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CADTH OPTIMAL USE REPORT

Tisagenlecleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report

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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.

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Abbreviations

AE	adverse event
ASCT	autologous stem cell transplantation
BIA	budget impact analysis
CAR	chimeric antigen receptor
CAR T-cell therapy	chimeric antigen receptor modified T-cell therapy
CI	confidence interval
CRS	cytokine release syndrome
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
DSA	deterministic sensitivity analysis
EFS	event-free survival
FACT	Foundation for the Accreditation of Cellular Therapy
G-CSF	granulocyte-colony stimulating factor
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICU	intensive care unit
ICUR	incremental cost-utility ratio
IVIG	intravenous immunoglobulin
MAIC	matching-adjusted indirect comparisons
QALY	quality-adjusted life-year
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
R-CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab
RCT	randomized controlled trial
R-DHAP	rituximab, dexamethasone, high-dose cytarabine, cisplatin
R-GDP	gemcitabine, cisplatin, and dexamethasone with or without rituximab
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
r/r	relapsed or refractory
SCT	stem cell transplantation
WTP	willingness to pay

Treatment	Tisagenlecleucel (Kymriah)
Indication	For the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
Reimbursement Request	As per indication
Dosage Form	Single-dose, one-time intravenous treatment. The recommended dose is 0.6 to 6.0 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells (non-weight based).
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 adult patients aged 18 years or older with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).[1] Tisagenlecleucel is recommended as a single, one-time treatment (0.6 to 6.0 x 10^8 CAR-positive viable T cells). 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). Before 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]

This 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 (BIA). 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 in adult patients aged 18 years or older with relapsed or refractory (r/r) DLBCL.[3] The base-case analysis was conducted from the perspective of the Canadian health care system over a 20-year time horizon with future costs and benefits discounted at 1.5%. The structure of the model was based on three health states (progression free, progressive disease, and death) partitioned survival model. Partitioned survival models estimate progression-free survival (PFS) and overall survival (OS) based on trial data while progressive disease (PD) is derived as the difference between the OS and the PFS curves. PFS was defined as the time from date of treatment to death due to any cause or to disease progression. The cycle length was 1 month.

OS and PFS for tisagenlecleucel were estimated by fitting parametric curves to the pooled trial data (JULIET and UPenn).[4,5] For salvage chemotherapy, the OS data were based on the parametric survival model fitted using SCHOLAR-1 study,[6] while the PFS was derived

from OS based on the assumption that cumulative hazard ratio between OS and PFS is constant. In the base case, 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 PFS data.

Scenario analyses were undertaken by: 1) using the JULIET data for tisagenlecleucel; and 2) deriving the comparative OS between tisagenlecleucel and salvage chemotherapy using the matching-adjusted indirect comparison (MAIC) approach. Health utility values were assumed to be dependent on health state but independent of treatment arm and based on health utility estimates from patients aged 65 to 90 with aggressive Non-Hodgkin lymphoma (NHL) who were entered into a randomized multicenter study comparing cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) with CHOP plus G-CSF.[7] Health utility decrements due to treatment were based on a published cost-effectiveness study that estimated computed tomography (CT) in the follow-up of patients with complete response after treatment for Hodgkin's disease. Costs (pre-treatment, treatment, adverse event, subsequent HSCT, follow-up, post-progression medical care, and terminal care) were based on Canadian sources. Resource use among patients receiving tisagenlecleucel was obtained from JULIET trial. For salvage chemotherapy, the manufacturer used the cost of the R-GDP regimen containing the rituximab, gemcitabine, cisplatin, and dexamethasone. The proportions of subsequent stem cell transplant (SCT) for tisagenlecleucel and salvage chemotherapy were based on JULIET and SCHOLAR-1, respectively.

The manufacturer reported that tisagenlecleucel was associated with a gain of 2.81 years in life expectancy and 2.98 quality-adjusted life-years (QALYs), at an additional $392,638 compared with salvage chemotherapy, over a 20-year time horizon. This results in an incremental cost-utility ratio (ICUR) of $131,716 per QALY.

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

Firstly, the manufacturer's economic model was based on two single-arm trials and one international cohort study. Despite the lack of comparative evidence, PFS and OS data used in the base-case analysis were not adjusted for potential difference in baseline characteristics and risk factors between studies. The difference in study design, setting and patient characteristics between the studies increases the uncertainty in the cost-effectiveness results. Although the results of the matching-adjusted indirect comparison (MAIC) were provided by the manufacturer, the validity of these results was questionable given that limited patient characteristics were presented in the SCHOLAR-1 study and the manufacturer did not report baseline characteristics before and after matching in the MAIC report. CADTH was unable to assess how well the MAIC approach could balance observed the cross-study differences.

Secondly, it is unclear whether salvage chemotherapy regimens used in the SCHOLAR-1 study represented standard practices in Canada. The SCHOLAR-1 study pooled data from randomized controlled trials (RCTs) and observational studies but the specific salvage chemotherapy regimens was not reported in the publication. Although several salvage chemotherapy regimens are available for r/r DLBCL, the clinical expert consulted by CADTH suggested that PFS and OS data derived from the SCHOLAR-1 study are acceptable given that more than 50% of SCHOLAR-1 participants were part of the LY.12 and CORAL studies that used treatments widely available in Canada (R-GDP, R-ICE, or R-DHAP). CADTH

believed that it would be more appropriate to derive PFS and OS data from the LY.12 and CORAL studies as opposed to the SCHOLAR-1 study.

Thirdly, 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 JULIET trial, nearly 90% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. CADTH considered the cost of bridging therapy (from Lin et al.) in a revised base case.[8]

Additionally, the impact of subsequent SCT was partially accounted in the manufacturer's economic model. Only additional costs and health utility decrement were taken into account. The model did not consider the possibility that subsequent SCT may slow disease progression and improve survival. Although clinical experts consulted by CADTH, suggested that the benefit of subsequent SCT was less relevant in r/r non-Hodgkin's lymphoma, from the economic modelling perspective, the omission of the benefits of SCT may underestimate the ICUR because the greater proportion of patients in the salvage chemotherapy option received subsequent SCT and would incur higher costs and larger health utility decrements.

Finally, the manufacturer's economic model may underestimate the uncertainty in the cost-effectiveness results. Nearly all parameter values used variance estimates assuming a fixed 25% variance from the mean value. 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, accounting for most of these limitations, suggested that tisagenlecleucel was associated with an additional cost of $398,520 and a gain of 2.10 life-years and 1.97 QALYs, resulting in an ICUR of $211,870 per QALY. The probability that tisagenlecleucel is cost-effective was 0% at a willingness-to-pay (WTP) threshold of $50,000 per QALY and 1.8% and at a WTP threshold of $100,000 per QALY. 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 BIA that assessed the financial impact of the potential reimbursement of tisagenlecleucel (Kymriah) for adult patients with relapsed/refractory (r/r) DLBCL in Canada.[9] 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 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 ((R)-GDP, (R)-ICE, (R)-DHAP, investigational therapy), 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.

The total number of adult r/r DLBCL patients expected to receive tisagenlecleucel or other treatment in the Reference Scenario and the New Treatment Scenario was estimated by combining 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 Canadian DLBCL 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 (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 adult patients with r/r DLBCL in Canada are expected to be $56,721,130 in Year 1, $59,026,762 in Year 2, and $75,971,344 in Year 3.

CADTH identified a number of key sources of uncertainty and potential limitations relating to the manufacturer's BIA. The inclusion of investigational therapy (i.e., patients entering clinical trials) as relevant comparator in the manufacturer's BIA may be problematic as patients entering trials are not receiving approved regimens in the treatment of r/r DLBCL. The inclusion of investigational therapy does 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 caregivers and the cost of travel and accommodation for patients, families and/or caregivers that do not live near the designated treatment facilities.

CADTH attempted to account for some of the important shortcomings by: removing investigational therapy as relevant comparator and adjusting the market shares accordingly; considering the costs of bridging therapy associated with tisagenlecleucel; assuming drug wastage for comparators; and, including out-of-pocket costs as a one-time cost for patients receiving tisagenlecleucel. CADTH found that the incremental expenditures associated with the reimbursement of tisagenlecleucel in adult patients with r/r DLBCL in Canada are expected to be $117,629,787 in Year 1, $122,411,266 in Year 2, and $157,551,391 in Year 3; the cumulative three-year net budget impact of reimbursing tisagenlecleucel was predicted to be $397,592,444.

Conclusions

A key limitation of the manufacturer's economic evaluation was the uncertainty associated with the short- and long-term comparative efficacy and safety of tisagenlecleucel and salvage chemotherapy. The lack of transparency in the manufacturer's economic model made both the assessment of validity and the ability to conduct reanalysis challenging. Results may warrant careful interpretation.

CADTH found that tisagenlecleucel was more expensive and associated with life-years and QALY gained with an ICUR of $211,870 per QALY. At a price reduction of 70%, for the ICUR be less than $50,000per QALY. The estimated ICUR of tisagenlecleucel was highly sensitivity to assumptions regarding the long-term PFS and OS outcomes, the relative impact of tisagenlecleucel and salvage chemotherapy on OS, and the analysis time horizon.

CADTH estimated that the incremental expenditures associated with the reimbursement of tisagenlecleucel in adult patients with r/r DLBCL in Canada to be $117,629,787 in Year 1, $122,411,266 in Year 2, and $157,551,391 in Year 3. In scenario analyses, CADTH considered a situation where re-treatment with tisagenlecleucel may be necessary, and the cumulative three-year net budget impact of reimbursing tisagenlecleucel may be greater than $840 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 $78 million. Where tisagenlecleucel-related production failure is accounted for in the analysis, the cumulative three-year budget impact of funding tisagenlecleucel was estimated at approximately $381 million. However, these 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 the cost-effectiveness of tisagenlecleucel and salvage chemotherapy (which was assumed to consist of rituximab, gemcitabine, cisplatin, and dexamethasone), in adult patients with r/r DLBCL who are ineligible for or relapse after auto subsequent stem cell transplant (SCT).[3] The modelled patients were assumed on average to be 54 years at the time of entry into the model; patients were also predominantly male (61%). The average body surface area was 1.92 m^2 and the average body weight was 78.7 kg. The model was run using a monthly cycle over a 20-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 DLBCL among patients receiving treatment with tisagenlecleucel or salvage chemotherapy. The partitioned survival model consists of three mutually exclusive health states including progression-free survival (PFS), progressive disease (PD) and death (Figure 1) to simulate the health system costs and health outcomes in terms of life expectancy and quality-adjusted life-years (QALYs) over 20 years. At the start of the model, patients were assumed to stay in the PFS 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, which was based on the overall survival (OS) curve and the proportion of PFS patients. At any point, patients could transition to death. The effects of subsequent SCT, including both allogeneic SCT (allo SCT) and autologous SCT (auto SCT) on costs and health utilities were added separately for each treatment arm.

Model Inputs

OS and PFS inputs for tisagenlecleucel in the base case were based on pooled data from the JULIET (NCT02445248) and UPenn (NCT02030834) trials.[4,5] The manufacturer claimed that the characteristics of patients enrolled in both studies were similar. Individual patient data from JULIET trial were combined with data extracted from the published Kaplan-Meier (K-M) curves of the UPenn trial without a meta-analysis. Because both studies are single-arm trials, the efficacy of salvage chemotherapy was obtained from a large international multi-cohort retrospective study that deemed to have a comparable population to that of JULIET trial. The study reported OS data of mixed but unspecified salvage chemotherapy regimens among patients with refractory DLBCL. In the base-case analysis, the observed OS data from pooled JULIET and UPenn trials was used for tisagenlecleucel and the observed OS data from SCHOLAR-1 study were used for salvage chemotherapy until 39 months. Long-term OS data based on the SCHOLAR-1 study was used for extrapolation beyond the trial period (i.e., 39 months) for both treatments. For PFS, the manufacturer used data from pooled JULIET and UPenn trials for tisagenlecleucel until 39 months. For salvage chemotherapy, PFS was derived based on OS data assuming a constant cumulative HR over time because SCHOLAR-1 did not report PFS data. The ratios were estimated based on the R-ICE and R-DHAP arms from Gisselbrecht et al.[10] The manufacturer calculated the

natural log of OS probability divided by the natural log of PFS probability at yearly intervals until the end of the observed period. The overall cumulative HR between OS and PFS was then calculated as the average of cumulative HRs at all yearly intervals. For both treatment options, the manufacturer used parametric survival models to predict OS and PFS (for tisagenlecleucel) data beyond the trial. A model averaging approach was used to weight all plausible survival functions. 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 spline with two knots and spline with three knots fitted best to tisagenlecleucel OS and PFS data, respectively.

Health utility values used in the base case were based on health utility estimates obtained from a randomized multicenter study comparing CHOP with CHOP plus G-CSF in patients aged 65 to 90 with aggressive NHL. Health utility decrements due to treatment were obtained from a study by Guadagnolo et al. that evaluated follow-up strategies for patients with Hodgkin's disease. To capture short-term adverse events (AEs) associated with treatments (except for the cytokine release syndrome [CRS]), a disutility of 0.15 was applied over the duration of induction chemotherapy for salvage chemotherapy and for the duration of the hospitalization starting from the pre-treatment lymphodepleting regimen for tisagenlecleucel. For tisagenlecleucel, additional treatment disutilities were considered for grade 3 or 4 CRS and intensive care unit (ICU) stays not due to CRS. The CRS rate was derived from JULIET trial data. Patients were assumed to have a utility of 0 (a disutility of –0.83 based on PFS utility) for the duration of the CRS-related or non-CRS-related ICU stay as shown by JULIET trial. Depending on the type of SCT, the additional utility decrement was applied for patients receiving subsequent SCT. The disutility associated with SCT was assumed to last for 365 days.

Costs included were those for pre-treatment (for tisagenlecleucel), treatment, subsequent SCT, disease management during the pre- and post-progression states, AEs and terminal care costs. Pre-treatment cost is only considered for tisagenlecleucel 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). For salvage chemotherapy, the cost of R-GDP regimen was used in the base-case analysis. All costs were reported in 2017 Canadian dollars.

Manufacturer’s Base Case

The manufacturer reported that over a 20-year time horizon tisagenlecleucel was associated with additional $396,939, 3.29 life-years, and 2.86 QALYs gained when compared with salvage chemotherapy. This resulted in an incremental cost-effectiveness ratio of $143,018 per 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	562,004	396,939	4.49	6.73	2.86	$139,024
Salvage chemotherapy	165,065		1.64	3.44		

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 sensitivity analyses (DSAs) and probabilistic sensitivity analyses (PSAs).

DSAs were performed to determine the impact of individual model parameter inputs on the base-case results, where the manufacturer considered several parameters (e.g., cumulative hazard ratio of PFS and OS for salvage chemotherapy, subsequent SCT rates, costs, utility values, body surface area, and discount rates).

Moreover, a series of scenario analysis were conducted by:

1. replacing the base-case utility values with JULIET trial data
2. extending a time horizon from 20 years to lifetime
3. changing the cost of a comparator from the cost of R-GDP alone to the weighted average cost of three common salvage chemotherapy regimens (R-GDP, R-ICE, R-DHAP) or R-ICE
4. using alternative data sources for allogeneic SCT procedure and follow-up costs
5. using alternative parametric survival models and assumptions to extrapolate long-term PFS and OS data.

The parameters that had the largest impact on the manufacturer's base case were: parametric survival models for OS (ICURs ranging from $213,066 per QALY for gamma distribution to $537,718 per QALY for exponential distribution) and PFS data (ICURs ranging from $193,684 per QALY for gamma distribution to $463,646 per QALY for exponential distribution) data, the cost of tisagenlecleucel (ICURs ranging from $91,253 to $172,179 per QALY) and the cumulative hazard ratio of PFS vs OS for salvage chemotherapy(ICURs ranging from $113,793 to $158,704 per QALY).

In addition to a DSA, key variables used in the model were included as part of PSAs, and the inputs for these variables were drawn randomly and simultaneously, based on specified distributions, to calculate a corresponding ICUR value. The process was repeated 1,000 times, and the results of the PSA were expressed by a cost-effectiveness acceptability curve.

PSA results revealed that tisagenlecleucel continued to be more expensive and more effective than salvage chemotherapy (100% of the simulations) and resulted in an incremental cost-effectiveness ratio of $139,024 per QALY gained. At the WTP threshold of $50,000 per QALY gained, the probability that tisagenlecleucel being cost-effective was 1%.

This probability increased to 17% and 63% if the WTP values increase to $100,000 and $150,000 per QALY gained, respectively.

As scenario analysis, the manufacturer conducted a cost-utility analysis from a societal perspective. Compared with salvage chemotherapy, tisagenlecleucel was associated with an additional $316,485 and 2.86 QALYs gained, resulting in an ICUR of $110,846 per QALY. It should be noted that this scenario analysis underestimated the ICUR because the manufacturer only considered productivity gains but did not capture any patient-related costs, such as parking fees, travels, accommodations, and informal care costs.

Limitations Identified With the Manufacturer's Economic Submission

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

Lack of head-to-head comparative efficacy and safety of tisagenlecleucel and salvage chemotherapy. PFS and OS data were derived from two data sources: pooled JULIET and UPenn trials as well as the SCHOLAR-1 study. Despite the lack of comparative efficacy and safety evidence, the manufacturer did not adjust for potential difference in baseline characteristics and risk factors between the two data sources. The difference in study design, setting and patient characteristics between the studies increases the uncertainty in the cost-effectiveness results. Although the manufacturer submitted partially OS hazard ratio (HR) based on matching-adjusted indirect comparison (MAIC) approach, the validity of the HR estimate is questionable because the manufacturer did not report patient characteristics before and after matching and the SCHOLAR-1 study reported limited data regarding patient baseline characteristics. CADTH was therefore unable to assess how well the MAIC approach could balance observed cross-study differences.

The salvage chemotherapy regimens used in the SCHOLAR-1 study were not specified. The submitted model derived PFS and OS data for salvage chemotherapy from the SCHOLAR-1 study. Although this international study pooled data from large observational studies and RCTs, the name of salvage chemotherapy regimens was not reported in the publication. The clinical expert consulted by CADTH suggested that PFS and OS data derived from the SCHOLAR-1 study are acceptable given that more than 50% of SCHOLAR-1 participants were part of the LY.12 and CORAL studies that used treatments widely available in Canada (R-GDP, R-ICE, or R-DHAP). CADTH believed that it would be more appropriate to derive PFS and OS data from the LY.12 and CORAL studies as opposed to the SCHOLAR-1 study.

The total cost of tisagenlecleucel was underestimated. The pre-treatment cost considered in the manufacturer's model only considered costs associated with leukapheresis, cryopreservation and lymphodepleting regimens. According to JULIET trial, nearly 90% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. The most frequently used (≥ 15% of patients) bridging therapies were rituximab (54.5%), gemcitabine (38.4%), dexamethasone (25.3%), etoposide (22.2%), cytarabine (19.2%), cisplatin (18.2%), and cyclophosphamide (15.2%). CADTH included the cost of bridging therapy in a revised base case.[8]

The impact of subsequent SCT was partially accounted in the model. Although the manufacturer claimed that the efficacy benefit of subsequent SCT were captured in the PFS and OS estimations, the manufacturer's model only accounted for the additional costs and disutilities associated with subsequent SCT. Although clinical experts consulted by CADTH

suggested that the benefit of subsequent SCT was less relevant in r/r non-Hodgkin's lymphoma, from the economic modelling perspective, the omission of the benefits of SCT may underestimate the ICUR because the greater proportion of patients in the salvage chemotherapy option received subsequent SCT and would incur higher costs and larger health utility decrements.

Probabilistic and uncertainty analyses were 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:

Model parameters were assumed to be independent. The manufacturer assumed independence of treatment effects from secondary outcomes, including SCT rate, adverse event, 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 PFS and OS), the model will still assume the same percentage of patients receive subsequent SCTs.

The base-case deterministic model applies the expected mean values for their primary effect of interest, PFS, and the other secondary features of the model, including SCT 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 SCT rate, AEs, intensity of management or terminal care, etc. 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 these characteristics were different between tisagenlecleucel and salvage chemotherapy. CADTH observed younger age (55 vs 56), fewer previous regimen (2 vs 3%) and larger percentage of DLBCL (87 vs 79%) among patients receiving salvage chemotherapy compared with 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 non-probabilistic: The reference case results of the model use 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.

There is a lack of consistency in the use of progression-free survival definitions. The manufacturer used PFS data to represent the proportion of r/r DLBCL patients who did not experience disease progression but used event-free survival (EFS) for r/r B-cell ALL patients. . Due to time constraints, CADTH was unable to test the effect of replacing PFS with EFS data. CADTH believed that the use of PFS as opposed to EFS in the DLBCL model may underestimate ICUR of tisagenlecleucel because the progression-free probabilities were higher than event-free probabilities (Appendix 2, Figure 3).

CADTH Reanalyses

As noted in the limitations, CADTH identified important limitations with 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. Therefore, CADTH revised base case was based on:

- probabilistic analysis involving a run of 5,000 iterations
- PFS, OS and health utility data derived from JULIET trial as opposed to the pooled JULIET and UPenn studies because clinical experts believe that it is inappropriate to pool patient-level data and pseudo patient-level data extracted from a published K-M curves. More importantly, UPenn trial was not considered as part of Health Canada submission
- cost of bridging therapy (C$19,816.24) obtained from the most recent cost-effectiveness of CAR T-cell therapy.[8]

CADTH reanalysis, accounting for most of these limitations, suggested that tisagenlecleucel was associated with an additional cost of $416,750 and a gain of 2.10 life-years and 1.97 QALYs, resulting in an ICUR of $211,870 per QALY. The probability that tisagenlecleucel was cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 0%, and at a willingness-to-pay threshold of $100,000, it was 1.8%.

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	581,530	416,750	4.11	5.12	1.97	$211,870
Salvage chemotherapy	164,780		2.14	3.01		

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 (Table 3).

Given the significant variation in estimated PFS and OS curves over time, CADTH randomly selected predicted PFS 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 scenario showed a significant decrease in the probability of tisagenlecleucel being cost-effective compared with salvage therapy due to a much larger variance in expected outcomes. CADTH also performed scenario analysis on the impact of infusion locations on the overall cost-effectiveness of the treatment (Scenario D and E). Increasing inpatient infusion to 100% had a minor effect on the ICUR due to the base case asserting the vast majority of patients will be hospitalized. Assuming 100% outpatient infusion had the overall impact of lower expected cost but did not differentiate QALY or LY outputs, leading to a moderate improvement in the odds of tisagenlecleucel being cost-effective.

Three scenarios were run examining changes in utility calculations; disutility was applied to the proportion of patients who acquired CRS as an adverse event (Scenario B), 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 utility standard errors from the original study

were applied instead of fixed 10% of mean estimates (Scenario J). Each of these scenarios had relatively small effects on the estimated ICUR.

Two scenarios were run examining changes in the OS HR; the manufacturer model excluded an OS HR from its base case, but reported a pooled estimate of 0.67 (95% CI, 0.48 to 0.95) for overall survival for tisagenlecleucel compared with salvage chemotherapy, which was incorporated into the revised probabilistic analysis (Scenario G), and the MAIC reported OS HR for tisagenlecleucel versus salvage chemotherapy which was different from that was used in the manufacturer's model, with an HR of 0.41 (95% CI, 0.31 to 0.54) (Scenario I). Including the manufacturer assigned HR had moderate impact on the ICUR calculation, though the probability that tisagenlecleucel is cost-effective was slightly higher than the base-case results. Using the MAIC HR significantly impacted the long-term expected QALYs with relatively small increases in expected costs, leading to a lower estimated ICUR and a higher likelihood that the treatment would be cost-effective. The estimated ICUR was however associated with high uncertainty as the MAIC approach adjusted for limited patient characteristics.

Additionally, CADTH tested whether assigning a limit of five to the number of years in PFS had a notable impact on the cost-effectiveness of tisagenlecleucel (Scenario J). The analysis showed that applying no limit to PFS had minimal impact on the overall cost-effectiveness of the treatment. This is most likely due to progression rates above five years being low.

Moreover, CADTH assessed the impact of a time horizon on the cost-effectiveness of tisagenlecleucel compared with salvage chemotherapy. Reducing an analytical time horizon from 20 to 10, 5, and 1 years lead to a substantial increase in ICURs (Scenario K to M).

CADTH tested the effect of including productivity loss and direct non-medical costs such as travel and accommodation time for patients and one caregiver in order to determine how a societal perspective impacts the ICUR estimate. A literature search returned a mean estimate of direct non-medical cost of $16,544 per patient. Costs were incorporated as a lump sum addition to tisagenlecleucel costs. Including these costs resulted in a roughly $8,000 increase in the estimated ICUR.

Table 3: CADTH Scenario Analyses

		Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICER
Scenario A	Tisagenlecleucel	$620,095	$497,404	3.35	3.71	2.21	$225,070
OS and PFS Randomize	Salvage chemotherapy	$122,691		1.14	1.62		
Scenario B	Tisagenlecleucel	$581,660	$416,880	4.08	5.11	1.94	$214,887
Extended CRS duration	Salvage chemotherapy	$164,780		2.14	3.01		
Scenario C	Tisagenlecleucel	$581,660	$416,880	3.98	5.11	1.84	$226,565
Applied febrile neutropenia disutility	Salvage chemotherapy	$164,780		2.14	3.01		
Scenario D	Tisagenlecleucel	$583,567	$418,787	4.11	5.11	1.97	$212,582
100% inpatient infusion	Salvage chemotherapy	$164,780		2.14	3.01		
Scenario E	Tisagenlecleucel	$553,320	$388,540	4.16	5.11	1.97	$197,228

		Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICER
100% outpatient infusion	Salvage chemotherapy	$164,780		2.14	3.01		
Scenario F	Tisagenlecleucel	$598,294	$433,514	4.11	5.11	1.97	$220,058
Societal perspective	Salvage chemotherapy	$164,780		2.14	3.01		
Scenario G	Tisagenlecleucel	$584,433	$419,427	4.08	5.15	1.94	$216,199
Include Manufacturer HR	Salvage chemotherapy	$165,006		2.14	3.01		
Scenario H	Tisagenlecleucel	$612,652	$447,646	5.15	6.53	3.01	$148,720
MAIC HR adjustment	Salvage chemotherapy	$165,006		2.14	3.01		
Scenario I	Tisagenlecleucel	$586,171	$416,357	4.09	5.11	1.97	$211,349
No limit PFS	Salvage chemotherapy	$169,814		2.12	3.01		
Scenario J	Tisagenlecleucel	$581,660	$416,880	4.1	5.11	1.97	$211,614
Utility SEs based on original	Salvage chemotherapy	$164,780		2.133	3.01		
Scenario K	Tisagenlecleucel	$581,660	$416,880	4.08	5.11	1.94	$214,887
Shorten time horizon to 10 years	Salvage chemotherapy	$164,780		2.14	3.01		
Scenario L Shorten time horizon to 5 years	Tisagenlecleucel	$575,769	$449,639	1.56	2.01	0.695	$646,609
	Salvage chemotherapy	$126,130		0.87	1.31		
Scenario M Shorten time horizon to 1 year	Tisagenlecleucel	$565,993	$455,773	0.48	0.68	0.165	$2,764,202
	Salvage chemotherapy	$110,219		0.32	0.58		

CRS = cytokine release syndrome; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; MAIC = matching-adjusted indirect comparison; SE = standard error.

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 15, Table 16).

The CADTH undertook a price-reduction analysis based on the manufacturer's and CADTH's revised base case. The price-reduction scenarios based on the CADTH scenario analysis indicated that with a 70% price reduction for tisagenlecleucel, the ICUR would be lower than $50,000 per QALY (Table 4).

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs of Submitted Tisagenlecleucel Versus Salvage Chemotherapy		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CADTH**
Submitted	$131,716	$211,870
10% reduction	$116,620	$185,586
15% reduction	$109,072	$173,868
20% reduction	$101,524	$162,149
25% reduction	$93,976	$150,431
30% reduction	$86,428	$138,712
40% reduction	$71,332	$115,275
50% reduction	$56,237	$91,838
60% reduction	$41,141	$68,401
70% reduction	$26,045	$44,963

ICUR = incremental cost-utility ratio.

Information on the Budget Impact Analysis

Manufacturer's Budget Impact Analysis

The manufacturer submitted a budget impact analysis (BIA) that assessed the financial impact of the potential reimbursement of tisagenlecleucel (Kymriah) for adult patients with relapsed/refractory (r/r) DLBCL in Canada.[9] 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 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 (see 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 diagnosed with DLBCL using estimates of disease prevalence (for Year 1) or annual incidence (for years 2+). This population was further narrowed down to include only persons with DLBCL who are relapsed/refractory and eligible to receive tisagenlecleucel; this included the following patient groups:

- Ineligible for subsequent ASCT and relapsed/refractory to second-line treatment;
- Considered for ASCT, but who do not receive ASCT;
- Relapse following ASCT.

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 adult r/r DLBCL patients expected to receive tisagenlecleucel or other treatment in the Reference Scenario and the New Treatment Scenario was estimated by combining 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 Canadian DLBCL 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 regimens 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, adverse event management costs, subsequent therapy costs (hematopoietic stem cell transplantation), and indirect costs (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 salvage 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 adult patients with r/r DLBCL in Canada are expected to be $56,721,130 in Year 1, $59,026,762 in Year 2, and $75,971,344 in Year 3. 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 DLBCL (budget impact between $172,547,313 and $210,891,160 when estimates of prevalence/incidence varied +/- 10% of base-case values), the market share of tisagenlecleucel (budget impact between $172,983,078 and $210,455,395 when varied +/- 10% of base-case values), and subsequent therapy costs (budget impact of $212,354,478 when excluded). 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 Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Tisagenlecleucel	$0	$0	$ 0	$0
(R)-GDP	[redacted]	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]
(R)-DHAP	[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]
(R)-GDP	[redacted]	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]
(R)-DHAP	[redacted]	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$56,721,130**	**$59,026,762**	**$75,971,344**	**$191,719,236**

(R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

Sources of Uncertainty Relating to the Manufacturer's Submission

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

Inclusion of investigational therapy as relevant comparator in the base-case analysis. The inclusion of investigational therapy (i.e., patients entering clinical trials) as relevant comparator in the manufacturer's BIA may be problematic as these patients are not receiving approved regimens in the treatment of r/r DLBCL, and allocation a proportion of market shares to non-approved therapies may bias the predictive accuracy of the budget impact estimates. Moreover, investigational therapy was not included as comparator in the manufacturer's economic analysis base case,[3] which brings into question its relevance for the assessment of budget impact.

Consideration for bridging therapy associated with tisagenlecleucel pre-treatment. The budget impact model appropriately 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 JULIET trial which examined the efficacy and safety of tisagenlecleucel in adults with r/r DLBCL, nearly 90% 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; this effectively resulted in an underestimation of the total costs associated with tisagenlecleucel.

Potential uptake of tisagenlecleucel. The market adoption rates for tisagenlecleucel in the New Treatment Scenario (where tisagenlecleucel is reimbursed) were estimated based on a survey of Canadian experts in DLBCL care commissioned by the manufacturer. [redacted]
Notwithstanding this limitation, the potential uptake of tisagenlecleucel is uncertain and market share estimates elicited from Canadian clinical experts cannot be validated as they are based on the manufacturer's internal estimates.

Potential 'commercialization' constraints not accounted for in the analysis: [redacted][11] This is problematic as the total number of patients per year eligible for treatment with tisagenlecleucel based on the manufacturer's BIA estimates (Table 21 in Appendix 3) 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 on future expenditures 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 with this novel therapy. 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 adult treatment centres, 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 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 patient with r/r DLBCL and by the estimated proportion of patients in EFS.[9] While productivity gains are an important element of indirect costs associated with DLBCL treatment, other potential sources of indirect costs (e.g., cost of travel and accommodation for persons who do not reside near designated treatment facilities) should also be considered. Accounting for all relevant indirect costs would provide a more complete portrait of the expected indirect costs associated with the potential reimbursement of tisagenlecleucel in patients with r/r DLBCL.

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:

- Investigational therapy was removed as relevant comparator, with market shares adjusted accordingly.
- Tisagenlecleucel was assumed to occupy 100% of the total CAR T market shares; accordingly, the market uptake of tisagenlecleucel in the New Treatment Scenario was expected to reach [redacted] of the analysis.
- 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.[8]
- Drug wastage was accounted for by assuming 0% vial sharing.
- 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.[12] and the medical coinsurance amounts, copayments and deductible costs reported by Maziarz et al.[13] 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 adult patients with r/r DLBCL in Canada are expected to be $117,629,787 in Year 1, $122,411,266 in Year 2, and $157,551,391 in Year 3; the cumulative three-year net budget impact of reimbursing

tisagenlecleucel was predicted to be $397,592,444. 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).Results of the CADTH base case from the public payer perspective are presented in Table 7.

Table 6: Summary of Results of the 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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
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]
(R)-DHAP	[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	**$ 117,629,787**	**$ 122,411,266**	**$ 157,551,391**	**$ 397,592,444**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

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

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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 114,605,454**	**$ 119,263,998**	**$ 153,500,650**	**$ 387,370,103**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = Etoposide, ifosfamide, and carboplatin with or without rituximab.

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), where 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 DLBCL patients may increase to $248,685,571 in Year 1, $258,794,277 in Year 2, and $333,085,343 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 DLBCL was estimated at $29,069,361 in Year 1, $28,036,906 in Year 2, and $20,449,176 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 costs 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 DLBCL accounting for tisagenlecleucel-related manufacturing issues was estimated at $112,675,911 in Year 1, $117,256,023 in Year 2, and $150,916,253 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. [8](

Table 31), as well as reimbursement based on clinical performance outcomes (Table 32, Table 33). 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 DLBCL was approximately $386 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 $179 million (based on average PFS over 12 months) and $212 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 become too sick to tolerate treatment with the CAR T cells. Moreover, 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. JULIET trial reported that 6.1% of patients enrolled in the trial experienced manufacturing failure. The manufacturing failure is likely to 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 worsen hospital overcrowding problem in Canada. This concern is supported from JULIET trial data indicating that approximately 93.7% of patients was hospitalized starting from lymphodepleting with an average hospital length of stay of 26.5 days. The prolonged hospitalization may also impose additional financial burden, such as travel and accommodation costs, to patients and their caregiver.
- Although tisagenlecleucel has shown very encouraging results in adult patients with r/r DLBCL who are ineligible for or relapse after auto SCT, it is not yet clear whether tisagenlecleucel can be used at different stages of therapy, such as in first-line use or post SCT.
- The limited clinical experience with tisagenlecleucel along with a small sample size 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 DLBCL, the patients will incur future costs to the health care system. Considering the future costs in the cost-effectiveness model will increase ICUR and make tisagenlecleucel less economically attractive.

Patient Input

Patient input was received from Lymphoma Canada. Patients described their experience with treatments as affecting their physical, emotional, and mental health in a multiplicity of ways. Physically, patients undergoing treatment for DLBCL treatment experienced a host of side physical effects. Patients described the stress of life with DLBCL. Patients' and their families financial well-being was strained the patient born costs of treatment and reduction in ability to work. The adverse effects associated with treatments were captured as part of the

manufacturer's economic evaluation. Other aspects such as the stress of living with DLBCL and impact of caregivers were considered by the manufacturer.

Conclusions

CADTH reanalysis of the manufacturer economic evaluation found that compared with salvage chemotherapy tisagenlecleucel was associated with the additional cost of $416,750 and a gain in 2.10 life-years and 1.97 QALYs, resulting in an ICUR of $211,870 per QALY. Tisagenlecleucel had a 0% probability being cost-effective at a willingness-to-pay threshold of $50,000 per QALY and a 1.8% probability of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY. If the submitted price is reduced by 70%, the ICUR of tisagenlecleucel would be lower than $50,000 per QALY.

It should be noted that the economic model submitted by the manufacturer was unnecessarily complex and lacked transparency, which made both the assessment of validity and the ability to conduct reanalysis challenging. Thus, interpretation of results is subject to the identified limitations.

Moreover, as noted in the report, there exist clinical uncertainties — 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.

The manufacturer estimated that [redacted] patients with relapsed/refractory DLBCL will be treated with tisagenlecleucel in years 1 to 3 of funding, respectively. CADTH estimated that the incremental expenditures associated with the reimbursement of tisagenlecleucel in adult patients with r/r DLBCL in Canada to be $117,629,787 in Year 1, $122,411,266 in Year 2, and $157,551,391 in Year 3. In scenario analyses, CADTH considered a situation where re-treatment with tisagenlecleucel may be necessary, and the cumulative three-year net budget impact of reimbursing tisagenlecleucel may be greater than $840 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 $78 million. Where tisagenlecleucel-related production failure is accounted for in the analysis, the cumulative three-year budget impact of funding tisagenlecleucel was estimated at approximately $381 million. These 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 manufacturer’s base case, 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 SCT on PFS and OS was considered. The Visual Basics Macros used in the submitted Excel model were unnecessarily complex and lacked transparency. 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		

OS = overall survival; PFS = progression-free survival; SCT = stem cell transplantation.

Table 9: Authors Information

Authors of the Economic 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	

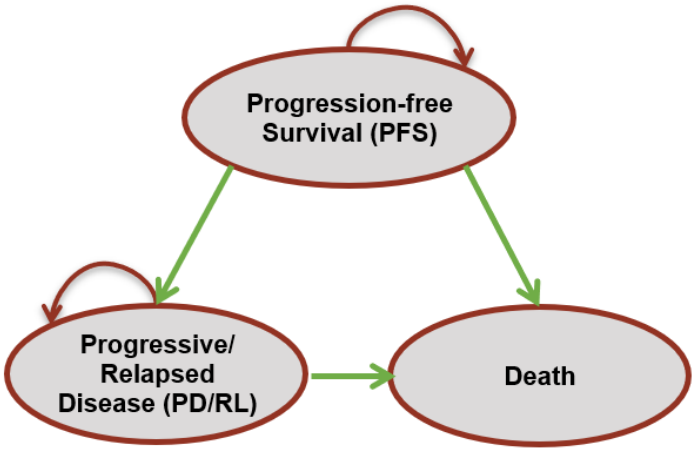
Appendix 2: Detailed Information — Economic Submission

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis that compared tisagenlecleucel and salvage chemotherapy.[3] A partition-survival model with three health states (progression free, post progression, and death) was used to forecast the costs and QALYs over a 20-year time horizon. Despite previous progression, all patients enter the model in the progression-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 progression-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. Clinical data from JULIET and UPenn trials was pooled and used to inform the impact of tisagenlecleucel on OS and PFS. The combined JULIET and UPenn trial data provided evidence covering 39 months; hence OS and PFS values for tisagenlecleucel beyond the 39 months were assumed to be equivalent to salvage chemotherapy. OS data for salvage chemotherapy was based on observed data from SCHOLAR-1 until month 39 and used extrapolated data based on parametric survival models afterwards. The manufacturer approximated PFS for salvage chemotherapy by applying a cumulative hazard ratio between OS and PFS (0.65 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 to salvage chemotherapy in adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) from a Canada payer perspective?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with r/r DLBCL who are ineligible for or relapse after autologous stem cell transplant (ASCT)
Treatment	Tisagenlecleucel as a single intravenous treatment
Outcome	QALYs
Comparator(s)	Salvage chemotherapy: regimen of gemcitabine (1,000 mg/m^2 on day 1 and 8), dexamethasone (40 mg daily from day 1 to day 4) and cisplatin (75 mg/m^2 on day 1) in combination with rituximab (375 mg/m^2 on day 1)
Perspective	Canada payer perspective
Time Horizon	20 years
Results for Base Case	ICUR = $131,716 per QALY gained
Key Limitations	• Lack of head-to-head comparative efficacy and safety of tisagenlecleucel and salvage chemotherapy. • The total cost of tisagenlecleucel was underestimated. • The impact of subsequent ASCT on progression and survival was not accounted in the model. • Heterogeneity of patient characteristics impacting treatment effectiveness was not considered. • Probabilistic ICURs 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. • Input parameters used in the model were assumed to be independent.
CADTH Estimate(s)	• There was substantial uncertainty in the CADTH estimates due to the lack of evidence comparing the safety and efficacy of tisagenlecleucel and salvage chemotherapy. • Tisagenlecleucel was associated with an additional cost of $416,750 and a gain in 2.10 life-years and 1.97 QALYs, resulting in an ICUR of $211,870 per QALY. The probability that tisagenlecleucel is cost-effective was 0% at a willingness-to-pay (WTP) threshold of $50,000 per QALY and 1.8% at a WTP threshold of $100,000. • Scenario analyses conducted by CADTH suggested that the cost-effectiveness of tisagenlecleucel was highly sensitive to assumptions regarding the long-term PFS and OS outcomes, the relative impact of tisagenlecleucel and salvage chemotherapy on OS, and the analysis time horizon. At a price reduction of 70%, the ICUR would be lower than $50,000 per QALY.

ASCT = autologous stem cell transplant; r/r DLBCL = relapsed or refractory diffuse large B-cell lymphoma; ICUR = incremental cost-utility ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Starting age and the percentage of female were based on JULIET trial. The SCHOLAR-1 study reported limited baseline patient and clinical characteristics.	CADTH believes that it is inappropriate to pool data from JULIET and UPenn trials because UPenn trial was a proof-of-concept study with different target populations. 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. CADTH performed scenario analysis by using adjusted OS HR obtained from the MAIC analysis submitted by the manufacturer. Notably, results of the MAIC analysis were questionable because the adjustment was based on limited baseline characteristics.
Efficacy	• For tisagenlecleucel, the manufacturer combined patient-level data from JULIET trial and pseudo data extracted from K-M curves of UPenn trial and estimated OS and PFS up to month 39. After month 39, the manufacturer assumed no incremental long-term survival benefit associated with tisagenlecleucel. The predicted OS data estimated using weighted distribution fitted to the SCHOLAR-1 data was therefore used for tisagenlecleucel. • The PFS of tisagenlecleucel was based on the data pooled from JULIET (data cut-off: December 8, 2017) and UPenn (as published in Schuster 2017) trials. To predict PFS beyond the trial data, a weighted distribution based on various parametric survival curves (or parametric functions) was derived and applied in the base-case analysis. • For salvage chemotherapy, OS was based on observed data from the SCHOLAR-1 study up to month 39. A weighted parametric survival models were used to extrapolate the long-term survival after 39 months. • Because the SCHOLAR-1 study did not report PFS data, the manufacturer derived the PFS curve from the OS curve assuming a constant cumulative HR over time, i.e., the cumulative hazard function for PFS would be proportional to cumulative hazard function for OS.	• There is a lack of comparative efficacy and safety 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 included in the SCHOLAR-1 study received various salvage chemotherapy regimens; the name of drug regimens used was however not reported. It is unclear whether OS observed in the SCHOLAR-1 study is generalizable to r/r DLBCL patients in Canada. • The manufacturer derived PFS of salvage chemotherapy from OS, assuming that the cumulative hazard function for PFS would be proportional to cumulative hazard function for OS. The ratio was based on OS and PFS observed in the R-ICE and R-DHAP arms from a single study. This ratio may vary by the type of salvage chemotherapy. CADTH was unable to test whether the constant cumulative hazard assumption is appropriate. The manufacturer claimed that the efficacy of subsequent SCT was captured in the PFS and OS estimations; however, the submitted model only incorporated costs and health utility decrements due to SCT. The omission of benefit of SCT on patient survival and progress may underestimate the ICUR given that the greater proportion in the salvage chemotherapy group received subsequent SCT.
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 PFS curves.	A partition-survival model assumes that the modelled survival endpoints are structurally independent. This structural assumption is potentially problematic because several survival endpoints are dependent. PFS and OS curves, for example, have the same pre-progression death. In addition, progression can be

Data Input	Description of Data Source	Comment
		considered as prognostic for mortality.
Utilities	• Utility values associated with health states were obtained from a previous cost-effectiveness study that obtained health utility estimates from a randomized multicenter study comparing CHOP with CHOP plus G-CSF in patients aged 65 to 90 with aggressive NHL. • Treatment disutility values were obtained a published decision-analytical study evaluating follow-up strategies for patients with Hodgkin's disease. • Utility decrement (0.15) 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 and ICU stays not due to CRS. For both events, the patients were assumed to have a disutility of –0.83 based on PFS utility for the duration of the CRS-related or non-CRS-related ICU stay based on JULIET trial. • Patients receiving either subsequent auto SCT or allo SCT were assumed to have additional SCT disutility, derived from published literature (Guadagnolo). The disutility associated with SCT was assumed to last for 365 days.	• Health utility values for PFS and PD health states were not specific to r/r DLBCL patients. Health utility values derived from JULIET trial should be used. • The submitted base case may underestimate the cost and health decrements associated with CRS. According to JULIET trial, the median duration of CRS was 7.0 days (range: 2 to 30 days). Twenty-five patients (43.9% of patients with CRS) were admitted to the ICU for a median duration of 6 days (range: 2 to 34 days).
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.	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 cost of regimen GDP. The manufacturer claimed that the regimen was the most commonly used regimen for	Appropriate.

Data Input	Description of Data Source	Comment
	salvage chemotherapy in r/r DLBCL 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 (6.3%), a unit cost of $199 was added to capture delivery of chemotherapy. • All patients receiving (R)-GDP were assumed to be managed in the outpatient setting for all cycles of treatments based on Canada's Alberta health guideline. The administration cost was calculated based on the duration of the treatment cycle and the duration of the administration.	Appropriate.
Bridging therapy and lymphodepleting chemotherapy	• The submitted 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 JULIET trial, nearly 90% of patients who received tisagenlecleucel required bridging chemotherapy before the infusion. The most frequently used (≥ 15% of patients) bridging therapies were rituximab (54.5%), gemcitabine (38.4%), dexamethasone (25.3%), etoposide (22.2%), cytarabine (19.2%), cisplatin (18.2%), and cyclophosphamide (15.2%).
Subsequent SCT	• The model assumed patients could receive subsequent SCT, including allo SCT and auto SCT after initial treatment. The rates of subsequent SCT were obtained from the same clinical trial study used for the efficacy estimation. Allo and auto SCT 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 for allo SCT and up to 1 year for auto SCT, respectively. The unit costs of SCT 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 JULIET trial for tisagenlecleucel and published literature (Corazzelli) for salvage chemotherapy (based on the Gem-Ox regimen). • The AE cost per case was estimated based on the Ontario case Costing Initiative from the Ontario Ministry of Health 2015-2016.	The AE profiles of the Gem-Ox regimen may not be representative of AE profiles of other salvage chemotherapy regimens. 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. • For patients receiving salvage chemotherapy who remained in the PFS state, the frequency	• Given the limited real-world experience with CAR T-cell therapy in Canada, it seems appropriate to use the same frequency of visits as reported in JULIET trial.

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

AE = adverse event; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; HR = hazard ratio; ICU = intensive care unit: MAIC = matching-adjusted indirect comparison; MOHLTC = Ministry of Health and Long-Term Care; OS = overall survival; PFS = progression-free survival; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-GDP = gemcitabine, cisplatin, and dexamethasone with or without rituximab; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; 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 9.2 days for a CRS-related admission and a mean of 0.86 days for a non-CRS-related admission). The submitted base case may underestimate the cost and health decrements associated with CRS. According to JULIET trial, the median duration of CRS was 7.0 days (range: 2 to 30 days). Twenty-five patients (43.9% of patients with CRS) were admitted to the ICU for a median duration of 6 days (range: 2 to 34 days). A maximum ICU day, i.e., 34 days, should be used in one of the scenario analyses.
Efficacy benefit of subsequent SCT was captured in the PFS and OS estimations.	This assumption is questionable because subsequent SCT rates were not one of primary or secondary outcomes of JULIET trial. The trial reported that no patient underwent SCT after infusion and before disease progression, suggesting that reported PFS did not capture the benefit of subsequent SCT. In addition, the benefit of subsequent SCT on OS is unknown because post-infusion SCT was censored at time of SCT in a full analysis test of JULIET trial. According to clinical experts consulted by CADTH, subsequent SCT is expected to delay progression and improve patient survival. None of these clinical benefits was however considered in the submitted model.
After the end of observed data (i.e., month 39), the model considered no incremental survival benefit associated with tisagenlecleucel and assumed the same mortality rate as the salvage chemotherapy arm. The long-term OS data from the SCHOLAR-1 study was used for survival extrapolation.	Appropriate.

Assumption	Comment
PFS data are not reported for salvage chemotherapy in the literature and is 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 PFS observed in the R-ICE and R-DHAP arms from a single study. This ratio may vary by the type of salvage chemotherapy.

AE = adverse event; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ICU = intensive care unit: OS = PFS = progression-free survival; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-GDP = gemcitabine, cisplatin, and dexamethasone with or without rituximab; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; SCT = stem cell transplantation.

Manufacturer's Results

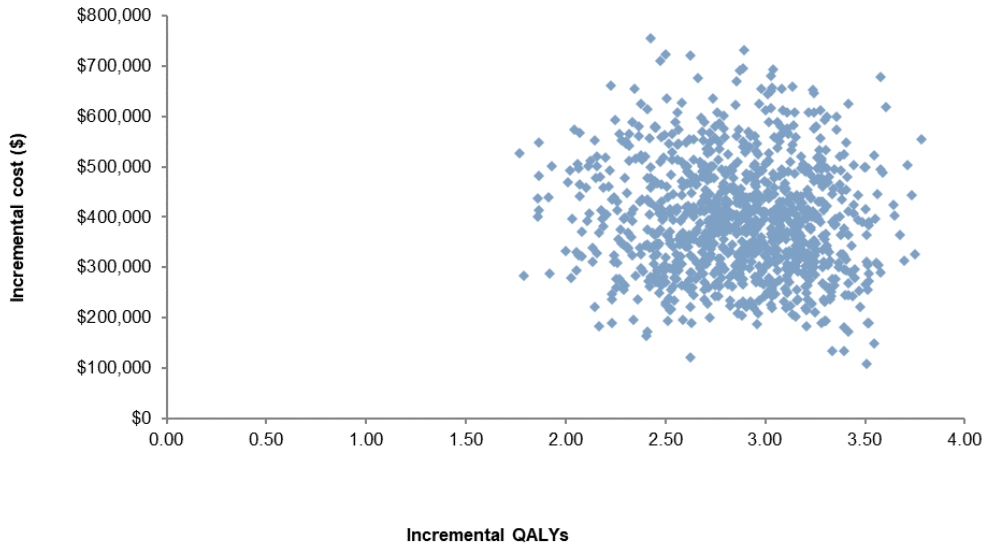
Table 13: Summary of Deterministic Results of the Manufacturer's Base Case

	Tisagenlecleucel	Salvage Chemotherapy
Costs		
Pre-treatment	[redacted]	$0
Treatment	[redacted]	$18,849
Drug/procedure	[redacted]	$269
Administration	[redacted]	$2,388
Hospitalization	[redacted]	$16,192
AEs	[redacted]	$5,235
Other medical costs before progression	[redacted]	$490
Subsequent SCT	[redacted]	$78,013
Rate of subsequent SCT	[redacted]	0.40
Cost post progression	[redacted]	$57,053
Terminal care	[redacted]	$6,979
Total costs	$559,257	$166,619
Incremental costs	**$392,638**	
Effectiveness		
Life-years (LYs)	5.82	3.01
PFS	5.41	1.38
Progressive disease (PD)	0.41	1.63
Quality-adjusted life-years (QALYs)	4.62	1.64
PFS	4.49	1.15
PD	0.16	0.64
Treatment and AE disutilities	-0.02	-0.03
Subsequent SCT disutilities	-0.02	-0.12
QALYs gained	**2.98**	
ICUR	**$131,716**	

AE = adverse event; ICUR = incremental cost-utility ratio; PD=progressive disease; PFS = progression-free survival; SCT = stem cell transplantation.

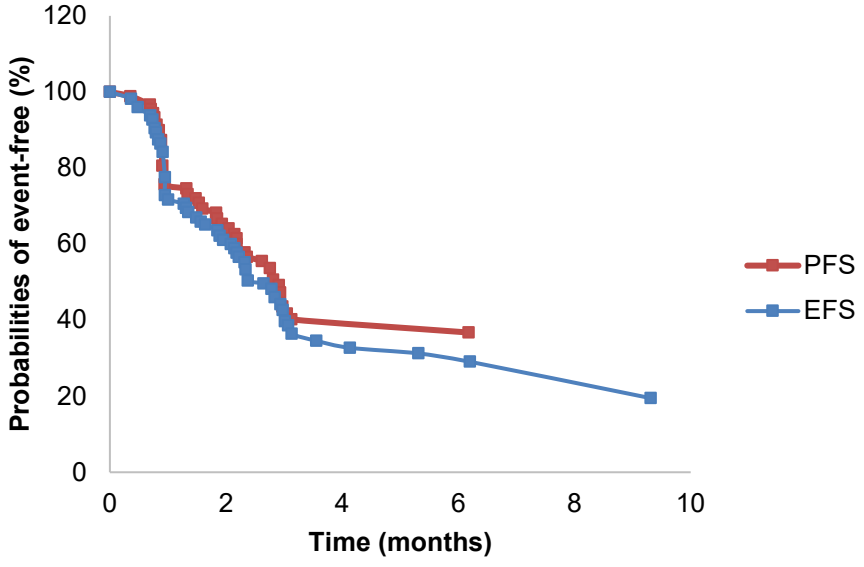
Source: Manufacturer's economic submission.[3]

Figure 2: Cost-Effectiveness Plane Obtained From the Manufacturer's Base Case (Tisagenlecleucel versus Salvage Chemotherapy)



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

Figure 3: Comparison of Progression-Free and Event-Free Probabilities



EFS = event-free survival; PFS = progression-free survival.
Source: Digitized from JULIET trial.

CADTH Reanalyses

Table 14: CADTH Scenario Analysis CEAC Results

	WTP = $50,000	WTP = $100,000	WTP = $150,000
Base case	0.0%	1.8%	18.9%
Scenario A OS and PFS Randomize	0.0%	1.6%	16.8%
Scenario B CRS Disutility	0.0%	1.9%	18.1%
Scenario C AE Disutility	0.0%	1.4%	15.6%
Scenario D 100% patient infused as inpatient	0.0%	2.0%	18.4%
Scenario E 0% patient infused as inpatient	0.3%	4.6%	25.4%
Scenario F Societal perspective	0.0%	1.6%	16.1%
Scenario G Include Hazard Ratio	0.0%	4.2%	21.5%
Scenario H MAIC HR adjustment	0.3%	12.6%	53.3%
Scenario I No limit PFS	0.1%	2.1%	18.5%
Scenario J Utility SE based on original study	0.1%	3.4%	21.1%
Scenario K Shorten time horizon to 10 years	0.0%	0.0%	0.7%

AE = adverse event; CEAC = cost-effectiveness acceptability curve; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; SE = side effect; WTP = willingness to pay.

CADTH performed additional scenario analyses. The results are shown in Table 14. Varying a hazard ratio of OS and PFS used in salvage chemotherapy from 0.48 to 0.81 led to a slight change in ICUR. Assuming none of the patients receiving tisagenlecleucel require subsequent SCT caused a considerable decrease of ICUR from $211,870 to $189,233 per QALY. Extended IVIG (intravenous immunoglobulin) duration from the manufacturer's base case (11.4 months) to the entire PFS had minimal impact on ICUR. Moreover, CADTH ran the revised base case asserting all PFS 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 PFS data beyond the trial.

Table 15: Results of CADTH Additional Scenario Analyses

Scenario	Comparator	Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICUR ($/QALY)
Weibull	Tisagenlecleucel	$ 605,136	$480,438	1.70	2.28	0.554	866,935
	Salvage chemotherapy	$ 124,698		1.14	1.62		
Gompertz	Tisagenlecleucel	$ 574,402	$405,995	3.83	4.69	1.687	240,659
	Salvage chemotherapy	$ 168,407		2.14	2.98		
Exponential	Tisagenlecleucel	$ 598,815	$478,743	1.29	1.76	0.357	1,342,230
	Salvage chemotherapy	$ 120,072		0.93	1.34		
Log-Logistic	Tisagenlecleucel	$ 598,267	$457,693	1.90	2.50	0.635	720,649
	Salvage chemotherapy	$ 140,573		1.26	1.83		
Cubic Splines	Tisagenlecleucel	$ 582,791	$416,945	4.11	5.09	1.963	212,399
	Salvage chemotherapy	$ 165,846		2.15	3.00		
HR PFS Lower Bound	Tisagenlecleucel	$ 581,530	$394,338	4.11	5.09	2.047	192,601
	Salvage chemotherapy	$ 187,192		2.06	2.99		
HR PFS Upper Bound	Tisagenlecleucel	$ 581,530	$444,136	4.11	5.09	1.871	237,381
	Salvage chemotherapy	$ 137,395		2.24	2.99		
No SCT for Tisagenlecleucel	Tisagenlecleucel	$ 537,003	$372,223	4.11	5.09	1.967	189,233
	Salvage chemotherapy	$ 164,780		2.14	2.99		
Extended IVIG	Tisagenlecleucel	$ 599,399	$434,619	4.106	5.085	1.967	220,954
	Salvage chemotherapy	$ 164,780		2.139	2.994		

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

Table 16: Additional Exploratory Analyses — Based on Performance Outcomes

Scenario	Comparator	Total Cost	Incremental Cost	Total QALY	LYs	Incremental QALY	ICER
ORR at 3 months (JULIET trial) (57.6%)	Tisagenlecleucel	$390,436	$225,427	4.11	5.11	1.97	$118,185
	Salvage chemotherapy	$165,009		2.14	3.01		
Average PFS over 12 months (43%)	Tisagenlecleucel	$325,035	$160,026	4.11	5.11	1.97	$83,963
	Salvage chemotherapy	$165,009		2.14	3.01		

ICER = incremental cost-effectiveness ratio; LY = life-year; PFS = progression-free survival; QALY = quality-adjusted life-year.
Note: analyses 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	0.03	0.00	0.00	0.00	0.00
	Salvage chemotherapy	0.11	0.03	0.00	0.00	0.00
Gompertz	Tisagenlecleucel	0.27	0.26	0.26	0.26	0.26
	Salvage chemotherapy	0.14	0.13	0.13	0.13	0.13
Exponential	Tisagenlecleucel	0.03	0.00	0.00	0.00	0.00
	Salvage chemotherapy	0.07	0.00	0.00	0.00	0.00
Log-Logistic	Tisagenlecleucel	0.11	0.05	0.02	0.01	0.01
	Salvage chemotherapy	0.07	0.03	0.01	0.00	0.00
Cubic Splines	Tisagenlecleucel	0.20	0.11	0.04	0.01	0.00
	Salvage chemotherapy	0.15	0.13	0.11	0.10	0.09

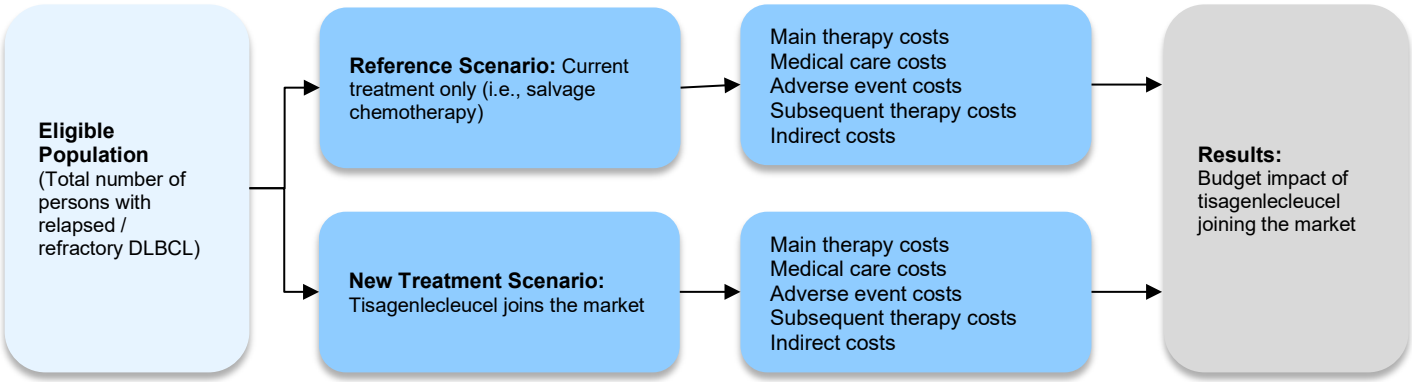
OS = overall survival.

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.[9] Two scenarios were compared in the model: 1) a Reference Scenario, where only treatment with salvage chemotherapy 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 appropriate 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 BIA Modelling Approach

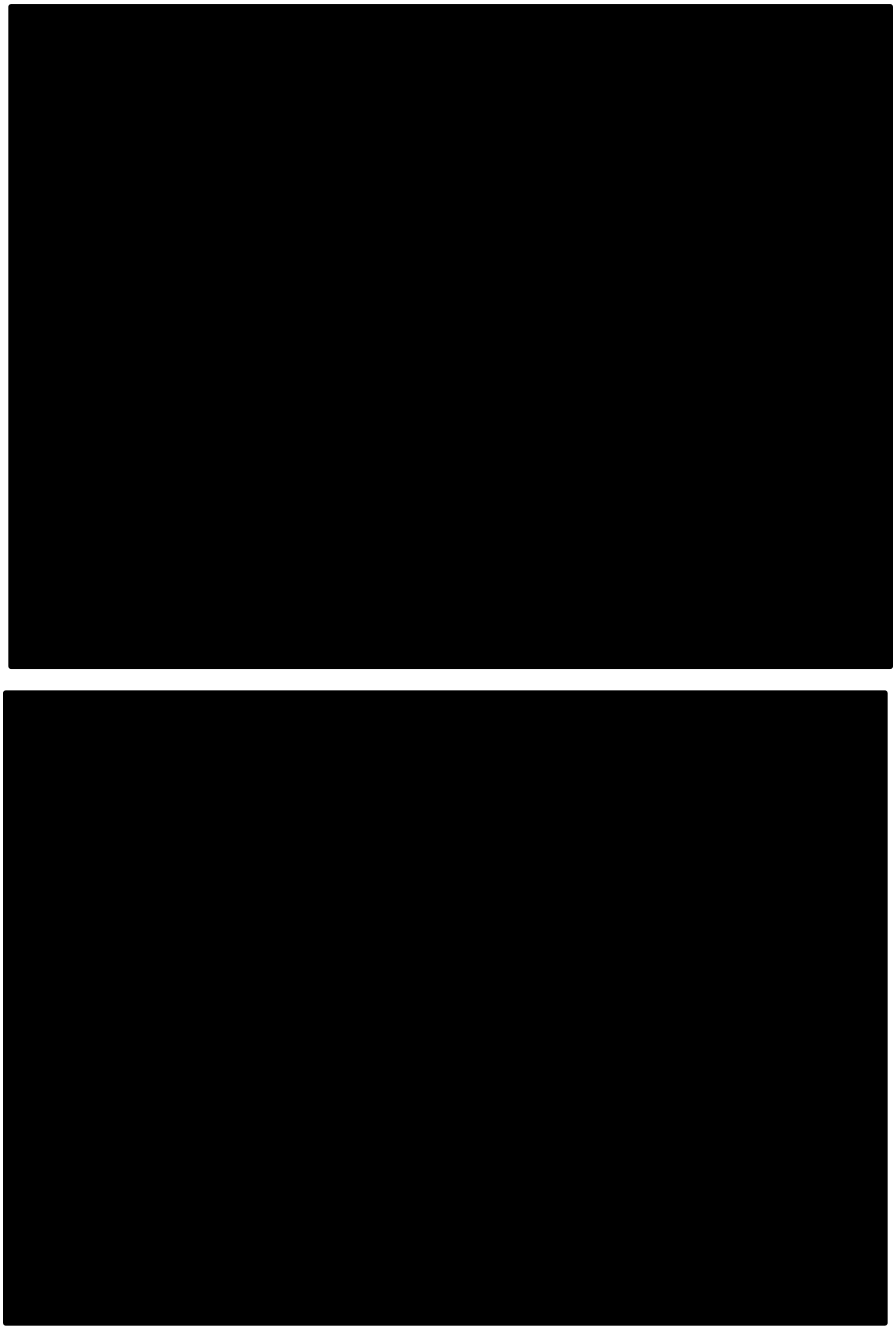


BIA = budget impact analysis; DLBCL = diffuse large B-cell lymphoma.
Source: Manufacturer's BIA submission.[9]

The population of patients eligible for treatment with tisagenlecleucel was estimated via a funnel-down approach (see 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 diagnosed with diffuse large B-cell lymphoma (DLBCL) using estimates of disease prevalence (for Year 1) or annual incidence (for years 2+). This population was further narrowed down to include only persons with DLBCL who are relapsed/refractory and eligible to receive tisagenlecleucel; this included the following patient groups:

- ineligible for subsequent autologous stem cell transplantation (ASCT) and relapsed/refractory to second-line treatment
- considered for ASCT, but who do not receive ASCT
- relapse following ASCT.

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 budget impact analysis submission.[9]

The market shares of treatment options in the Reference Scenario (Table 18) were assumed based on current availability of treatments for DLBCL, with market shares estimated based on Canadian expert opinion and a survey of Canadian DLBCL care 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%
(R)-GDP	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]
(R)-DHAP	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	**100.0%**	**100.0%**	**100.0%**

(R)-DHAP = Dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = Gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = Etoposide, ifosfamide, and carboplatin with or without rituximab.

The potential uptake of tisagenlecleucel (Table 19) was estimated based on a survey of Canadian experts in DLBCL care commissioned by the manufacturer, [redacted] The manufacturer also assumed that the proportion of DLBCL patients entering clinical trials (i.e., receiving investigational therapy) would decrease proportionally to the uptake of tisagenlecleucel, and that the market shares from salvage chemotherapies would remain proportional to their usage before CAR T availability (i.e., Reference Scenario).

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

Comparators	Year 1	Year 2	Year 3
Tisagenlecleucel	[redacted]	[redacted]	[redacted]
(R)-GDP	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]
(R)-DHAP	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	**100.0%**	**100.0%**	**100.0%**

(R)-DHAP = Dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = Gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = Etoposide, ifosfamide, and carboplatin with or without rituximab.

Table 20 and Table 21 present the number of patients likely to receive tisagenlecleucel versus salvage chemotherapy 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 the Reference Scenario

Comparators	Year 1	Year 2	Year 3
Tisagenlecleucel	0	0	0
(R)-GDP	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]
(R)-DHAP	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

(R)-DHAP = Dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = Gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = Etoposide, ifosfamide, and carboplatin with or without rituximab.

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]
(R)-GDP	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]
(R)-DHAP	[redacted]	[redacted]	[redacted]
Investigational therapy	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

(R)-DHAP = Dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = Gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = Etoposide, ifosfamide, and carboplatin with or without rituximab.

Annual budget costs in the analysis included the cost of main therapy (composed of drug acquisition costs and administration and hospitalization costs), medical costs, adverse event management costs, subsequent therapy costs, and indirect costs. 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]
(R)-GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(R)-DHAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; (R)-DHAP = Dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = Gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = Etoposide, ifosfamide, and carboplatin with or without rituximab.

[redacted]

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	[redacted]
Persons entering clinical trials	[redacted]
Proportion of patients with DLBCL	[redacted]
Rate of diagnosis of DLBCL	[redacted]
Proportion of patients with public health coverage	[redacted]
Proportion of DLBCL patients who are relapsed/refractory following first-line therapy	[redacted]
Proportion of patients who are eligible for second-line ASCT	[redacted]
Proportion of patients who successfully receive an ASCT in second-line	[redacted]
Proportion of patients who relapse following an ASCT in second-line	[redacted]
Proportion of patients who are ineligible for ASCT and 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]

Parameter	Assumption
	[redacted]
Salvage chemotherapy pre-treatment	[redacted]
Main treatment with tisagenlecleucel	[redacted]
Main treatment with salvage chemotherapy regimens	[redacted]
Maintenance therapy	[redacted]
Medical resource use	[redacted]
Adverse events	[redacted]
Subsequent therapy	[redacted]
Productivity gains	[redacted]
Population growth	[redacted]

AE = adverse event; ASCT = autologous stem cell transplantation; DLBCL = diffuse large B-cell lymphoma; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-GDP = gemcitabine, cisplatin, and dexamethasone with or without rituximab; R-ICE = rituximab, ifosfamide, carboplatin; etoposide; SCT = stem cell transplantation.

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]

Sensitivity Analysis Scenario	Scenario Description
	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]

DLBCL = diffuse large B-cell lymphoma; R/R = relapsed/refractory.

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]
	[redacted]		[redacted]
3	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
4	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
5	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
6	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
7	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
8	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
9	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
10	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
11	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]

	Sensitivity Analysis Scenario	Base-Case Inputs	Sensitivity Analysis Inputs
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]

1L = first line; 2L = second line; DLBCL = diffuse large B-cell lymphoma.

Manufacturer's Base Case

Results of the manufacturer's BIA base case revealed that the incremental expenditures associated with the reimbursement of tisagenlecleucel in adult patients with R/R DLBCL in Canada are expected to be $56,721,130 in Year 1, $59,026,762 in Year 2, and $75,971,344 in Year 3. Table 26 presents the net budget impact, including the annual costs for each treatment in each reimbursement year for the two modelled 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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Reference Scenario: Current Treatment Only				
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$56,721,130**	**$59,026,762**	**$75,971,344**	**$191,719,236**

AE = adverse event; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-GDP = gemcitabine, cisplatin, and dexamethasone with or without rituximab; R-ICE = rituximab, ifosfamide, carboplatin; etoposide.

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 adult patients with relapsed/refractory DLBCL (see Table 24). Table 27 presents 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 DLBCL (according to estimates of prevalence/incidence), the market share of tisagenlecleucel, and subsequent therapy costs.

Table 27: Sensitivity Analysis Results — Incremental Budget Impact

		Year 1	Year 2	Year 3	Three-Year Total
	Base Case	**$56,721,130**	**$59,026,762**	**$75,971,344**	**$191,719,236**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[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]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1L = first line; 2L = second line; ASCT = autologous stem cell transplantation; DLBCL = diffuse large B-cell lymphoma; R/R = relapsed/refractory.
CADTH noted discrepancies between the manufacturer's results in the manufacturer's budget impact analysis report and the output from the BIA model.

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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
(R)-DHAP	[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	**$ 248,685,571**	**$ 258,794,277**	**$ 333,085,343**	**$ 840,565,191**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

Table 29: Scenario Analysis — Commercialization Constraints Associated 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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 29,069,361**	**$ 28,036,906**	**$ 20,449,176**	**$ 77,555,443**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

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
(R)-GDP	[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]
(R)-ICE	[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
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 112,675,911**	**$ 117,256,023**	**$ 150,916,253**	**$ 380,848,187**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab,

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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
(R)-DHAP	[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	**$ 114,268,230**	**$ 118,913,067**	**$ 153,048,978**	**$ 386,230,275**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

Table 32: Exploratory Analysis — Reimbursement for Patients Who Experienced Overall Response Rate (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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 62,725,585**	**$ 65,275,288**	**$ 84,013,611**	**$ 212,014,485**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.
[a] ORR estimate at three months (n/N [%] = 48/93 [51.6]) was sourced from the JULIET trial.[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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 52,945,301**	**$ 55,097,450**	**$ 70,914,061**	**$ 178,956,813**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

[a] Estimate of average PFS over 12 months (43.0) was sourced from the JULIET 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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	**$ 245,661,239**	**$ 255,647,010**	**$ 329,034,602**	**$ 830,342,850**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[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
(R)-DHAP	[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	**$ 27,539,933**	**$ 26,482,684**	**$ 18,712,728**	**$ 72,735,344**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[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]
(R)-ICE	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
(R)-DHAP	[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	**$ 109,651,579**	**$ 114,108,756**	**$ 146,865,512**	**$ 370,625,847**

AE = adverse event (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]
(R)-GDP	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 111,243,898**	**$ 115,765,800**	**$ 148,998,237**	**$ 376,007,935**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

Table 38: Exploratory Analysis From the Public Payer Perspective — Reimbursement for Patients Who Experienced Overall Response Rate (ORR) at Three Months 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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
Main therapy	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 59,701,252**	**$ 62,128,021**	**$ 79,962,870**	**$ 201,792,144**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.
[a] ORR estimate at 3 months (n/N [%] = 48/93 [51.6]) was sourced from the JULIET trial.[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	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
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[redacted]	[redacted]	[redacted]	[redacted]

Annual Cost Outcomes	Year 1	Year 2	Year 3	Three-Year Total
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]
(R)-GDP	[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]
(R)-ICE	[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]
(R)-DHAP	[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	**$ 49,920,969**	**$ 51,950,183**	**$ 66,863,320**	**$ 168,734,472**

AE = adverse event; (R)-DHAP = dexamethasone, high-dose cytarabine, and cisplatin, with or without rituximab; (R)-GDP = gemcitabine, dexamethasone, and cisplatin with or without rituximab; (R)-ICE = etoposide, ifosfamide, and carboplatin with or without rituximab.

[a] Estimate of average PFS over 12 months (43.0) was sourced from the JULIET 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 for adults with relapsed or refractory diffuse large B-cell lymphoma - A Canadian payer perspective. In: Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
4. Clinical study report: C2201 data cutoff Mar 8 2017. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2017 Oc 10.
5. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak O, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med.* 2017;377(26):2545-2554.
6. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood.* 2017;130(16):1800-1808.
7. Doorduijn J, Buijt I, Uyl-de Groot C, al. e. Quality of life (QOL) in elderly patients with aggressive non-Hodgkin's lymphoma (NHL) treated with CHOP. *Blood.* 2001;98:1803.
8. 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.
9. 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.
10. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010;28(27):4184-4190.
11. Novartis oncology [slide deck] In: Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.
12. 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.
13. 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.