.

Table 20: Number of Patients Receiving Salvage Chemotherapy Regimens in Reference Scenario

Comparators	Year 1	Year 2	Year 3
Tisagenlecleucel	0	0	0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Source: Manufacturer's budget impact analysis submission.[16]

Table 21: Number of Patients Receiving Tisagenlecleucel Versus Salvage Chemotherapy Regimens in the New Treatment Scenario

Comparators	Year 1	Year 2	Year 3
Tisagenlecleucel	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Source: Manufacturer's budget impact analysis submission.[16]

Annual budget costs in the analysis included the costs of main therapy (composed of drug acquisition costs and administration and hospitalization costs), routine monitoring medical costs, adverse event management costs, subsequent therapy costs (i.e., stem cell transplantation), and indirect costs (i.e., productivity loss). All costs were reported in 2017 Canadian dollars. The total aggregate and disaggregate costs for each comparator included in the analysis are presented below.

Table 22: Total Costs for Each Comparator

Comparator	Main Therapy [a]	Medical Costs [b]	AE Costs [c]	Subsequent Therapy Costs [d]	Indirect Costs [e] (Productivity Gains)	Total Costs
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event.

[redacted]

Source: Manufacturer's budget impact analysis submission.[16]

The following table summarizes the key assumptions made in the base-case analysis of this BIA:

Table 23: Base Case Assumptions

Parameter	Assumption
Persons eligible for treatment with tisagenlecleucel	It was assumed that persons eligible for treatment with tisagenlecleucel were persons diagnosed with B-cell ALL who (1) were refractory following first-line therapy, or (2) relapse/refractory after second-line therapy. [redacted]
Proportion of patients with public health coverage	[redacted]
Proportion of patients with B-cell ALL	[redacted]
Rate of diagnosis of B-cell ALL	[redacted]
Proportion of B-cell ALL patients who are relapsed/refractory following first-line therapy	[redacted]
Proportion of B-cell ALL patients who are relapsed/refractory following second-line therapy	[redacted]
Market shares in the Reference Scenario (Year 1 to Year 3)	[redacted]
Uptake of tisagenlecleucel in Year 1 to Year 3	[redacted]
Tisagenlecleucel pre-treatment	[redacted]
Salvage chemotherapy and blinatumomab pre-treatment	[redacted]
Main treatment with tisagenlecleucel	[redacted]
Main treatment with salvage chemotherapy or blinatumomab	[redacted]
Maintenance therapy	[redacted]

Parameter	Assumption
Medical resource use	[redacted]
Adverse events	[redacted]
Subsequent therapy	[redacted]
Productivity gains	[redacted]
Population growth	[redacted]

ALL = acute lymphoblastic leukemia.

Table 24: Summary of Sensitivity Analyses

Sensitivity Analysis Scenario	Scenario Description
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]

ALL = acute lymphoblastic leukemia; R/R =relapsed/refractory.
Source: Manufacturer's budget impact analysis submission.[16]

Table 25: Base Case Inputs Versus Sensitivity Analysis Inputs

	Sensitivity Analysis Scenario	Base-Case Inputs	Sensitivity Analysis Inputs
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]

	Sensitivity Analysis Scenario	Base-Case Inputs	Sensitivity Analysis Inputs
	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]

1L = first line; 2L = second line; pALL = pediatric acute lymphoblastic leukemia; R/R =relapsed/refractory; Y1 = year 1; Y2 = year 2; Y3 = year 3.
Source: Manufacturer's budget impact analysis submission.[16]

Manufacturer's Base Case

Results of the manufacturer's BIA base case revealed that the incremental expenditures associated with the reimbursement of tisagenlecleucel in Canadian patients aged 3 to 25 years with r/r B-cell ALL are expected to be $15,997,769 in Year 1, $5,710,309 in Year 2, and $6,163,222 in Year 3. Table 26 presents the net budget impact, by cost category, including the annual costs for each treatment in each reimbursement year for the two budget scenarios representing a world where tisagenlecleucel is not reimbursed and a world where tisagenlecleucel is available and joins the market.

Table 26: Summary of Results of the Manufacturer's Base Case, Costs by Category

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 15,997,769**	**$ 5,710,309**	**$ 6,163,222**	**$ 27,871,300**

AE = adverse event.
Source: Manufacturer's budget impact analysis submission.[16]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a number of sensitivity analyses to explore the impact of alternative assumptions on the net impact of reimbursing tisagenlecleucel for patients three to 25 years old with relapsed/refractory B-cell ALL (see Table 25).

Table 27 resents the absolute incremental budget impact over three years associated with the alternative inputs tested in sensitivity analysis by the manufacturer. Results of the manufacturer's sensitivity analyses revealed that the budget impact model results were most sensitive to the percentage of patients with relapsed/refractory B-cell ALL (according to estimates of prevalence/incidence), the proportions of patients relapsed/refractory, and the market share of tisagenlecleucel.

Table 27: Sensitivity Analysis Results — Incremental Budget Impact

		Year 1	Year 2	Year 3	Three-Year Total
	Base Case	**$ 15,997,769**	**$ 5,710,309**	**$ 6,163,222**	**$ 27,871,300**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1L = first line; 2L = second line; pALL = pediatric acute lymphoblastic leukemia; R/R =relapsed/refractory; Y1 = year 1; Y2 = year 2; Y3 = year 3.
Source: Manufacturer's budget impact analysis submission.[16]

CADTH Reanalyses

Table 28: Scenario Analysis — 100% Increase in Tisagenlecleucel Usage and Costs Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 31,159,485**	**$ 11,880,211**	**$ 13,536,965**	**$ 56,576,662**

AE = adverse event.

Table 29: Scenario analysis — Commercialization Constraints With Tisagenlecleucel Treatment Sites Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 6,009,763**	**$ 5,514,709**	**$ 6,283,762**	**$ 17,808,234**

Table 30: Scenario Analysis — Tisagenlecleucel-Related Production Failure Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 14,499,904**	**$ 5,528,395**	**$ 6,299,356**	**$ 26,327,655**

AE = adverse event.

Table 31: Exploratory Analysis — Alternative Inputs for Bridging Chemotherapy: 25% Increase in Pre-Treatment Costs Associated With Tisagenlecleucel Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 14,091,999**	**$ 5,372,872**	**$ 6,122,145**	**$ 25,587,016**

AE = adverse event.

Table 32: Exploratory Analysis — Reimbursement for Patients Who Experienced ORR at Three Months[a] Post Tisagenlecleucel, Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 11,947,212**	**$ 4,555,127**	**$ 5,190,362**	**$ 21,692,700**

AE = adverse event; ORR = overall admission rate.
[a] ORR estimate at 3 months (n [%] = 63 [81.8]) was sourced from the ELIANA trial full analysis set (N = 77).[4]

Table 33: Exploratory Analysis — Reimbursement for Patients Who Experienced PFS Over 12 Months[a] Post Tisagenlecleucel, Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Indirect costs	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
; AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel joins the market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 10,673,372**	**$ 4,069,448**	**$ 4,636,953**	**$ 19,379,773**

AE = adverse event.
[a] Estimate of average PFS over 12 months (72.6%) was sourced from the ELIANA trial.[4]

CADTH Reanalyses — Public Payer Perspective

Table 34: Scenario Analysis From the Public Payer Perspective — 100% Increase in Tisagenlecleucel Usage and Costs Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 30,791,966**	**$ 11,740,087**	**$ 13,377,300**	**$ 55,909,353**

AE = adverse event.

Table 35: Scenario Analysis From the Public Payer Perspective — Commercialization Constraints Associated With Tisagenlecleucel Treatment Sites 100% Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 5,787,663**	**$ 5,374,584**	**$ 6,124,097**	**$ 17,286,344**

AE = adverse event.

Table 36: Scenario Analysis From the Public Payer Perspective — Tisagenlecleucel-Related Production Failure Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 14,132,385**	**$ 5,388,270**	**$ 6,139,691**	**$ 25,660,346**

AE = adverse event.

Table 37: Exploratory Analysis From the Public Payer Perspective — Alternative Inputs for Bridging Chemotherapy: 25% Increase in Pre-Treatment Costs Associated With Tisagenlecleucel Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 13,724,480**	**$ 5,232,748**	**$ 5,962,480**	**$ 24,919,707**

AE = adverse event.

Table 38: Exploratory Analysis From the Public Payer Perspective — Reimbursement for Patients Who Experienced ORR at Three Months[a] Post Tisagenlecleucel, Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 11,579,693**	**$ 4,415,002**	**$ 5,030,696**	**$ 21,025,392**

AE = adverse event; ORR = overall response rate.

[a] ORR estimate at three months (n [%] = 63 [81.8]) was sourced from the ELIANA trial full analysis set (N = 77).[4]

Table 39: Exploratory Analysis From the Public Payer Perspective — Reimbursement for Patients Who Experienced PFS Over 12 Months[a] Post Tisagenlecleucel, Applied to CADTH Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	3-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	**$ 0**	**$ 0**	**$ 0**	**$ 0**
Main therapy	$ 0	$ 0	$ 0	$ 0
Medical Costs	$ 0	$ 0	$ 0	$ 0
AEs	$ 0	$ 0	$ 0	$ 0
Subsequent therapy	$ 0	$ 0	$ 0	$ 0
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
New Treatment Scenario: Tisagenlecleucel Joins the Market				
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 10,305,853**	**$ 3,929,324**	**$ 4,477,287**	**$ 18,712,464**

AE = adverse event.

[a] Estimate of average PFS over 12 months (72.6%) was sourced from the ELIANA trial.[4]

References

1. PrKymriah™ (tisagenlecleucel) cell suspension in infusion bag, 2.0 x 10^6 to 6.0 x 10^8 CAR-positive viable T-cells, for intravenous use [product monograph]. Dorval (QC): Novartis Pharma Canada Inc; 2018 Sept 5.
2. Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
3. Cost-effectiveness model of tisagenlecleucel in pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia - A Canadian perspective. In: Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
4. Clinical study report: B2202. A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2017 Sep 22.
5. Clinical study report: B2205J. A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2016 Nov 23.
6. Clinical study report: B2101J. A phase I/IIA study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR zeta and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2017 Sep 27.
7. von Stackelberg A, Volzke E, Kuhl JS, Seeger K, Schrauder A, Escherich G, 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.* 2011;47(1):90-97.
8. Kelly MJ, Pauker SG, Parsons SK. Using nonrandomized studies to inform complex clinical decisions: the thorny issue of cranial radiation therapy for T-cell acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2015;62(5):790-797.
9. Lin JK, Lerman BJ, Barnes JI, Boursiquot BC, Tan YJ, Robinson AQL, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. *J Clin Oncol.* 2018:Jco2018790642.
10. Budget impact analysis of tisagenlecleucel (Kymriah) for patients with relapsed/refractory diffuse large B-cell lymphoma. In: Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
11. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. *Pediatr Blood Cancer.* 2007;48(4):460-467.
12. Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet.* 2010;376(9757):2009-2017.
13. Sung L, Buckstein R, Doyle JJ, Crump M, Detsky AS. Treatment options for patients with acute myeloid leukemia with a matched sibling donor: a decision analysis. *Cancer.* 2003;97(3):592-600.
14. Jaime-Perez JC, Heredia-Salazar AC, Cantu-Rodriguez OG, Gutierrez-Aguirre H, Villarreal-Villarreal CD, Mancias-Guerra C, et al. Cost structure and clinical outcome of a stem cell transplantation program in a developing country: the experience in northeast Mexico. *Oncologist.* 2015;20(4):386-392.
15. Maziarz RT, Hao Y, Guerin A, Gauthier G, Gauthier-Loiselle M, Thomas SK, et al. Economic burden following allogeneic hematopoietic stem cell transplant in patients with diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2018;59(5):1133-1142.
16. Budget impact analysis of tisagenlecleucel (Kymriah) for patients aged 3-25 with relapsed/refractory B-cell acute lymphoblastic leukemia. In: Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
17. Novartis oncology [slide deck] In: Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
18. Raetz EA, Borowitz MJ, Devidas M, Linda SB, Hunger SP, Winick NJ, et al. Reinduction platform for children with first marrow relapse of acute lymphoblastic leukemia: A Children's Oncology Group study [corrected]. *J Clin Oncol.* 2008;26(24):3971-3978.