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CADTH Reimbursement Review

Axicabtagene ciloleucel (Yescarta)

Sponsor: Gilead Sciences Canada Inc.
Therapeutic area: Relapsed or refractory follicular lymphoma

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Abbreviations

AE	adverse event
allo-SCT	allogeneic stem cell transplant
auto-SCT	autologous stem cell transplant
CAR	chimeric antigen receptor
CI	confidence interval
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FAS	full analysis set
FL	follicular lymphoma
FLIPI	Follicular Lymphoma Internal Prognostic Index
GELF	Groupe d'Étude des Lymphomes Folliculaires
HR	hazard ratio
HRQoL	health-related quality of life
KM	Kaplan-Meier
LC	Lymphoma Canada
MZL	marginal zone lymphoma
NE	not evaluable
NHL	non-Hodgkin lymphoma
OH-CCO	Ontario Health-Cancer Care Ontario
ORR	objective response rate
OS	overall survival
OR	odds ratio
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
POD24	progression of disease within 24 months
r/r	relapsed or refractory
SAE	serious adverse event
SCT	stem cell transplant
SD	standard deviation

SMR	standardized mortality ratio
TEAE	treatment-emergent adverse event
TTNT	time to next treatment

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Axicabtagene ciloleucel (Yescarta); cell suspension in patient-specific single-infusion bag, for IV infusion
Sponsor	Gilead Sciences Canada Inc.
Indication	For the treatment of adult patients with relapsed or refractory grade 1, 2, or 3a follicular lymphoma (FL) after 2 or more lines of systemic therapy.
Reimbursement request	As per indication
Health Canada approval status	NOC/c
Health Canada review pathway	Standard review
NOC date	September 28, 2022
Recommended dose	A single-dose, 1-time treatment; target dose of 2×10^6 CAR-positive T cells/kg body weight (range, 1×10^6 cells/kg to 2.4×10^6 cells/kg) to a maximum of 2×10^8 CAR-positive viable T cells for patients weighing ≥ 100 kg

CAR = chimeric antigen receptor; NOC/c = Notice of Compliance with conditions.

Introduction

Non-Hodgkin lymphoma (NHL) encompasses a heterogenous group of more than 80 closely related cancers.[1] It is characterized by the abnormal and uncontrolled proliferation of cells (i.e., T cells, B cells, and natural killer cells) of the lymphatic system.[2,3] Follicular lymphoma (FL), a subtype of NHL, is an indolent B-cell lymphoma originating from the germinal centre of lymphoid tissues[2-6] and characterized by slow growth and spread.[7] It makes up 20% to 30% of all NHL cases.[1] The sponsor-calculated overall incidence rate of FL in Canada (based on the NHL age-standardized incidence rates [25.7 per 100,000] and the proportion of FL among NHL cases [25%])[4,6] reported was 7.21 per 100,000.[4,8,9] Although responsive to initial first- or second-line therapies, FL is characterized by a relapsing and remitting disease course, especially in advanced disease stages. Patients will eventually require multiple treatments to manage or slow disease progression throughout their lifetime as response to treatments decline upon repeated therapy.[3,10-12] The clinical experts consulted by the sponsor reported that approximately 30.95% of incident FL patients would progress to third-line treatment, of whom 60% would proceed to receive active therapy.[13-15] FL can be further classified into 3 grades (1, 2, and 3 [a and b]) based on cell structures under the microscope, specifically, the number of large FL cells (centroblasts) observed.[16] Grades 1, 2, and 3a diseases are generally considered low grade or slow growing compared to grade 3b, which grows fast and is considered high-grade lymphoma. According to the Canadian Cancer Society, 91% of patients considered "low risk" at diagnosis as per the Follicular Lymphoma Internal Prognostic Index (FLIPI) score have a 5-year survival rate and 71% have a 10-year survival rate; 78% of patients considered "intermediate risk" have a 5-year survival rate and 51% have a 10-year survival rate; and 53% of patients considered "high risk" have a 5-year survival rate and 36% have a 10-year survival rate.[17]

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of axicabtagene ciloleucel, at a target dose of 2×10^6 chimeric antigen receptor (CAR)-positive T cells/kg body weight, to a maximum of 2×10^8 CAR-positive viable T cells, by IV infusion, in the treatment of adult patients with relapsed or refractory (r/r) FL after 2 or more lines of systemic therapy.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

One patient advocacy group, Lymphoma Canada (LC), provided input for this review. LC is a national Canadian registered charity whose mission is to empower patients and the lymphoma community through education, support, advocacy, and research. The LC patient group expressed the need for accessible treatment options for patients, emphasizing that local access to treatments would significantly improve patients' quality of life and experience by reducing fear and the risk of getting sick while travelling.

LC gathered information for this input via online surveys completed anonymously by patients between April 21, 2022, and April 3, 2023. Of the 143 responses submitted, 3 respondents reported prior experience with axicabtagene ciloleucel. Respondents indicated that fatigue (50%), body aches and pain (33%), enlarged lymph nodes (33%), indigestion (32%), and bodily swelling (21%) were the most challenging symptoms that impacted their quality of life at the time of diagnosis. Respondents described FL symptoms as challenges in their daily lives that impacted their ability to travel (46%), spend time with family or friends (41%), exercise (37%), concentrate (36%), and work or complete school or volunteer activities (35%) . About half (49%) of the respondents reported that they went through a period of "watchful waiting" before commencing treatment. Most respondents (43%) had received 1 line of treatment. The most common treatments reported by respondents who had received 1 or 2 lines of systemic therapy included chemotherapy, chemoimmunotherapy, rituximab with or without bendamustine, or radiation. The posttreatment symptoms that most significantly negatively impacted respondents included treatment-related fatigue (28%), immediate side effects of treatment (26%), and low activity level (23%). Fatigue (69%), hair loss (41%), and constipation (38%) were the most common side effects reported by respondents. The most important outcomes highlighted by respondents included long life (84%), longer disease remission (82%), improved quality of life and ability to perform daily activities (69%), ability to control disease symptoms (63%), and ability to normalize blood counts (58%). Two-thirds of the respondents indicated that they were willing to tolerate nonsevere side effects for a short-term as a trade-off for a novel treatment. Two respondents who had previously received axicabtagene ciloleucel reported having access to the drug via a clinical trial. Reported side effects were cytokine release syndrome (CRS), neutropenia, febrile neutropenia, thrombocytopenia, constipation, and swelling. Some of the challenges the respondents associated with receiving axicabtagene ciloleucel included the frequent monitoring of side effects postinfusion, the inability to perform daily

activities, and being away from family and friends. Both respondents said that they had a good or very good experience with axicabtagene ciloleucel and would recommend this treatment to other patients with r/r FL.

Clinician Input

Input From Clinical Experts Consulted by CADTH

A panel of 4 experts with experience treating r/r FL were consulted to determine the unmet needs, place in therapy, the patient population identified as most and least likely to benefit from treatment, when to start treatment, how best to assess response to treatment, and guidance for discontinuing treatment. The clinical experts indicated that the most important goals for treatment are to prolong life, and that the greatest unmet needs exist in patients with cancer that progresses within 2 years after their initial therapy, the patients who have already received autologous stem cell transplant (auto-SCT) or are ineligible for auto-SCT, or those who have been double refractory to earlier line treatments (implying limited treatment options available to them). The clinical panel suggested that axicabtagene ciloleucel be used as third- or later-line treatments for patients with r/r FL. These patients usually have a treatment response that lasts less than 6 months after their last treatment (medication or SCT).

The clinical panel indicated that, in practice, CAR T-cell therapy is used in a patient population that is broader than the population selected and recruited for clinical trials. The panel indicated that in clinical practice, patients are evaluated and followed in a manner similar to that described in the clinical trials of FL treatments. Remission and survival are measured. Physical exams and imaging exams are routinely conducted to assess the patient's response to CAR T-cell therapy. The panel suggested that meaningful responses to treatment with axicabtagene ciloleucel would include a high complete remission rate, durability of treatment response, and long-term progression-free survival (PFS) and overall survival (OS). The panel indicated that in the event of treatment failure after infusion with axicabtagene ciloleucel, patients may participate in a clinical trial. In the absence of clinical trial, they may try a different chemoimmunotherapy that they have not been exposed to or undergo auto-SCT if they have not already received this therapy. The panel emphasized the importance of an accredited multidisciplinary team involving hematologists, infectious disease specialists, neurologists, an intensive care unit team, and other specialists to diagnose, treat, and monitor the patients receiving axicabtagene ciloleucel and to ensure the safe and effective delivery of this treatment.

Clinician Group Input

Input from 1 clinician group, the Ontario Health — Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee, was summarized for this review. The disease course of FL varies for every patient. Some patients may present with long remissions between therapies while others would have refractory disease. Current treatment goals for patients with FL, according to the clinician group include palliative care and, in some scenarios, treatment with curative intent using allogeneic stem cell transplant (allo-SCT). The most important goals outlined were to delay disease progression, improve patient health-related quality of life, and alleviate symptoms. The OH-CCO Hematology Cancer Drug Advisory Committee acknowledged that current treatment options do not meet the needs of patients with r/r FL. The clinicians in the committee mentioned that patients who become refractory to chemotherapy have no other treatment options to delay

the disease. In addition, the clinicians highlighted that repeated administration of cytotoxic therapy may be associated with marrow damage (myelodysplastic syndrome), which further limits the ability to treat patients, and adversely affects quality of life. Hence, there is a need for treatment options that patients can tolerate. Treatment with CAR T-cell therapy, according to the committee members, is not anticipated to cause long-term marrow damage issues. The clinicians noted that a third-line therapy with a CAR T-cell therapy would be appropriate, given that current therapy provides less benefit to patients with r/r FL disease. Patients eligible to receive axicabtagene ciloleucel in clinical practice would be similar to patients included in the clinical trial, according to the experts. However, patients with severe organ dysfunction, poor performance status, and uncontrolled infections would be ineligible. The clinicians pointed out that patients who had received prior CD19-directed therapy should be considered for treatment with CAR T-cell therapy and highlighted the need for flexibility around patients' Eastern Cooperative Oncology Performance Status (ECOG PS) or Karnofsky Performance Status (KPS) scores. The committee members noted that some patients might become ineligible to receive CAR T-cell therapy during manufacturing, which may lead to discontinuation.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The drug plans identified implementation issues related to initiation, prescribing, generalizability, funding algorithm, care provision, system issues, and economic considerations. The clinical experts consulted by CADTH for this review weighed evidence from the included study and other clinical considerations to provide responses to the drug plan's implementation questions.

Clinical Evidence

Systematic Review

Description of Studies

ZUMA-5 is a multicentre, international, open-label, single-arm phase II trial.[18] The study objective was to determine the efficacy and safety of axicabtagene ciloleucel in patients with r/r FL or marginal zone lymphoma (MZL) after 2 or more lines of systemic therapy. Between [redacted], 127 FL patients were enrolled at 15 sites in the US and 2 in France. There were no study sites in Canada. Prior to receiving any treatments, patients underwent leukapheresis to obtain T cells as part of the manufacturing process for axicabtagene ciloleucel. Patients were then treated with cyclophosphamide and fludarabine lymphodepleting chemotherapy between 5 and 3 days before axicabtagene ciloleucel infusion. After 2 days of rest, patients received axicabtagene ciloleucel through IV infusion with a target dose of 2×10^6 anti-CD19 CAR T cells/kg body weight. Analyses were conducted at 18 months, 24 months, and 36 months. The statistical analysis plan prespecified that tests on the inferential analysis set be conducted at 18 months, that is, on the date when 80 patients had been followed for at least 18 months. Using all enrolled patients, analyses were conducted at 18 months, 24 months (not presented), and 36 months. The data cut-off for the 18-month analysis was September 14, 2020; the data cut-off for the 36-month analysis was March 31, 2022.

At the 36-month time point for analysis, the median age was 60 years (range, 34 years to 79 years) and 62% of patients had an ECOG PS score of 0. Of the enrolled patients, 69% were refractory, defined as progressing within 6 months of their most recent treatment. Most patients enrolled in ZUMA-5 had received 2 prior therapies [redacted], 26% had received 3 prior therapies, 20% had received 4 prior therapies, and 17% had received 5 or more prior therapies. The proportion of patients who had received a prior auto-SCT was 24%, while the proportion of patients with high bulk tumour was 51%. The proportion of patients who had progressed within 24 months of anti-CD20 chemotherapy combination therapy (i.e., progression of disease within 24 months [POD24]) was 55%.

Efficacy Results

A summary of the efficacy results in the ZUMA-5 trial is shown in Table 2.

Overall Survival

The proportion of patients who had died due to any cause was [redacted] after 36 months of follow-up. The median OS had not been reached. Clinical experts considered OS to be the ideal survival end point for decision-making, but acknowledged that due to the extended survival periods seen in r/r FL, immature OS results are common. The Kaplan-Meier (KM) survival probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 75.5% (95% confidence interval [CI], 66.9% to 82.2%).

Progression-Free Survival

The proportion of patients who experienced a progression event was [redacted] after 36 months of follow-up. The median PFS was 40.2 months (95% CI, 28.9 months to not evaluable [NE]). The KM PFS probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 54.4% (95% CI, 44.2% to 63.5%).

Objective Response Rate

At the 36-month time point, the estimated objective response rate (ORR) as per investigator assessment was a clinically meaningful 94% (95% CI, 88% to 97%) in the full analysis set (FAS), while the complete response rate (CRR) was 79% [redacted]. According to clinical experts, and within the context of the extended survival periods in r/r FL, ORR and CRR are considered acceptable surrogate end points for more important survival end points.

The primary end point in the ZUMA-5 trial was ORR at the 18-month analysis in the inferential analysis set, with a prespecified threshold of 40% for ORR and 15% for CRR. The estimated ORR as per central assessment in the 18-month inferential analysis set was 94% [redacted] and the CRR was 79% [redacted]. Subgroup analyses conducted on prespecified baseline characteristics were consistent with the overall results.

Duration of Response

At the 36-month time point for analysis, [redacted] of patients with a response had experienced a loss-of-response event. The estimated median duration of response (DOR) was 38.6 months (95% CI, 29.0 months to NE), which was considered clinically meaningful by the clinical experts consulted by CADTH. The KM-estimated

event-free probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was [redacted].

Time to Next Treatment

At the 36-month time point for analysis, [redacted] of patients had experienced a time-to-next-treatment (TTNT) event. The median TTNT was NE months (95% CI, 37.8 months to NE). The KM-estimated event-free probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 59.5% (95% CI, 50.2% to 67.6%).

Harms Results

At the 36-month time point for analysis, a total of [redacted] of patients in the safety analysis set experienced a treatment-emergent adverse event (TEAE) with pyrexia [redacted], hypotension [redacted], headache [redacted], and fatigue [redacted] the most frequently reported TEAEs. A total of [redacted] of patients in the safety analysis experienced a serious adverse event (SAE), with pyrexia [redacted] and pneumonia [redacted] the most frequently reported SAEs. At the 36-month time point, [redacted] of patients in the safety analysis set had died. The most common reason for death was progressive disease [redacted], following by an adverse event (AE) due to reasons other than progressive disease or subsequent therapy [redacted] and secondary malignancy [redacted].

Notable harms identified included CRS, neurologic events, cytopenias, infection, and hypogammaglobulinemia. At the 36-month analysis [redacted] of patients in the safety analysis set had experienced CRS, with [redacted] experiencing a grade 3 or higher CRS. Neurologic events were reported in [redacted] of patients, with [redacted] reporting a grade 3 or higher neurologic event. Cytopenias were reported in [redacted] of patients, with [redacted] of patients reporting a grade 3 or higher cytopenia. Infections were reported in [redacted] of patients, with [redacted] reporting a grade 3 or higher infection. Hypogammaglobulinemia was reported in [redacted] of patients, with [redacted] of patients reporting a grade 3 or higher hypogammaglobulinemia.

Table 2: Summary of Key Results From Pivotal Studies and RCT Evidence

Measure	ZUMA-5		
	Inferential analysis set 18 months (N = 86)	FAS 18 months (N = 127)	FAS 36 months (N = 127)
OS			
Number of patients with event, n (%)	[redacted]	[redacted]	[redacted]
OS time (months), median (95% CI)	NE (31.6 to NE)	[redacted]	NE (NE to NE)
PFS			
Number of patients with event, n (%)	[redacted]	[redacted]	[redacted]
PFS time (months), median (95% CI)	NE (23.5 to NE)	[redacted]	40.2 (28.9 to NE)
Response			
ORR, n (% [95% CI])	81 (94 [redacted])	[redacted]	119 (94 [88 to 97])
CRR, n (% [95% CI])	68 (79 [redacted])	[redacted]	100 (79 [redacted])

Measure	ZUMA-5		
	Inferential analysis set 18 months (N = 86)	FAS 18 months (N = 127)	FAS 36 months (N = 127)
DOR			
–	[redacted]	[redacted]	**N = 119**
Number of patients with events, n (%)	[redacted]	[redacted]	[redacted]
DOR time (months), median (95% CI)[a]	NE (NE to NE)	[redacted]	38.6 (29.0 to NE)
TTNT			
Number of patients with events, n (%)	[redacted]	[redacted]	[redacted]
TTNT time (months), median (95% CI)[a]	NE (NE to NE)	[redacted]	NE (37.8 to NE)
Harms, n (%)			
N	NA	[redacted]	[redacted]
Patients with any TEAE	NA	[redacted]	[redacted]
Patients with any SAE	NA	[redacted]	[redacted]
Deaths	NA	[redacted]	[redacted]
AESI: CRS	NA	[redacted]	[redacted]
AESI: CRS grade ≥ 3	NA	[redacted]	[redacted]
AESI: Neurologic event	NA	[redacted]	[redacted]
AESI: Neurologic event grade ≥ 3	NA	[redacted]	[redacted]
AESI: Cytopenias	NA	[redacted]	[redacted]
AESI: Cytopenias grade ≥ 3	NA	[redacted]	[redacted]
AESI: Infection	NA	[redacted]	[redacted]
AESI: Infection grade ≥ 3	NA	[redacted]	[redacted]
AESI: Hypogammaglobulinemia	NA	[redacted]	[redacted]
AESI: Hypogammaglobulinemia grade ≥ 3	NA	[redacted]	[redacted]

AESI = adverse event of special interest; CI = confidence interval; CRR = complete response rate; CRS = cytokine release syndrome; DOR = duration of response; FAS = full analysis set; NA = not applicable; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTNT = time to next treatment.

Note: ORR, CRR, PFS, and DOR are reported according to central assessment at the 18-month analysis and as per investigator assessment for the 36-month analysis.

Source: ZUMA-5 Clinical Study Report.[18]

Critical Appraisal

The ZUMA-5 trial, the only eligible study identified by the sponsor, was a phase II, single-arm, open-label clinical trial. The lack of comparative data is a key limitation to the interpretation of the results from a single-arm trial, as it is difficult to distinguish between the effect of the intervention, a placebo effect, or the effect of natural history. Due to the open-label design of the trial, the response outcomes measures (i.e., ORR, CRR, DOR, PFS) and subjective harms are at risk of measurement or reporting bias, though the direction of

this bias is unclear. It is noted that these limitations are partly addressed through the use of a prespecified threshold for ORR and CRR end points and the use of central assessment.

Another important limitation of the ZUMA-5 trial is related to the insufficient follow-up time to draw strong conclusions on the long-term survival impacts of axicabtagene ciloleucel for patients with r/r FL. The clinical experts consulted by CADTH noted that r/r FL is a disease that can have very long periods of PFS and survival, suggesting that the follow-up duration was not long enough to fully capture the effects on OS and PFS. In addition, subsequent treatments could confound the long-term survival results of the ZUMA-5 trial.

According to the clinical experts consulted by CADTH, the ZUMA-5 trial patient population is overall representative of the patients in the population with r/r FL in Canada who would be receiving axicabtagene ciloleucel. However, the clinical experts noted that patients seen in clinical practice would include those with poorer performance status (the ZUMA-5 trial only included patients with an ECOG PS score of 0 or 1, whereas clinical experts suggest that an ECOG PS score of 2 may be treated in the clinical setting), and patients with more comorbidities. The clinical experts had different opinions regarding patients who received prior CD19-targeted therapy; some suggested that any prior CD19-targeted therapy would preclude the use of axicabtagene ciloleucel, whereas others suggested that only patients who are refractory to CD19-targeted therapy (did not respond or relapsed within 6 months) would not be suitable candidates for treatment with axicabtagene ciloleucel. According to the clinical experts consulted by CADTH, the efficacy outcomes used in this study are clinically relevant and important for the clinical trials in r/r FL, with the notable exception of health-related quality of life (HRQoL) outcomes, which are important to patients but were excluded from the ZUMA-5 trial. As such, it is not possible to determine how the introduction of axicabtagene ciloleucel will impact the HRQoL of patients in Canada.

Long-Term Extension Studies

No long-term extension studies were submitted as part of this review.

Indirect Comparisons

No indirect treatment comparisons were submitted as part of this review.

Studies Addressing Gaps in the Evidence From the Systematic Review

The aim of the sponsor was to provide an estimate of relative efficacy against standard of care therapies in patients with r/r FL who have received 2 or more lines of therapy.[19]

Description of Studies

The relative efficacy of axicabtagene ciloleucel versus standard of care estimated among the ZUMA-5 treated population using propensity scores with standardized mortality ratio (SMR) weights. The SCHOLAR-5 trial, the standard of care cohort, is a retrospective, observational, multicentre, database study of patients with r/r FL (grades 1 to 3a) who have received 2 or more systemic therapies. Patient-level data for the ZUMA-5 and SCHOLAR-5 trials were used to inform the comparative analysis. Propensity scores were calculated for each patient in the pooled analysis set to account for differences in baseline characteristics across populations. Selection of variables for the propensity score model was determined in a hierarchal

manner and based on the advice of investigators/clinical experts with the goal of minimizing the imbalance in prognostically important covariates.

Efficacy Results

The ORR in the ZUMA-5 population was 93.7% compared to 54.0% in the propensity score–weighted SCHOLAR-5 population (odds ratio [OR] = 12.66; 95% CI, 5.24 to 30.57). The CRR in the ZUMA-5 population was 78.7% compared to 34.9% in the propensity score–weighted SCHOLAR-5 population (OR = 6.90; 95% CI, 3.62 to 13.18). The median DOR in the ZUMA-5 population was 38.64 months (95% CI, 29.04 months to NE) compared to [redacted] in the propensity score–weighted SCHOLAR-5 population (hazard ratio [HR] = [redacted]).

The median PFS in the ZUMA-5 population was 40.21 months (95% CI, 28.94 months to NE) compared to 12.97 months (95% CI, 7.75 months to 15.47 months) in the propensity score–weighted SCHOLAR-5 population (HR = 0.27; 95% CI, 0.18 to 0.41). The median OS in the ZUMA-5 population was NE (95% CI, NE to NE) compared to NE (38.40 months to NE) in the propensity score–weighted SCHOLAR-5 population (HR = 0.56; 95% CI, 0.33 to 0.95). The median TTNT in the ZUMA-5 population was NE (95% CI, 37.85 months to NE) compared to 26.61 months (95% CI, 12.65 months to NE) in the propensity score–weighted SCHOLAR-5 population, with HR of 0.60 (95% CI, 0.39 to 0.93).

Harms Results

Safety end points were not included in the analysis.

Critical Appraisal

Due to differences between the ZUMA-5 and SCHOLAR-5 cohorts in treatment allocation, it is possible that the treatment effect estimate is confounded by imbalances in prognostic covariates across populations. The sponsor identified and adjusted for several important variables, resulting in a suitable balance of these characteristics across both populations; however, important characteristics such as FLIPI score could not be adjusted for due to missing data. Characteristics such as ECOG PS, FL grade, and whether patients were double refractory differed significantly between populations after propensity score weighting. The clinical experts consulted by CADTH suggested that differences in ECOG PS score and the proportion of patients who are double refractory could impact how patients respond to treatment. The direction of this impact is uncertain, with some differences (e.g., double refractory status and FL grade) potentially favouring the SCHOLAR-5 comparator over axicabtagene ciloleucel, and some differences (e.g., ECOG PS score) potentially favouring axicabtagene ciloleucel over the SCHOLAR-5 comparator.

There is additional uncertainty in the results due to the low effective sample sizes in both the ZUMA-5 trial and the SCHOLAR-5 cohort. The removal of the DELTA patients from the SCHOLAR-5 cohort resulted in a statistically significant change in the mean number (standard deviation [SD]) of lines of prior therapy: [redacted] in the SCHOLAR-5 trial compared to [redacted] in the ZUMA-5 trial. Differences between populations in the number of lines of prior therapy in particular affect determining how patients would be expected to respond to treatment. The proportion of patients with POD24 and the proportion of patients who were refractory to

their most recent treatment was also reduced with the exclusion of the DELTA cohort, indicating that their removal from the SCHOLAR-5 cohort resulted in a population with a lower risk prognosis.

Conclusions

Evidence from a single-arm study (the ZUMA-5 trial) suggests that treatment with axicabtagene ciloleucel affects clinically important tumour responses, including complete remission, in adult patients with r/r FL after 2 or more lines of systemic therapies. Due to the single-arm design of the trial and limited duration of follow-up, there is insufficient evidence to determine the magnitude of the effect of axicabtagene ciloleucel on OS and PFS. HRQoL outcomes were not included in the ZUMA-5 trial and therefore the impact of axicabtagene ciloleucel on patients HRQoL is unknown. The harms associated with the axicabtagene infusion are as expected given the mechanism of action and prior experience in other indications.
The comparison of the ZUMA-5 trial to the retrospective SCHOLAR-5 external control was limited by heterogeneity across study designs and populations. Specifically, the inability to adjust for ECOG PS and double refractory status can introduce bias to the estimation procedure within the comparative populations. Generalizability to individuals that do not meet the ZUMA-5 trial criteria is also in question. Therefore, the magnitude of the comparative efficacy estimates for axicabtagene ciloleucel against standard of care in the Canadian setting is uncertain.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of axicabtagene ciloleucel (target of 2×10^6 CAR-positive viable T cells/kg body weight, for IV use; range, 1×10^6 cells/kg to 2.4×10^6 cells/kg) in the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy.

Disease Background

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CADTH review team.

NHL encompasses a heterogenous group of more than 80 closely related cancers.[1] It is characterized by the abnormal and uncontrolled proliferation of cells (i.e., T cells, B cells, and natural killer cells) of the lymphatic system.[2,3] About 85% to 90% of NHLs develop from B lymphocytes, and the rest from T lymphocytes or natural killer cells.[2,20] NHL is the fifth most common cancer diagnosed in Canada, and is commonly diagnosed in adults aged 50 years or older.[1] In 2022, an estimated 11,400 new diagnoses of NHL and 3,000 deaths from NHL were projected for Canada.[21] The estimates were higher in males (6,600 new cases and 1,700 deaths) than in females (4,800 new cases and 1,250 deaths).[21] Risk factors for all NHL-related cancers include immune disorders (e.g., rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus), the use of immunosuppressive therapies, bacterial and viral infections (e.g., *Helicobacter pylori*, Epstein-Barr virus, and hepatitis C virus), family history and genetics, and occupational and lifestyle risk factors.[1-3,20] NHL can affect any organ in the body and has a wide range of clinical presentations.[3,20]

FL, a subtype of NHL, is an indolent B-cell lymphoma originating from the germinal centre of lymphoid tissues,[2-6] and characterized by slow growth and spread.[7] FL makes up 20% to 30% of all NHL cases[1] and up to 70% of all indolent NHL cases. There are limited epidemiological data on FL in Canada compared with other NHL-associated cancers. One study that looked at trends (incidence and mortality) of FL across Canada using data from 3 registries (the Canadian Cancer Registry, the Registre québécois du cancer, and the Canadian Vital Statistics database) reported that there were about 22,625 new cases of FL between 1992 and 2010. The mean age of patients was 60.8 years at diagnosis, with equal incidence rates observed in males and females (50% in each sex) in the study population.[6] The authors also reported a variability in incidence rates across provinces, with rates in Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island notably higher than the national average.[6,22] The sponsor-calculated overall incidence rate of FL in Canada (based on the age-standardized incidence rates of NHL [25.7 per 100,000] and the reported proportion of FL among NHL cases [25%])[4,6] was 7.21 per 100,000.[4,8,9]

Although responsive to initial first- or second-line therapies, FL is characterized by a relapsing and remitting disease course, especially in advanced disease stages. Patients will eventually require multiple treatments to manage or slow disease progression throughout their lifetime as response to treatments declines with repeated therapy.[3,10-12] The clinical experts consulted by the sponsor reported that approximately [redacted] of incident FL patients would progress to third-line treatment, of which [redacted] would proceed to receive active therapy.[13-15] In Canada, FL is common in people aged 50 years or older, and most are diagnosed at an advanced stage (i.e., 66% to 70% of patients are diagnosed at stage III or IV).[23] FL can be further classified into 3 grades (1, 2, and 3 [a and b]) based on cell structures visible under the microscope, specifically the number of large FL cells (centroblasts).[16] Grades 1, 2, and 3a diseases are generally considered low grade or slow growing compared to grade 3b disease, which grows fast and is considered high grade. FL may relapse or recur to more aggressive or high-grade forms of NHL, such as diffuse large B-cell lymphoma (DLBCL) during the disease, thus requiring other treatment options to manage the disease.[3,24] In a UK study that prospectively followed 325 patients diagnosed with FL between 1972 and 1999, the risk of histologic conversion to more aggressive forms was reported to be 28% (95% CI, 23% to 34%) by 10 years of diagnosis.[3,25] Some FL patients present with no symptoms, while others present with a range of symptoms, most of which are not specific to FL. Typical symptoms include adenopathy, splenomegaly, locally obstructing symptoms, fever, night sweats, and weight loss.[1,3,26]

Survival depends on the prognostic factors used in the FLIPI score.[24] The FLIPI prognostic score system takes into account the following factors: age (> 60 years versus ≤ 60 years), Ann Arbor stage (III to IV versus I to II), number of involved nodal areas (> 4 versus ≤ 4), hemoglobin level (< 120 g/L versus ≥ 120 g/L), and serum lactate dehydrogenase concentration (above normal versus normal or below).[27] Patients with "good" prognostic FLIPI scores respond well to treatment compared to patients with "poor" FLIPI scores, in whom cancer may recur following treatment.[24] According to the Canadian Cancer Society, 91% of patients considered "low risk" at diagnosis according to the FLIPI score have a 5-year survival rate and 71% have a 10-year survival rate; 78% of patients considered "intermediate risk" have 5-year survival rate and 51% have a 10-year survival rate; and 53% of patients considered high risk have a 5-year survival rate and 36% have a 10-year survival rate.[17] Casulo and colleagues (2015)[28] reported that patients with POD24 after

first-line rituximab therapy experienced particularly poor outcomes. In a previous study, the same authors reported that patients with POD24 had a 5-year survival rate of only 50% compared to 90% for patients without POD24.[28]

NHL, including FL, is diagnosed using immunohistochemical and genetic testing of tissue samples biopsied from lymph nodes.[20] Patients undergo diagnostic testing to confirm r/r FL grade 1, 2, or 3a disease after 2 or more lines of systemic therapies. Testing may include a history and physical examination, tissue biopsy to confirm relapse or rule out transformation to aggressive lymphoma, imaging tests (PET scans or CT scans), and laboratory tests (e.g., complete blood counts). The timing of diagnostic tests relative to receiving axicabtagene ciloleucel may vary between patients.[29]

Standards of Therapy

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CADTH review team.

The treatment goals for FL vary depending upon the stage of the FL and individual patient factors. In general, available treatments for stage I to II FL have curative potential; however, for most patients with stage III to IV FL, no curative therapies are available. Therefore, the main goals of treatment are to cure the lymphoma in patients with stage I to II FL, and to extend remission in patients with stage III to IV FL.[30]

Once a diagnosis of FL is confirmed, the gold standard for the management of asymptomatic patients with indolent FL is watchful waiting, also known as "watch and wait."[26,31] According to the clinical experts consulted by CADTH, watch and wait is a common practice for many patients with FL, even after disease relapse.

First-Line Treatments

For small, localized symptomatic FL, radiotherapy is considered the standard of care according to North American and European guidelines.[30,32,33] This is supported by several provincial guidelines in Canada.[34,35] For grade 1, 2, and 3a FL, the preferred chemoimmunotherapy regimen is bendamustine plus rituximab, based on high-level evidence of efficacy and favourable tolerability in this population.[26,30,36] In frail and older patients, rituximab monotherapy, a chemotherapy-free approach, is the preferred first-line regimen according to European and North American guidelines.[37,38] However, some treatment centres in Canada do not have access to rituximab monotherapy. Instead, physicians keep patients on bendamustine plus rituximab for several treatment cycles for as long as possible. Beyond first-line treatment, there is currently no gold standard of care for the r/r FL population.

Second-Line Treatments

Treatment options for second-line regimens for r/r FL depend on several factors, including level of fitness, prior treatment, and length of time to relapse.[30] The preferred treatment strategy in this patient population is combined immunochemotherapy, such as O-CHOP (obinutuzumab, cyclophosphamide, doxorubicin hydrochloride [hydroxydaunorubicin], vincristine sulphate [Oncovin], and prednisone).[30] SCT may be considered in young and fit patients with no comorbidities in the second-line setting. Auto-SCT is given

more often than allo-SCT in this population. However, only a small subset of FL patients would be eligible for transplant in the second line. SCT is limited by highly selective eligibility criteria and is typically reserved for younger, medically fit patients with chemotherapy-sensitive disease.[30,37,39,40] The clinical experts consulted by CADTH agreed with these strategies.

Third-Line Treatments

FL is a relapsing disease with continued unmet need in adult patients with r/r FL after 2 or more lines of therapy despite the availability of established therapies. Patients with r/r FL in the third- and later-line treatment setting represent a heavily pretreated and advanced-stage patient population. The standard of care in Canada for the third-line treatment of r/r FL is heterogenous and varies across regions. Based on Canadian clinician input, a heterogenous mix of immunochemotherapy (for most patients) and SCT (for a minority of patients) are the current treatment options in this hard-to-treat population.

Treatments in this setting may include SCT; however, there is controversy with regard to clinical benefit of SCT in patients with r/r FL, and both allo-SCT and auto-SCT may be associated with significant mortality and morbidity.[30,37,39-41] While SCT has been included in the third-line treatment algorithm diagram for r/r FL, few people with r/r FL are expected to be eligible for SCT in the third line.

According to clinical experts consulted by the sponsor, most patients in the third-line treatment setting will continue recycling combined immunochemotherapy that might have been used in previous lines, including the following regimens (which are the most frequently used options in Canada): rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin hydrochloride), oncovin (vincristine sulphate), and prednisone (R-CHOP); obinutuzumab, cyclophosphamide, doxorubicin hydrochloride [hydroxydaunorubicin], oncovin (vincristine sulphate), and prednisone (O-CHOP); rituximab plus gemcitabine, dexamethasone, and cisplatin (R-GDP); bendamustine plus rituximab; and rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE). Although it is used by some physicians in their clinical practice, lenalidomide plus rituximab regimen is currently not officially indicated for treatment of FL in Canada, as per the most recent Canadian product monograph for lenalidomide.[42] Furthermore, although no official submission has been made by the sponsor to Canadian health technology assessment agencies, CADTH conducted a health technology review of lenalidomide plus rituximab in r/r B-cell NHL and concluded that available evidence remains limited.[43] According to Canadian clinicians' input, access to lenalidomide plus rituximab is somewhat limited in some provinces. In the third-line setting and beyond, idelalisib, a phosphoinositide 3-kinase (PI3K) inhibitor, is indicated for the treatment of patients with r/r FL in Canada.[44] However, idelalisib is not publicly reimbursed across Canada and is inaccessible at some sites, according to several clinicians.[45] Furthermore, it is generally at the bottom of the treatment list due to serious side effects and is, therefore, used as a palliative treatment. In recent years, CAR T-cell therapy has emerged as another form of immunotherapy for the treatment of blood cancers, including lymphomas. While promising results have been reported for the CAR T-cell therapies for advanced-stage lymphomas, severe adverse effects related to CAR T-cell therapy, such as CRS and neurologic toxicities, have also been reported.[46] One CAR T-cell product, tisagenlecleucel, has been recently approved by Health Canada (December 2022) with a Notice of Compliance with conditions for the treatment of adult patients with r/r

FL grade 1, 2, or 3a after 2 or more lines of systemic therapy.[47] Note that at the time of writing this report, tisagenlecleucel has not been publicly funded for this indication.

In clinical practice, a patient's response to treatment is commonly assessed using the Lugano classification,[48] in which fluorodeoxyglucose-PET/CT is incorporated into the initial Ann Arbor Staging System for fluorodeoxyglucose-avid lymphomas.

Drug Under Review

Axicabtagene ciloleucel (Yescarta) is a CD19-directed genetically modified autologous T-cell immunotherapy (i.e., CAR T-cell therapy) that binds to CD19-expressing cancer cells and normal B cells.[49] Following anti-CD19 CAR T-cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.[49] Axicabtagene ciloleucel is a single-dose, 1-time treatment in a patient-specific infusion bag. Axicabtagene ciloleucel should be administered by experienced health professionals in specialized treatment centres. Each patient-specific, single-infusion bag contains a suspension of anti-CD19 CAR-positive viable T cells in approximately 60 mL for a target dose of 2×10^6 anti-CD19 CAR T cells/kg body weight (range, 1×10^6 cells/kg to 2.4×10^6 cells/kg), to a maximum of 2×10^8 anti-CD19 CAR T cells for patients weighing 100 kg or more.[49]

Axicabtagene ciloleucel was approved in Canada on September 28, 2022, for the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. Axicabtagene ciloleucel has been previously reviewed by CADTH for 2 indications. On August 15, 2019, CADTH issued a positive recommendation for axicabtagene ciloleucel for adult patients with r/r large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from FL. On January 5, 2023, another positive recommendation was posted for the treatment of adult patients with DLBCL or high-grade B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy, who are eligible for auto-SCT.

Key characteristics of axicabtagene ciloleucel are summarized in Table 3 with other treatments available for FL.

Table 3: Key Characteristics of Axicabtagene Ciloleucel

Characteristics	Axicabtagene ciloleucel[49]
Mechanism of action	A CD19-directed genetically modified autologous T-cell immunotherapy, that is, a CAR T-cell therapy that binds to CD19-expressing cancer cells and normal B cells
Indication[a]	The treatment of adult patients with relapsed or refractory grade 1, 2, or 3a FL after 2 or more lines of systemic therapy
Route of administration	IV infusion for 1-time treatment

Characteristics	Axicabtagene ciloleucel[49]
Recommended dose	1-time treatment 2×10^6 CAR-positive viable T cells/kg body weight (maximum of 2×10^8 cells/kg body weight)
Serious adverse effects or safety issues	• CRS • Neurologic AEs • Prolonged cytopenias • Hypogammaglobulinemia • Serious infections • Secondary malignancies • Tumour lysis syndrome

AE = adverse event; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; FL = follicular lymphoma.
[a]Health Canada–approved indication.
Source: Yescarta Product Monograph.[49]

Stakeholder Perspectives

Patient Group Input

This section was prepared by the CADTH review team based on the input provided by patient groups. The full original patient input received by CADTH has been included in the Stakeholder section of this report.

One patient advocacy group, LC, provided input for this review. LC is a national Canadian registered charity whose mission is to empower patients and the lymphoma community through education, support, advocacy, and research. LC collaborates with patients, caregivers, health care professionals, other organizations, and stakeholders to promote early detection, find new and better treatments for lymphoma patients, help patients access treatments, learn about the causes of lymphoma, and work together to find a cure. The LC patient group expressed the need for accessible treatment options for patients, highlighting that local access to treatments will significantly improve patients' experience by reducing fear and the risk of getting sick while travelling and patient quality of life. The LC patient group expressed the need for accessible treatment options for patients, highlighting that local access to treatments will significantly improve patients' quality of life and experience by reducing fear and the risk of getting sick while travelling.

LC gathered information for this input via online surveys completed anonymously by patients between April 21, 2022, and April 3, 2023. Of the 143 responses submitted, 3 respondents reported having experience with axicabtagene ciloleucel. Of the total surveyed, 86% of respondents lived in Canada, 71% were aged between 55 and 64 years, 64% were female, and 34% had received a FL diagnosis within the last 3 to 5 years. Respondents indicated that fatigue (50%), body aches and pain (33%), enlarged lymph nodes (33%), indigestion (32%), and bodily swelling (21%) were the most challenging symptoms with the biggest impact on their quality of life at the time of diagnosis. Respondents described FL symptoms as challenges in their daily lives that impacted their ability to travel (46%), spend time with family or friends (41%), exercise (37%), concentrate (36%), and work or complete school or volunteer activities (35%). Anxiety or worry (84%), stress

from diagnosis (77%), fear of progression (70%), and difficulty sleeping (48%) were the most common psychosocial symptoms that impacted patients.

About half (49%) of the respondents reported that they went through a period of watchful waiting before commencing treatment. Most respondents (43%) had received 1 line of treatment. The most common treatments reported by respondents who had received 1 or 2 lines of therapy included chemotherapy, chemoimmunotherapy, rituximab with or without bendamustine, or radiation. When asked to describe their treatment experience, 57% of respondents indicated that they were "satisfied" or "very satisfied" with the treatment options in the front-line setting. Only 22% of respondents indicated that they were "satisfied" or "very satisfied" with the current treatment options in the r/r setting. While describing how their current therapy (or most recent therapy) was able to manage their FL symptoms on a scale of 1 (strongly disagree) to 5 (strongly agree), 40% of respondents strongly agreed and 20% strongly disagreed. According to the respondents, the post-treatment symptoms that most significantly negatively impacted them included treatment-related fatigue (28%), immediate side effects of treatment (26%), and low activity level (23%). Fatigue (69%), hair loss (41%), and constipation (38%) were the most common side effects reported by respondents.

The most important outcomes (rated 5 on a scale of 1 to 5) included delaying disease progression (84%), longer disease remission (82%), improved quality of life, ability to perform daily activities (69%), ability to control disease symptoms (63%), and ability to normalize blood counts (58%). In total, 68% of respondents indicated a willingness to tolerate nonsevere side effects over the short-term period when undertaking a novel therapy, 42% expressed the importance of having a choice in deciding treatment options based on known side effects and expected outcomes, and 79% noted the need for more accessible treatment options that were proven to be effective for FL.

Two respondents completed all questions about axicabtagene ciloleucel in the survey. One survey respondent who confirmed that they had prior treatment experience with axicabtagene ciloleucel did not complete all other treatment questions. The 2 respondents who completed the survey reported having access to treatment via a clinical trial. One patient received treatment in the second-line and the other in the fifth-line setting. Reported side effects included CRS, neutropenia, febrile neutropenia, thrombocytopenia, constipation, and swelling. According to the respondents, the challenges that significantly impacted their physical and mental health during treatment included the frequent monitoring of side effects postinfusion, the inability to perform daily activities, and being away from family and friends. One respondent indicated they were away from home for 1 to 3 months, while the other was away for more than 3 months. Other highlighted challenges included financial issues due to absence from work and travel accommodation expenses accumulated during the clinical trial. Both respondents stated that they had a good or very good experience with axicabtagene ciloleucel and would recommend the treatment to other patients with r/r FL.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the review of axicabtagene ciloleucel, a panel of 4 clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion follows.

Unmet Needs

The clinical panel indicated that for patients with FL, the most important goals for an ideal treatment are to prolong survival (both OS and PFS) and to improve their quality of life. However, patients with r/r FL relapse after the front-line therapies or are refractory to the available treatments, which impacts their long-term PFS and quality of life. In addition, current treatments may not be well tolerated by some patients due to the related adverse events or complications associated with SCT. The clinical panel indicated that the greatest unmet needs for the current treatments exist for patients with cancer that progresses within 2 years after their initial therapy, for those who have already received auto-SCT or are ineligible for auto-SCT, and for those who have been double refractory to earlier line treatments (implying they have limited treatment options available to them). Patients who are eligible for CAR T-cell therapy but ineligible for auto-SCT would generally be older and less able to tolerate the auto-SCT process.

Place in Therapy

The treatment algorithm for adult patients with r/r FL is complicated. Many factors (e.g., patient characteristics, previous treatments, treatment effects and toxicity, drug plan coverage, disease progression and transformation, and patient preference) need to be considered before making decisions. Watch and wait is a common first-line approach for many patients with FL, and is also considered, though less commonly, after disease relapse. Patients who need active treatments typically receive bendamustine or rituximab-based therapies such as bendamustine plus rituximab, R-CVP, R-CHOP, or lenalidomide plus rituximab in the first- and second-line setting. PI3K inhibitors are rarely used. Patients with relapsed disease after treatment with chemoimmunotherapy, particularly those who progress within 2 years, may receive auto-SCT if they are suitable candidates. The clinical panel noted that some evidence suggests that auto-SCT cures half of the patients with POD24 and with PFS in the 20- to 30-year range. After all these treatments, some patients maintain the indolent status and some transform to large cell lymphoma; therefore, the proportion of patients who may be considered for treatment with CAR T-cell therapy is small. The clinical panel suggested that axicabtagene ciloleucel is most appropriate for use as a third or later line of treatment for patients

with r/r FL. These patients usually have a treatment response that lasts less than 6 months from their last treatment (medication or SCT). There are not many options available for the patients at this stage. CAR T-cell therapy would be considered because it has a different mechanism of action.

The clinical panel noted that an auto-SCT is not mandatory before axicabtagene ciloleucel can be given, since this is not standard of care in Canada. The clinical panel suggested that an auto-SCT before axicabtagene ciloleucel would be recommended if the patient had access to auto-SCT and was eligible, noting that 80% of auto-SCT are performed after the first or second relapse.

For patients who have received previous CD19-targeted therapy, there is a lack of evidence to suggest whether the use of axicabtagene ciloleucel is appropriate.

Patient Population

The clinical panel indicated that, in practice, CAR T-cell therapy is used in a patient population that is broader than that in clinical trials, to which a more select population is recruited. For example, the panel noted that suitable candidates for treatment with axicabtagene ciloleucel would be patients with acceptable rather than excellent organ function, which is what is generally required for an auto-SCT. When determining whether axicabtagene ciloleucel treatment is suitable for a particular patient, bulk of disease and rapid disease progression are among the factors that need to be taken into account. In clinical practice, patients' suitability can be determined based on clinical judgment, which combines medical history, laboratory and imaging findings, and often a lymph node biopsy.

The panel also noted that the patients who did not meet the eligibility criteria in the ZUMA-5 clinical trial (e.g., because they had certain comorbidities or disease status) would be the least suitable candidates for treatment with axicabtagene ciloleucel. Patients with an ECOG PS score of 3 or higher are also least suitable for treatment with axicabtagene ciloleucel.

The panel noted that there is no specific patient characteristic that can be used to predict who would respond better to axicabtagene ciloleucel than other patients.

Assessing the Response Treatment

The panel indicated that in clinical practice, patients are evaluated and followed in a manner similar to that described in the clinical trials of FL treatments. Remission and survival are measured. Physical exams and imaging exams are routinely conducted to assess the patient's response to CAR T-cell therapy.

The panel suggested that meaningful responses to treatment with axicabtagene ciloleucel would include a high complete remission rate, durability of treatment response, and long-term PFS and OS. Ideally, a successful treatment would show a plateau in the PFS and OS curves. In addition, the clinicians were interested in knowing if the treatment is cost-effective. Ideally, the treatment benefits of axicabtagene ciloleucel can be compared to the other treatments.

The panel noted that after CAR T-cell therapy, clinicians would assess the treatment response (e.g., via CT scan) every 3 months, or sooner if needed.

When Patients Go Through Pretreatment but Do not Receive Axicabtagene Ciloleucel

The panel noted that situations when patients go through pretreatment but do not receive axicabtagene ciloleucel are rare. However, this can happen because of rapid disease progression in the interim or because the patient has major complications such as a new myocardial infarction or stroke. Manufacturing failure is another reason for this situation, although it is not expected to be an issue with axicabtagene ciloleucel.

If patients do not receive axicabtagene ciloleucel after undergoing pretreatment, most of them (in particular, high-risk patients) can progress within 6 months of their last treatment, and limited treatment options are then available for them. Palliative chemotherapy can be given. Other options may include radiation therapy, more chemotherapy, novel agents, or a clinical trial, depending on each patient's clinical status.

Therapy Post Axicabtagene Ciloleucel Failure

The panel indicated that after infusion with axicabtagene ciloleucel and failure of treatment, patients may participate in a clinical trial. In the absence of a clinical trial, patients may try a different chemoimmunotherapy that they have not been exposed to or undergo auto-SCT if they have not already received this therapy.

Prescribing Considerations

The panel emphasized the importance of an accredited multidisciplinary team involving hematologists, infectious disease specialists, neurologists, an ICU team, and other specialists to diagnose, treat, and monitor the patients receiving axicabtagene ciloleucel and to ensure the safe and effective delivery of this treatment.

Clinician Group Input

This section was prepared by the CADTH review team based on the input provided by clinician groups. The full original clinician group input received by CADTH has been included in the Stakeholder section of this report.

Input from 1 clinician group, the OH-CCO Hematology Cancer Drug Advisory Committee, was summarized for this review. The OH-CCO Hematology Cancer Drug Advisory Committee provides timely, evidence-based clinical and health system guidance on drug-related issues supporting the OH-CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. Information in this input was obtained via video conferencing and email.

According to the clinicians consulted, the disease course of FL varies for every patient. Some patients may present with long remissions between therapies while others would have refractory disease. Current treatment goals for patients with FL, according to the clinician group, include palliative care and, in some scenarios, treatment with curative intent using allo-SCT. The most important goals outlined were to delay disease progression, improve patient HRQoL, and alleviate symptoms. Current standard of care for FL patients identified by the clinician group included chemotherapy, chemoimmunotherapy, auto-SCT, allo-SCT (for a selected group of patients), and radiation (to control symptoms and for palliative care scenarios). The OH-CCO Hematology Cancer Drug Advisory Committee acknowledged that current treatment options do not meet the needs of patients with r/r FL. The OH-CCO Hematology Cancer Drug Advisory Committee

mentioned that patients who become refractory to chemotherapy have no other treatment options to delay the disease. In addition, the committee members highlighted that repeated administration of cytotoxic therapy may be associated with marrow damage (myelodysplastic syndrome), which further limits the ability to treat patients, and adversely affects quality of life. Hence, there is a need for treatment options that patients can tolerate. Treatment with a CAR T-cell therapy, according to the clinical group, is not anticipated to cause long-term marrow damage issues. The committee members said that a third-line therapy with a CAR T-cell therapy would be appropriate, given that current therapy provides less benefit to patients with r/r FL. The OH-CCO Hematology Cancer Drug Advisory Committee clinicians could not ascertain whether CAR T-cell therapy would replace auto-SCT; however, they said that they suspect that CAR T-cell therapy might be tried first, rather than auto-SCT, for patients with a history of chemotherapy-refractory forms of FL. The clinician group noted that there would be a prevalent FL patient population that will become eligible for axicabtagene ciloleucel at the time of its implementation. According to the clinicians, patients eligible to receive axicabtagene ciloleucel in clinical practice should be similar to patients included in the clinical trial. However, patients with severe organ dysfunction, poor performance status, and uncontrolled infections would be ineligible. The clinicians pointed out that patients who had received prior CD19-directed therapy (these patients were excluded from the trial) should be considered for treatment with CAR T-cell therapy and highlighted the need for flexibility around patients' ECOG PS or KPS scores. The experts also noted that some patients might become ineligible to receive CAR T-cell therapy during the manufacturing process, which may lead to discontinuation. The clinician group noted that axicabtagene ciloleucel may have a toxicity profile that is different from that of tisagenlecleucel (Kymriah), another CAR T-cell therapy currently under review. The clinician group input aligned with the input provided by the clinical experts consulted during the CADTH review.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
Should patients with the following be considered for treatment with axicabtagene ciloleucel? • ECOG PS > 1 • prior CD19-targeted therapy (e.g., blinatumomab, tafasitamab) • prior allo-SCT • prior CAR T-cell therapy • active CNS involvement	ECOG PS > 1: The clinical experts agreed that despite the ZUMA-5 trial being limited to patients with ECOG PS of 0 and 1, physicians would likely use axicabtagene ciloleucel in patients with ECOG PS of 2. Patients with an ECOG PS ≥ 3 would not be suitable candidates for treatment with axicabtagene ciloleucel. Prior CD19-targeted therapy: The clinical experts had different opinions. Some suggested that any prior CD19-targeted therapy would preclude the use of axicabtagene ciloleucel. Others suggested that only patients who are refractory to CD19-targeted therapy (did not respond or relapsed within 6 months) would not be suitable candidates for

Drug program implementation questions	Clinical expert response
• other types of low-grade lymphoma (e.g., MZL, Waldenström macroglobulinemia, MALT lymphoma) • grade 3b FL	treatment with axicabtagene ciloleucel. Prior allogeneic transplant: The clinical experts had different opinions. Some suggested that prior allogeneic transplant would preclude the use of axicabtagene ciloleucel. Others suggested that axicabtagene ciloleucel should not be considered only if the allogeneic transplant was recent or if there were ongoing issues with graft-versus-host disease. Prior CAR T-cell therapy: The clinical experts agreed that patients who have received prior CAR T-cell therapy should not be given axicabtagene ciloleucel. Active CNS: The clinical experts agreed that patients with active CNS involvement should not be given axicabtagene ciloleucel. Other types of low-grade lymphoma: The clinical experts noted that a small number of patients with MZL were included in the ZUMA-5 trial and axicabtagene ciloleucel would be expected to be efficacious in this population. There is a lack of evidence for Waldenström macroglobulinemia and MALT lymphoma. The clinical experts did not expect axicabtagene ciloleucel to be used in these populations. Grade 3b FL: The clinical experts agreed that patients with grade 3b FL are not eligible for treatment with axicabtagene ciloleucel. The clinical experts noted that these patients would fall under the category of DLBCL and treatment decisions should be made from that perspective.
In the trial, monotherapy rituximab is not counted as a line of therapy. In some jurisdictions, single-agent rituximab is a funded option. What is the place in therapy for axicabtagene ciloleucel in these patients?	The clinical experts agreed with the design of the ZUMA-5 trial and did not believe that single-agent rituximab should be considered as a line of therapy. Single-agent rituximab is generally used for 4 weeks and then stopped. The clinical experts warned that considering the use of rituximab as a full line of therapy would make axicabtagene ciloleucel eligible earlier than is appropriate in the disease course.
Is there sufficient evidence to support re-treatment?	The clinical experts agreed that there was limited evidence to support re-treatment of patients with axicabtagene ciloleucel and that re-treatment would be unlikely to occur in the Canadian setting.
Considerations for prescribing of therapy	
Delivery must take place at specialized treatment centres that are accredited and certified by the manufacturer. There continues to be limited access to CAR T-cell therapy in Canada. While access is expanding, interprovincial travel or out-of-country funding remains necessary in many parts of Canada. Due to geographical site limitations, patients may need to travel for treatment requiring interprovincial agreements to ensure equitable access.	Comment from the drug plans to inform pERC deliberations.
The provincial advisory group noted that tisagenlecleucel is also under review for r/r FL. Should the criteria for axicabtagene ciloleucel be aligned with that of tisagenlecleucel?	The clinical experts agreed that given the similarities between axicabtagene ciloleucel and tisagenlecleucel, the prescribing criteria should be aligned.

Drug program implementation questions	Clinical expert response
Generalizability	
Should patients who recently started third or later line of systemic therapy be switched to CAR T-cell therapy provided all other criteria are met?	The clinical experts agreed that if a patient is responding to and tolerating a third or later line of therapy, it would not be appropriate to take them off that therapy and switch to axicabtagene ciloleucel.
Funding algorithm (oncology only)	
Under what clinical circumstances would axicabtagene ciloleucel be used over tisagenlecleucel and vice-versa?	The clinical experts noted that they expect axicabtagene ciloleucel and tisagenlecleucel to differ in regard to safety profiles, specifically in terms of neurologic toxicity and CRS. A patient who may not be able to tolerate axicabtagene ciloleucel would be given tisagenlecleucel instead. No comparative evidence is available to inform this decision.
Care provision issues	
Is postprogression biopsy needed to confirm that the disease has not transformed to DLBCL or other excluded histology before starting axicabtagene ciloleucel?	The clinical experts agreed that while a postprogression biopsy is preferred, it is not always feasible. As such, a postprogression biopsy should not be a requirement for access to axicabtagene ciloleucel.
System and economic issues	
Feasibility of adoption (including budget impact) must be addressed. Although the sponsor estimates a low uptake for axicabtagene ciloleucel, the provincial advisory group is concerned that this may be an underestimate and that existing capacity may not be able to meet demand.	Comment from the drug plans to inform pERC deliberations.
If manufacturing delays occur, how would this impact the clinical effectiveness of axicabtagene ciloleucel?	The clinical experts noted that given the slow growing nature of r/r FL, manufacturing delays are not expected to significantly impact clinical effectiveness like might occur with other, faster growing cancers.

CAR = chimeric antigen receptor; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; MALT = mucosa-associated lymphoid tissue; MZL = marginal zone lymphoma; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; r/r = relapsed or refractory.

Clinical Evidence

The objective of this Clinical Review was to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of axicabtagene ciloleucel, target dose of 2×10^6 CAR T cells/kg body weight, to a maximum of 2×10^8 CAR-positive viable T cells, by IV infusion, in the treatment of adult patients with r/r FL after 2 or more lines of systemic therapy. The focus is to compare axicabtagene ciloleucel to relevant comparators and identify gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of axicabtagene ciloleucel is presented in 2 sections, with CADTH's critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes a pivotal study that was selected according to the sponsor's systematic review protocol. The second section includes 1 additional study that was considered by the sponsor to address important gaps in the systematic review evidence.

Included Studies

Clinical evidence included in the CADTH review and appraised in this document:

- 1 pivotal study identified in systematic review
- 1 additional study addressing gaps in evidence.

Systematic Review

Contents within this section have been informed by materials submitted by the sponsor. The following have been summarized and validated by the CADTH review team.

Description of Studies

Details of the included studies are summarized in Table 5.

Table 5: Details of Studies Included in the Systematic Review

Detail	ZUMA-5
Designs and populations	
Study design	Open-label, single-arm, interventional phase II
Locations	**17 sites in 2 countries:** 15 sites in the US and 2 sites in France
Patient enrolment dates	[redacted]
Randomized (N)	N = 127 (FL, enrolled); N = 25 (MZL, enrolled) • The ZUMA-5 trial evaluated the efficacy of axicabtagene ciloleucel in r/r iNHL of FL and MZL histological subtypes. The indication to be reviewed is for FL only, which is the focus of the summary presented here. n = 124 (received axicabtagene ciloleucel; safety analysis set) n = 86 (inferential analysis set)
Inclusion criteria	• Eligible patients were aged 18 years or older and had histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL (grade 1, grade 2, or grade 3a). • Eligible patients had r/r disease after 2 or more lines of therapy (which must have included an anti-CD20 monoclonal antibody combined with an alkylating agent; single-agent anti-CD20 antibody did not count as an eligible line of therapy), and at least 2 weeks or 5 half-lives must have elapsed since any prior systemic therapy. Patients with stable disease (without relapse) > 1 year from completion of last therapy were not eligible. • Eligible patients had at least 1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma[48] and an ECOG PS score of 0 or 1.
Exclusion criteria	• Patients were excluded if they had transformed FL, FL histological grade 3b, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, or a history of malignancy other than nonmelanoma skin cancer or carcinoma. • Patients were excluded if they had prior allo-SCT, auto-SCT within 6 weeks of planned axicabtagene ciloleucel infusion, CD19-targeted therapy, or CAR or other genetically modified T-cell therapies. • Patients were ineligible if they had an infection or a history of CNS disorders, CSF malignant cells, cardiovascular disease, autoimmune disease, DVT or pulmonary embolism, or severe immediate hypersensitivity reaction to any of the agents used in this study.

Detail	ZUMA-5
Drugs	
Intervention	Patients received conditioning chemotherapy of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) administered over 3 days, 3 to 5 days before axicabtagene ciloleucel infusion. Axicabtagene ciloleucel infusion (target dose of 2 × 10^6 anti-CD19 CAR T cells/kg body weight).
Study duration	
Screening phase	28 days
Conditioning phase	Day −5 to day −3
Treatment phase	Day 0 single day infusion
Follow-up phase	Every 3 months (from month 6 to month 18) Every 6 months (from month 24 to month 60) Every 12 months (from month 72 to year 15)
Outcomes	
Primary end point	ORR by central assessment (18 and 36 months)
Secondary and exploratory end points	Secondary (18 and 36 months): • CRR by central assessment • ORR and CRR by central assessment in patients with ≥ 3 lines of prior therapy • ORR by investigator assessment • Best overall response (CR, PR, stable disease, progressive disease, or not evaluable as best response to treatment) by central and investigator assessment • DOR by central and investigator assessment • PFS by central and investigator assessment • OS • TTNT • Incidence of TEAEs and clinically significant changes in laboratory values • Incidence of immunogenicity against the anti-CD19 CAR • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum
Publication status	
Publications	Jacobson et al. (2020)[50] Jacobson et al. (2020)[51] Neelapu et al. (2021)[52] Jacobson et al. (2022)[53]
Clinical trial number	NCT03105336[18]

allo-SCT = allogeneic stem cell transplant; auto-SCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CNS = central nervous system; CR = complete response; CRR = complete response rate; CSF = cerebrospinal fluid; DOR = duration of response; DVT = deep vein thrombosis; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; MZL = marginal zone lymphoma; ORR = objective response rate; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; PR = partial response; r/r = relapsed or refractory; TEAE = treatment-emergent adverse event; TTNT = time to next treatment.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

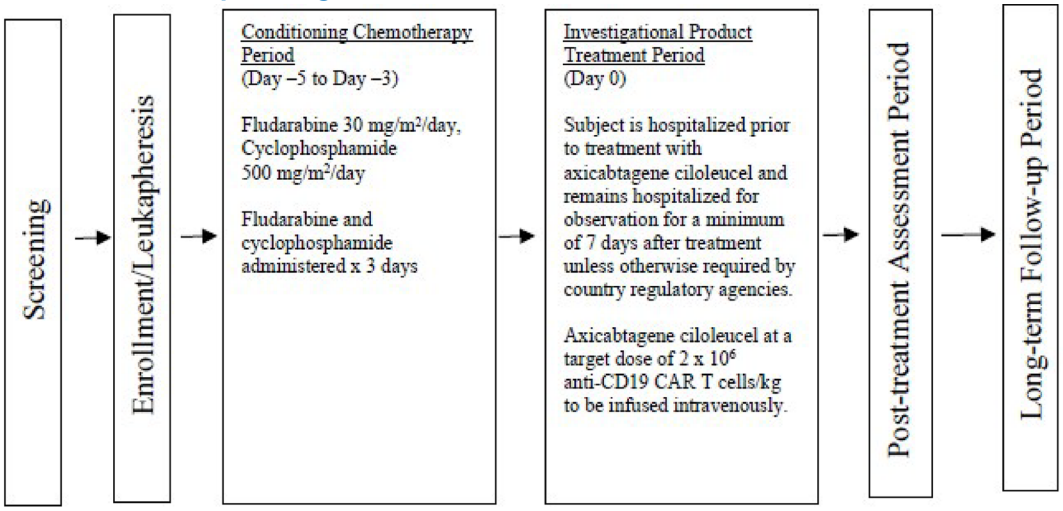
Source: ZUMA-5 Clinical Study Report.[18]

The ZUMA-5 trial is a multicentre, international, open-label, single-arm phase II trial. The study objective was to determine the efficacy and safety of axicabtagene ciloleucel in patients with r/r FL or MZL after 2 or more lines of systemic therapy. In line with the submitted reimbursement request and anticipated Health Canada indication, the r/r FL patient group will be the focus of this review. The ZUMA-5 study design, shown in Figure 1, consisted of screening, enrolment/leukapheresis, a conditioning chemotherapy period, a 1-time IV infusion of axicabtagene ciloleucel, posttreatment assessment, and long-term follow-up.

Between [redacted], 127 FL patients were enrolled at 15 sites in the US and 2 in France. There were no study sites in Canada. Prior to receiving any treatments, patients underwent leukapheresis to obtain T cells as part of the manufacturing process for axicabtagene ciloleucel. Patients were then treated with cyclophosphamide and fludarabine lymphodepleting chemotherapy between 5 and 3 days before axicabtagene ciloleucel infusion. After 2 days of rest, patients received axicabtagene ciloleucel through IV infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg body weight. PET-CT scans for disease assessment were conducted at week 4, month 3, month 6, month 9, month 12, month 15, month 18, month 24, and at any subsequent scheduled or unscheduled visit if disease progression was a clinical concern, as per standard of care.

Analyses were conducted at 18 months, 24 months (not presented), and 36 months. The statistical analysis plan prespecified that tests be conducted on the inferential analysis set at 18 months; this was defined as the point when 80 patients had been followed for at least 18 months. Using all enrolled patients, analyses were conducted at 18 months, 24 months, and 36 months; this population of patients is referred to as the FAS. The data cut-off for the 18-month analysis was September 14, 2020, and the data cut-off for the 36-month analysis was March 31, 2022.

Figure 1: ZUMA-5 Study Design



CAR = chimeric antigen receptor.

Source: Reproduced as is from ZUMA-5 Clinical Study Report.[18]

Populations

Inclusion and Exclusion Criteria

Patients eligible for inclusion in the ZUMA-5 trial were aged 18 years or older, with a confirmed diagnosis of r/r indolent NHL, with FL limited to grade 1, 2, or 3a, and with r/r disease after 2 or more lines of systemic therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. Eligible patients were required to have least 1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma,[48] an ECOG PS score of 0 or 1, and no known history of central nervous system involvement. Patients were excluded from the ZUMA-5 trial if they had transformed disease or if they had received auto-SCT within 6 weeks of the planned axicabtagene ciloleucel infusion.

Interventions

Five days before axicabtagene ciloleucel infusion, patients received an IV conditioning chemotherapy regimen of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day. Patients were treated with these chemotherapies over 3 days to induce lymphocyte depletion. Following 2 days of rest, patients received axicabtagene ciloleucel infusion at a target dose of 2 × 10^6 anti-CD19 CAR T cells/kg body weight. Patients who achieved a partial response at the 3-month assessment but subsequently experienced disease progression were eligible for an optional course of re-treatment with conditioning chemotherapy and axicabtagene ciloleucel.

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs were restricted for 7 days before leukapheresis and 5 days before axicabtagene ciloleucel administration. Systemic corticosteroids were restricted as premedication to patients for whom CT scans with contrast were contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Corticosteroids and other immunosuppressive drugs were restricted for 3 months after axicabtagene ciloleucel administration unless used to manage axicabtagene ciloleucel–related or other severe toxicities (e.g., anaphylaxis). Treatments for the patient's lymphoma other than what was defined/allowed in the protocol, such as chemotherapy, immunotherapy, targeted agents, radiation, high-dose corticosteroid, and other investigational agents, were prohibited, except as needed for treatment of disease progression after axicabtagene ciloleucel infusion.

Outcomes

A list of the efficacy end points assessed in this review is provided in Table 6. Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence as well as any outcomes identified as important according to the clinical experts consulted by CADTH and stakeholder input from patient and clinician groups and public drug plans. Using the same considerations, the CADTH review team selected end points they considered to be most relevant for informing the CADTH Canadian Drug Expert Committee (CDEC) in its deliberations and finalized this list of end points in consultation with members of the expert committee.

The primary end point of the ZUMA-5 trial was ORR, defined as the incidence of a complete response (CR) or a partial response, as determined by central assessment. These end points were defined by the Lugano

classification criteria. Key secondary end points determined by central assessment included the CRR, defined as the incidence of CR as the best response to treatment, and the ORR and CRR in patients who had 3 or more lines of prior therapy. Other secondary end points included the best overall response, defined as the incidence of CR, partial response, stable disease, progressive disease, or NE as the best response to treatment, as adjudicated by central assessment. The DOR was measured in patients who had an objective response and was defined as the time from the first objective response to disease progression or death. PFS was defined as the time from the date of axicabtagene ciloleucel infusion for the inferential or safety analysis sets (or date of leukapheresis for the FAS) to the date of disease progression or death, while OS was defined as the time from the date of axicabtagene ciloleucel infusion for the inferential or safety analysis sets (or date of leukapheresis for the FAS) to the date of death. TTNT was defined as the time from the date of axicabtagene ciloleucel infusion to the start of new lymphoma therapy or death. Patient-reported outcomes were not reported in the ZUMA-5 trial.

Safety outcomes that occurred with the onset or after infusion of axicabtagene ciloleucel were reported as TEAEs. The incidence of TEAEs and SAEs were summarized by preferred term, according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. The severity of AEs was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.03 or more recent editions. AEs of special interest were also reported and include CRS, neurologic events, cytopenias, infection, and hypogammaglobulinemia.

Table 6: Outcomes Summarized From the Studies Included in the Systematic Review

Outcome measure	Time point	ZUMA-5
ORR by central assessment	18 months	Primary
CRR by central assessment	18 months	Secondary
ORR and CRR by central assessment in patients with ≥ 3 lines of prior therapy[a]	18 months	Secondary
Best overall response (CR, PR, stable disease, progressive disease, or not evaluable as best response to treatment) by central and investigator assessment	18 months	Secondary
ORR by investigator assessment	18 and 36 months	Secondary
DOR by central assessment	18 months	Secondary
DOR by investigator assessment	18 and 36 months	Secondary
PFS by central assessment	18 months	Secondary
PFS by investigator assessment	18 and 36 months	Secondary
OS	18 and 36 months	Secondary
TTNT	18 and 36 months	Secondary
Safety outcomes after infusion of axicabtagene ciloleucel	18 and 36 months	Secondary

CR = complete response; CRR = complete response rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; TTNT = time to next treatment.

[a]All other outcomes were analyzed in patients with 2 or more lines of prior therapy unless otherwise specified.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]
Source: ZUMA-5 Clinical Study Report.[18]

Statistical Analysis

The FAS of the ZUMA-5 trial consists of all enrolled patients (n = 127). The inferential analysis set was defined as the first 80 patients followed for 18 months after axicabtagene ciloleucel treatment. For any patient who could have but did not attend the 18-month study visit, an additional patient was added, resulting in 86 patients included in the inferential analysis set. This sample size (n = 86) provided 93% power to reject the null hypothesis of an ORR of less than or equal to 40% at the alpha level of 0.0237 under an assumed alternative ORR of 60%.

An interim analysis was conducted for efficacy outcomes when 30 patients had been followed for 6 months after axicabtagene ciloleucel infusion. The nominal alpha level for the assessment of efficacy for this analysis was 0.0003. Another interim analysis was conducted when 80 patients had been followed for 6 months after axicabtagene ciloleucel infusion. The nominal alpha level for the assessment of efficacy for this analysis was 0.0005. Another interim analysis was conducted when at least 80 patients had been followed for at least 9 months after the first disease response assessment. The nominal alpha level for the assessment of efficacy for this analysis was 0.0005. Primary analysis was to be performed when at least 80 patients in the inferential analysis set had been followed for 12 months after the first disease response assessment, reserving alpha of 0.0237 for the final significance test.

At each interim analysis, 4 hypotheses were tested in the inferential analysis set using a fixed sequence procedure to control overall type I error at 1-sided alpha level of 0.025. In order, the hypotheses tested were ORR as determined by central assessment, CRR as determined by central assessment, ORR as determined by central assessment in the patients who had had 3 or more lines of prior therapy, and CRR as determined by central assessment in the patients who had had 3 or more lines of prior therapy. Each significance test used the alpha allocated at the time of interim analysis.

Analyses conducted on the FAS at the 18-month and 36-month cut-off dates were intended to be descriptive, and power calculations were not conducted.

Subgroup Analyses

Prespecified baseline subgroups used to examine key efficacy and safety analyses include age (< 65 years, ≥ 65 years), sex, race, ethnicity, FLIPI total score, ECOG PS score (0, 1), meeting the criteria for high tumour bulk load as per the Groupe d'Étude des Lymphomes Folliculaires (GELF) versus not meeting these criteria, relapsed versus refractory at study entry, time to relapse from initiation of first anti-CD20 chemotherapy combination therapy (≥ 24 months, < 24 months), prior treatment with PI3K inhibitor, number of lines of prior therapy, and double refractory status.

Table 7: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
ORR[a]	95% CI calculated using the Clopper-Pearson method	NA	Patients who do not meet the criteria for an ORR by the analysis cut-off date will be considered nonresponders.	Conducted in the FAS and the safety analysis set
Best overall response rate (including CRR)[a]	95% CI calculated using the Clopper-Pearson method	NA	Derivation of this end point only includes response assessments obtained after initiation of axicabtagene ciloleucel infusion and up to progressed disease or the disease assessments before subsequent anticancer therapy.	Conducted in the FAS and the safety analysis set
DOR	KM estimates, 2-sided 95% CI	NA	Patients who do not meet the criteria for progression or death by the analysis cut-off date will be censored at their last evaluable disease assessment date.	Conducted in the FAS and the safety analysis set[a]
PFS	KM estimates, and 2-sided 95% CI	NA	Patients who do not meet the criteria for progression by the analysis cut-off date will be censored at their last evaluable disease assessment date.	Conducted in the FAS and the safety analysis set[a]
OS	KM estimates, 2-sided 95% CI	NA	Patients who have not died by the analysis cut-off date will be censored by their last date known to be alive before the data cut-off date.	Conducted in the FAS and the safety analysis set
TTNT	KM estimates, 2-sided 95% CI	NA	Patients who have not received subsequent new therapy and are still alive will be censored at the last contact date.	Conducted in the FAS and the safety analysis set

CI = confidence interval; CR = complete response; DOR = duration of response; FAS = full analysis set; KM = Kaplan-Meier; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTNT = time to next treatment.

[a]Per central assessment.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: ZUMA-5 Clinical Study Report.[18]

Analysis Populations

A summary of the analysis populations in the ZUMA-5 trial is shown in Table 8.

Results

Patient Disposition

A summary of patient disposition in the ZUMA-5 trial is presented in Table 9. At the 36-month analysis, [redacted] patients with either FL or MZL had been screened, with 127 patients enrolled in the FL group and included in the FAS. Discontinuation from the study occurred for [redacted] of patients, with the majority discontinuing due to

death ([redacted]). Median follow-up at the 36-month analysis was [redacted]). The safety analysis set included only the 124 patients who received an axicabtagene ciloleucel infusion. Patient disposition for the inferential 18-month analysis was not reported.

Table 8: Analysis Populations in the ZUMA-5 Trial

Population	Definition
FAS	All enrolled (leukapharesed) patients
Safety analysis set	All patients treated with any dose of axicabtagene ciloleucel
Inferential analysis set	Enrolled patients treated with any dose of axicabtagene ciloleucel who met the eligibility criteria stipulated in protocol amendment 2 or higher. The first 86 patients treated with axicabtagene ciloleucel who reached the 18-month follow-up were included.
Re-treatment analysis set	All participants who underwent re-treatment with axicabtagene ciloleucel

FAS = full analysis set.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: ZUMA-5 Clinical Study Report.[18]

Table 9: Summary of Patient Disposition From Studies Included in the Systematic Review

Patient disposition	ZUMA-5	
	Axicabtagene ciloleucel FAS[a] 18 months (N = 127)	Axicabtagene ciloleucel FAS[a] 36 months (N = 127)
Screened, N	181[b]	[redacted]
Reason for screening failure, n (%)	[redacted]	[redacted]
Failed to meet eligibility criteria, n	[redacted]	[redacted]
Investigator decision, n	[redacted]	[redacted]
Enrolled, N (%)	127	127
Discontinued from study, n (%)	[redacted]	[redacted]
Reason for discontinuation by patients who did not receive axicabtagene ciloleucel, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patient withdrawal of consent from further follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Reason for discontinuation by patients who received axicabtagene ciloleucel, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]

Patient disposition	ZUMA-5	
	Axicabtagene ciloleucel FAS[a] 18 months (N = 127)	Axicabtagene ciloleucel FAS[a] 36 months (N = 127)
Investigator decision	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Patient withdrawal of consent from further follow-up	[redacted]	[redacted]
FAS, N	127	127
Follow-up time (months), mean (SD)	[redacted]	[redacted]
Follow-up time (months), median (range)	[redacted]	[redacted]
PP, N	124	124
Safety, N	124	124

FAS = full analysis set; PP = per protocol; SD = standard deviation.

[a]Patient disposition was not reported for the 18-month inferential analysis set.

[b]Reported number of patients screened includes patients with follicular lymphoma (FL) or marginal zone lymphoma. The number of patients with FL only was not reported.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: ZUMA-5 Clinical Study Report.[18]

Baseline Characteristics

A summary of baseline characteristics in the ZUMA-5 trial is shown in Table 10. In the FAS, the median age was 60 years (range, 34 years to 79 years) and 62% of patients had an ECOG PS score of 0. Of the enrolled patients, 69% were refractory, defined as progressing within 6 months of their most recent treatment. Most patients enrolled in the ZUMA-5 trial had received 2 prior therapies ([redacted]), 26% had received 3 prior therapies, 20% had received 4 prior therapies, and 17% had received 5 or more prior therapies. The proportion of patients who had received a prior auto-SCT was 24%, while the proportion of patients with high bulk tumour was 51%. The proportion of patients who had progressed within 24 months of anti-CD20 chemotherapy combination therapy (i.e., POD24) was 55%.

The baseline characteristics outlined in Table 10 are limited to those most relevant to this review as prognostic or effect-modifying variables.

Table 10: Summary of Baseline Characteristics From Studies Included in the Systematic Review

Characteristic	ZUMA-5	
	Inferential analysis set 18 months (N = 86)	FAS 36 months (N = 127)
Age (years), median (range)	[redacted]	60 (34 to 79)
< 65 years, n (%)	[redacted]	87 (69)
Male, n (%)	48 (56)	75 (59)
Female, n (%)	38 (44)	52 (41)
Race, n (%)		
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
White	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG PS, n (%)		
0	[redacted]	79 (62)
1	[redacted]	48 (38)
Histological category at study entry, n (%)		
Grade 1	20 (23)	34 (27)
Grade 2	43 (50)	63 (50)
Grade 3a	23 (27)	30 (24)
Disease stage, n (%)		
I	2 (2)	[redacted]
II	9 (10)	[redacted]
III	35 (41)	[redacted]
IV	40 (47)	[redacted]
FLIPI total score, n (%)		
0	3 (3)	[redacted]
1	10 (12)	[redacted]
2	33 (38)	[redacted]
3	25 (29)	[redacted]
4	12 (14)	[redacted]
5	3 (3)	[redacted]

Characteristic	ZUMA-5	
	Inferential analysis set 18 months (N = 86)	FAS 36 months (N = 127)
Low risk (0 to 1)	13 (15)	[redacted]
Intermediate risk (2)	33 (38)	[redacted]
High risk (3 to 5)	40 (47)	56 (44)
Relapsed or refractory subgroup[a]		
Relapsed	23 (27)	40 (31)
Refractory	63 (73)	87 (69)
Number of prior therapies, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	33 (26)
4	[redacted]	25 (20)
≥ 5	[redacted]	22 (17)
Response to last line of therapy, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
NE	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Receiving prior auto-SCT	21 (24)	30 (24)
POD24, n (%)	49 (57)	70 (55)
High tumour bulk, n (%)	[redacted]	65 (51)
Prior therapies, n (%)		
PI3K inhibitor	[redacted]	36 (28)
Anti-CD20 single agent	[redacted]	40 (31)
Alkylating agent	[redacted]	[redacted]
Anti-CD20 + alkylating agent	[redacted]	[redacted]
Lenalidomide	[redacted]	38 (30)

auto-SCT = autologous stem cell transplant; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FAS = full analysis set; FLIPI = Follicular Lymphoma International Prognostic Index; NE = not evaluable; PI3K = phosphoinositide 3-kinase; POD24 = progression of disease within 24 months; PR = partial response.

[a]Patients with FL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Patients with FL who progressed 6 months after completing the most recent prior treatment are defined as relapsed.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]
Source: ZUMA-5 Clinical Study Report.[18]

Exposure to Study Treatments

As axicabtagene ciloleucel is a single infusion, treatment exposure measures such as total patient-weeks, duration, and adherence are not applicable. Patients in the ZUMA-5 trial were eligible for re-treatment (n = 11 in the 18-month FAS and n = 13 in the 36-month FAS). It is not anticipated that axicabtagene ciloleucel will be eligible for use in re-treatment in Canada.

Table 11: Summary of Concomitant and Subsequent Treatment in the ZUMA-5 Trial

Exposure	ZUMA-5	
	Safety analysis set 18 months (N = 124)	Safety analysis set 36 months (N = 124)
Concomitant medications and procedures		
Received concomitant therapy of interest, n (%)	[redacted]	[redacted]
Corticosteroids, n (%)	[redacted]	[redacted]
Tocilizumab, n (%)	[redacted]	[redacted]
Vasopressors	[redacted]	[redacted]
Nonsteroidal immunosuppressive agents	[redacted]	[redacted]
Immunoglobulins	[redacted]	[redacted]
Endotracheal intubation	[redacted]	[redacted]
Subsequent therapy		
Received subsequent stem cell transplant, n (%)	[redacted]	[redacted]
Received subsequent anticancer therapy, n (%)	[redacted]	[redacted]

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]
Source: ZUMA-5 Clinical Study Report.[18]

Efficacy

Overall Survival

A summary of the OS results from the ZUMA-5 trial is shown in Table 12. At the 36-month FAS time point, [redacted] of patients had died due to any cause, and the median OS had not been reached. The KM-estimated survival probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 75.5% (95% CI, 66.9% to 82.2%). Results for the 18-month inferential analysis set and FAS are shown for context. The estimated OS curve in the ZUMA-5 trial is shown in Figure 2.

Table 12: OS in the ZUMA-5 Trial

Characteristic	ZUMA-5		
	Inferential analysis set 18 months (N = 86)	FAS 18 months (N = 127)	FAS 36 months (N = 127)
Death from any cause, n (%)	[redacted]	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]	[redacted]
OS time (months), median (95% CI)	NE (31.6 to NE)	[redacted]	NE (NE to NE)
Survival probability at 18 months,% (95% CI)[a]	88.3 (79.4 to 93.5)	[redacted]	[redacted]
Survival probability at 24 months, % (95% CI)[a]	[redacted]	[redacted]	[redacted]
Survival probability at 36 months, % (95% CI)[a]	NE	[redacted]	75.5 (66.9 to 82.2)

CI = confidence interval; FAS = full analysis set; NE = not evaluable; OS = overall survival.

[a]Survival probabilities are according to Kaplan-Meier estimates.

Source: ZUMA-5 Clinical Study Report.[18]

Figure 2: Redacted

CI = confidence interval; FL = follicular lymphoma; NE = not evaluable.

This figure has been redacted.

Source: ZUMA-5 Clinical Study Report.[18]

Progression-Free Survival

A summary of the PFS results from the ZUMA-5 trial is shown in Table 13. At the 36-month FAS time point, [redacted] of patients had experienced a progression event. The median PFS was 40.2 months (95% CI, 28.9 months to NE). The KM-estimated PFS rate at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 54.4% (95% CI, 44.2% to 63.5%). Results for the 18-month inferential analysis set and 18-month FAS are shown for context. The estimated PFS curve in the ZUMA-5 trial is shown in Figure 3.

Table 13: PFS in the ZUMA-5 Trial

Characteristic	ZUMA-5		
	Inferential analysis set 18 months (N = 86)	FAS 18 months (N = 127)	FAS 36 months (N = 127)
Events, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]
PFS time (months), median (95% CI)	NE (23.5 to NE)	[redacted]	40.2 (28.9 to NE)
PFS probability at 18 months, % (95% CI)[a]	68.8 (57.4 to 77.8)	[redacted]	[redacted]
PFS probability at 24 months, % (95% CI)[a]	[redacted]	[redacted]	[redacted]
PFS probability at 36 months, % (95% CI)[a]	NE	[redacted]	54.4 (44.2 to 63.5)

CI = confidence interval; FAS = full analysis set; NE = not evaluable; PFS = progression-free survival.

Note: PFS is reported according to central assessment at the 18-month analysis and as per investigator assessment for the 36-month analysis.

[a]Survival probabilities are according to Kaplan-Meier estimates.

Source: ZUMA-5 Clinical Study Report.[18]

Figure 3: Redacted

CI = confidence interval; FAS = full analysis set; NE = not evaluable; PFS = progression-free survival.

This figure has been redacted.

Note: PFS is reported as per investigator assessment for the 36-month analysis.

Source: ZUMA-5 Clinical Study Report.[18]

Objective Response Rate

A summary of the response results for the ZUMA-5 trial is shown in Table 14. At the 36-month FAS time point, the ORR as per investigator assessment was 94% (95% CI, 88% to 97%), while the CRR was 79% ([redacted]). The primary end point in the ZUMA-5 trial was ORR at the 18-month analysis in the inferential analysis set. The estimated ORR as per central assessment was 94% ([redacted]) and the CRR was 79% ([redacted]), sufficient to reject the null hypotheses of 40% for ORR and 15% for CRR.

Table 14: ORR in the ZUMA-5 Trial

Characteristic	ZUMA-5		
	Inferential analysis set 18 months (N = 86)	FAS 18 months (N = 127)	FAS 36 months (N = 127)
ORR, n (%, [95% CI][a])	81 (94 [ ])		119 (94 [88 to 97])
P value	NA[b]	NA	NA
CRR, n (%, [95% CI][a])	68 (79 [ ])		100 (79 [ ])
P value	NA[b]	NA	NA
PR, n (%)	13 (15)		19 (15)
Stable disease, n (%)			2 (2)
Progressive disease, n (%)			2 (2)
Undefined/no disease, n (%)			
Not done, n (%)[c]			4 (3)

CI = confidence interval; CRR = complete response rate; FAS = full analysis set; NA = not applicable; NE = not evaluable; ORR = objective response rate; PR = partial response.

[a]95% CI from the Clopper-Pearson method.

[b]Hypothesis testing was conducted on an earlier 18-month data cut-off with 84 patients yielding significant P values (P < 0.0001) for both ORR and CRR.

[c]Patients who were treated with axicabtagene ciloleucel but died before first disease assessment were recorded as having a "not done" response.

Note: ORR is reported according to central assessment at the 18-month analysis and as per investigator assessment for the 36-month analysis.

Source: ZUMA-5 Clinical Study Report.[18]

The ORR results for selected subgroups, based on discussion with clinical experts consulted by CADTH, are presented in Table 15. The results appear to be consistent across all subgroups, with the ORR from in patients who received 1 prior line of therapy to in patients whose disease had progressed within less than 24 months.

The CRR results for selected subgroups, based on discussions with clinical experts consulted by CADTH, are presented in Table 16. The results appear to be consistent across all subgroups, with the CRR from | in patients who received 1 prior line of therapy to in patients who received 3 prior therapies.

Table 15: Subgroup Analysis of ORR as per Investigator Assessment — 36-Month FAS

Subgroup	ZUMA-5 36-month FAS	
	N	ORR, n (% [95% CI[a]])
Number of lines of prior therapy		
1		
2		
3		

Subgroup	ZUMA-5 36-month FAS	
	N	ORR, n (% [95% CI[a]])
≥ 4	[redacted]	[redacted]
Relapsed or refractory		
Relapsed	[redacted]	[redacted]
Refractory	[redacted]	[redacted]
High tumour bulk per GELF criteria		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Time to relapse from first anti-CD20 chemotherapy combination therapy		
< 24 months	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; GELF = Groupe d'Étude des Lymphomes Folliculaires; ORR = objective response rate.
Note: ORR is reported as per investigator assessment for the 36-month analysis.
[a]95% CI is from the Clopper-Pearson method.
Source: ZUMA-5 Clinical Study Report.[18]

Table 16: Subgroup Analysis of CRR as per Investigator Assessment — 36-Month FAS

Subgroup	ZUMA-5 36-month FAS	
	N	CRR, n (% [95% CI[a]])
Number of lines of prior therapy		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
Relapsed or refractory		
Relapsed	[redacted]	[redacted]
Refractory	[redacted]	[redacted]
High tumour bulk per GELF criteria		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Time to relapse from first anti-CD20 chemotherapy combination therapy		

Subgroup	ZUMA-5 36-month FAS	
	N	CRR, n (% [95% CI[a]])
< 24 months	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]

CI = confidence interval; CRR = complete response rate; FAS = full analysis set; GELF = Groupe d'Étude des Lymphomes Folliculaires.

Note: CRR is reported as per investigator assessment for the 36-month analysis.

[a]95% CI is from the Clopper-Pearson method.

Source: ZUMA-5 Clinical Study Report.[18]

Duration of Response

A summary of the DOR results from the ZUMA-5 trial is shown in Table 17. At the 36-month FAS time point, [redacted] of patients no longer demonstrated a response, and the median DOR was 38.6 months (95% CI, 29.0 months to NE). The KM-estimated event-free probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 57.1% (95% CI, 46.6% to 66.3%).

Table 17: DOR in the ZUMA-5 Trial

Characteristic	ZUMA-5		
	Inferential analysis set 18 months (N = 81)	FAS 18 months (N = 117)	FAS 36 months (N = 119)
Number of patients with events, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)[a]	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	NE (NE to NE)	[redacted]	38.6 (29.0 to NE)
Event-free probability at 18 months, % (95% CI)[b]	[redacted]	[redacted]	[redacted]
Event-free probability at 24 months, % (95% CI)[b]	[redacted]	[redacted]	[redacted]
Event-free probability at 36 months, % (95% CI)[b]	[redacted]	[redacted]	57.1 (46.6 to 66.3)
Follow-up time (months), median (95% CI)[c]	[redacted]	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; NE = not evaluable; NR = not reported.

Note: DOR is reported according to central assessment at the 18-month analysis and as per investigator assessment for the 36-month analysis.

[a]Reasons for censoring for DOR may include: response ongoing, lost to follow-up, investigator decision, started new anticancer therapy, stem cell transplant, re-treatment.

[b]Survival probabilities are according to Kaplan-Meier estimates.

[c]Median follow-up time derived using the reverse Kaplan-Meier approach.

Source: ZUMA-5 Clinical Study Report.[18]

Time to Next Treatment

A summary of the TTNT results from the ZUMA-5 trial is shown in Table 18. At the 36-month FAS time point, [redacted] of patients had experienced a TTNT event; the median TTNT was NE months (95% CI, 37.8 months to NE). The KM-estimated event-free probability at 18 months was [redacted], at 24 months was [redacted], and at 36 months was 59.5% (95% CI, 50.2% to 67.6%).

Table 18: TTNT in the ZUMA-5 Trial

Characteristic	ZUMA-5		
	Inferential analysis set 18 months (N = 86)	FAS 18 months (N = 127)	FAS 36 months (N = 127)
Events, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)[a]	[redacted]	[redacted]	[redacted]
TTNT time (months), median (95% CI)	NE (NE to NE)	[redacted]	NE (37.8 to NE)
Event-free probability at 18 months, % (95% CI)[b]	[redacted]	[redacted]	[redacted]
Event-free probability at 24 months, % (95% CI)[b]	[redacted]	[redacted]	[redacted]
Event-free probability at 36 months, % (95% CI)[b]	NR	[redacted]	59.5 (50.2 to 67.6)
Follow-up time (months), median (95% CI)[c]	[redacted]	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; NE = not evaluable; NR = not reported; TTNT = time to next treatment.

[a]Reasons for censoring for TTNT may include: alive and without new anticancer therapy, lost to follow-up, withdrawal of consent, investigator decision, and end of study due to other reason.

[b]Survival probabilities are according to Kaplan-Meier estimates.

[c]Median follow-up time derived using the reverse Kapan-Meier approach.

Source: ZUMA-5 Clinical Study Report.[18]

Harms

Refer to Table 19 for a summary of harms data in the ZUMA-5 trial.

Adverse Events

At the 36-month time point for analysis, a total of [redacted] of patients in the safety analysis set experienced a TEAE, with pyrexia ([redacted]) hypotension ([redacted]), headache ([redacted]), and fatigue ([redacted]) the most frequently reported TEAEs.

Serious Adverse Events

At the 36-month analysis, a total of [redacted] of patients in the safety analysis set experienced an SAE, with pyrexia ([redacted]), pneumonia ([redacted]), encephalopathy ([redacted]), and confusional state ([redacted]) the only SAEs reported by at least 5% of patients.

Withdrawals Due to Adverse Events

As axicabtagene ciloleucel is a 1-time infusion, withdrawals due to adverse events are not applicable.

Mortality

At the 36-month time point of analysis, [redacted] of patients in the safety analysis set had died. The most common reason was due to progressive disease ([redacted]), following by AE due to reasons other than progressive disease or subsequent therapy ([redacted]) and secondary malignancy ([redacted]). Most "other" classifications of death were related to various infections.

Notable Harms

Notable harms identified by CADTH in consultation with the clinical experts consulted on this review included CRS, neurologic events, cytopenias, infection, and hypogammaglobulinemia. At the 36-month analysis, [redacted] of patients in the safety analysis set had experienced CRS, with [redacted] experiencing a grade 3 or higher CRS. Neurologic events were reported in [redacted] of patients, with [redacted] reporting a grade 3 or higher neurologic event. Cytopenias were reported in [redacted] of patients, with [redacted] of patients reporting a grade 3 or higher cytopenia. Infections were reported in [redacted] of patients, with [redacted] reporting a grade 3 or higher infection. Hypogammaglobulinemia was reported in [redacted] of patients, with [redacted] of patients reporting a grade 3 or higher hypogammaglobulinemia.

Table 19: Summary of Harms Results From Studies Included in the Systematic Review

AEs	ZUMA-5	
	Safety analysis set 18 months (N = 124)	Safety analysis set 36 months (N = 124)
Most common AEs, n (%)[a]		
Patients with any TEAE	123 (99)	[redacted]
Pyrexia	103 (83)	[redacted]
Hypotension	59 (48)	[redacted]
Headache	55 (44)	[redacted]
Fatigue	51 (41)	[redacted]
Nausea	45 (36)	[redacted]
Anemia	44 (35)	[redacted]
Neutropenia	[redacted]	[redacted]
Sinus tachycardia	41 (33)	[redacted]
Tremor	36 (29)	[redacted]
Chills	33 (27)	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Diarrhea	33 (27)	[redacted]

AEs	ZUMA-5	
	Safety analysis set 18 months (N = 124)	Safety analysis set 36 months (N = 124)
Constipation	35 (28)	[redacted]
Vomiting	29 (23)	[redacted]
Decreased appetite	28 (23)	[redacted]
Hypoxia	27 (22)	[redacted]
Confusional state	28 (23)	[redacted]
Cough	27 (22)	[redacted]
Thrombocytopenia	[redacted]	[redacted]
SAEs, n (%)[b]		
Patients with any SAE	57 (46)	[redacted]
Pyrexia	16 (13)	[redacted]
Pneumonia	8 (6)	[redacted]
Encephalopathy	8 (6)	[redacted]
Confusional state	7 (6)	[redacted]
Patients who stopped treatment due to AEs, n (%)		
Patients who stopped treatment	[redacted]	[redacted]
Deaths, n (%)		
Patients who died	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
AE due to reasons other than progressive disease or subsequent therapy	[redacted]	[redacted]
Secondary malignancy	[redacted]	[redacted]
Other, COVID-19	[redacted]	[redacted]
Other, COVID pneumonia with hypoxic respiratory failure	[redacted]	[redacted]
Other, infection	[redacted]	[redacted]
Other, lung infection	[redacted]	[redacted]
Other, sepsis	[redacted]	[redacted]
Other, *Escherichia coli* bacteremia/*E. coli* sepsis with superimposed infection or diarrhea due to *Clostridioides difficile* infection	[redacted]	[redacted]
Other, complications of GVHD	[redacted]	[redacted]
Other, unknown	[redacted]	[redacted]

AEs	ZUMA-5	
	Safety analysis set 18 months (N = 124)	Safety analysis set 36 months (N = 124)
Other, unknown, found via public record	[redacted]	[redacted]
AESIs identified by sponsor, n (%)		
CRS	97 (78)	[redacted]
Grade ≥ 3	8 (6)	[redacted]
Neurologic event	70 (56)	[redacted]
Grade ≥ 3	19 (15)	[redacted]
Cytopenias	[redacted]	[redacted]
Grade ≥ 3	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Grade ≥ 3	19 (15)	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]
Grade ≥ 3	[redacted]	[redacted]

AE = adverse event; AESI = adverse event of special interest; CRS = cytokine release syndrome; GVHD = graft vs. host disease; NA = not applicable; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a]Present in ≥ 20% of patients.

[b]Present in > 5% of patients.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: ZUMA-5 Clinical Study Report.[18]

Critical Appraisal

Internal Validity

The ZUMA-5 trial, the only eligible study identified by the sponsor, was a phase II, single-arm, open-label clinical trial. The lack of comparative data is a key limitation to the interpretation of the results from a single-arm trial, as it is difficult to distinguish between the effect of the intervention, a placebo effect, or the effect of natural history.[54,55] It is acknowledged that there may be practical limitations to conducting a randomized controlled trial in patients with r/r FL (beyond first-line treatment), such as decreasing population size with subsequent lines of therapy and lack of a standard treatment in these later lines of treatment. However, the sponsor's submission included information on the phase III ZUMA-22 trial,[56] which is studying axicabtagene ciloleucel compared to standard of care, and which is currently recruiting patients with results expected in 2027;[56] this suggests that it is possible to conduct a phase III comparative trial in this population. The hypothesized historical control of 40% ORR and 15% CRR was used to determine a clinically meaningful benefit. The prespecified thresholds were established against the response rate derived from studies of available PI3K inhibitors for the treatment of r/r FL.[57] The clinical experts consulted by CADTH supported using a CRR of 15% and an ORR of 40% as clinically relevant thresholds.

Due to the open-label design of the trial, the response outcomes measures (i.e., ORR, DOR, PFS) and subjective harms are at risk of measurement or reporting bias, though the direction of this bias is unclear. The primary end point of ORR was assessed by central assessment at the 18-month primary analysis, which reduces the likelihood that the open-label nature of the trial impacted ORR. Although response rates at the 36-month time point were only assessed by the investigator, which can impact reporting of AEs, response rates as measured by central and investigator assessments were similar at the 18-month analysis, which suggests accurate reporting of the ORR by investigators.

Follow-up time was deemed sufficient for assessing tumour response and safety outcomes associated with axicabtagene ciloleucel. The clinical experts consulted by CADTH noted that r/r FL is a disease that can have very long periods of PFS and survival, suggesting that the follow-up duration was not long enough to fully capture the effects on OS and PFS. In addition to the duration of the study and the noncomparative design, subsequent treatments make it difficult to interpret the OS results. After the infusion of axicabtagene ciloleucel, [redacted] of the patients received at least 1 subsequent antineoplastic medication, and [redacted] of them received SCT. The estimated clinical end point curve (OS) should be interpreted in cases where subsequent treatments are given as the magnitude of patient benefit due to treatment is difficult to quantify.

As treatment with axicabtagene ciloleucel is a 1-time infusion, adherence to treatment is not a concern for internal validity. Of the 127 patients included in the 36-month FAS, [redacted] patients ([redacted]) had discontinued the study before receiving axicabtagene ciloleucel. Clinical experts consulted by CADTH considered this to be a realistic proportion of patients who are unable to complete the treatment process, and representative of clinical practice.

External Validity

According to the clinical experts consulted by CADTH, the ZUMA-5 study population overall represents the patients in the population with r/r FL in Canada who would be receiving axicabtagene ciloleucel. However, the clinical experts noted that patients seen in clinical practice would include those with poorer performance status (the ZUMA-5 trial only included patients with an ECOG PS score of 0 or 1, whereas clinical experts suggest that patients with an ECOG PS score of 2 may be treated in the clinical setting), as well as patients with more comorbidities. The clinical experts differed in their opinions regarding patients who received prior CD19-targeted therapy; some suggested that any prior CD19-targeted therapy would preclude the use of axicabtagene ciloleucel, whereas others suggested that only patients who were refractory to CD19-targeted therapy (did not respond or relapsed within 6 months) would not be suitable candidates for treatment with axicabtagene ciloleucel.

After screening, the procedures and co-interventions (including manufacturing process, depleting chemotherapy, bridging therapy, and post–axicabtagene ciloleucel interventions) were consistent with those adopted in the Canadian setting, although some minor discrepancies exist. The ZUMA-5 trial results can nevertheless be generalized to the population of patients in Canada.

Subgroup analyses were conducted based on prespecified patient characteristics. Due to insufficient follow-up time to observe a large number of survival end points, the OS and PFS subgroup analyses were

considered unstable and therefore uninformative. Based on the subgroup analyses conducted for ORR and CRR, efficacy appears to be present for each patient population based on prior therapies, POD24, tumour bulk, or r/r status.

According to the clinical experts consulted by CADTH, the efficacy outcomes used in this study are clinically relevant and important for the clinical trials in r/r FL, with the notable exception of HRQoL outcomes, which are important to patients but were excluded from the ZUMA-5 trial. As such, it is not possible to determine how the introduction of axicabtagene ciloleucel will impact the HRQoL of patients in Canada.

Lack of long-term data on patients' survival and response rates is another limitation, given that FL is an indolent and slowly progressing disease. Clinical benefits of the treatment need to be evaluated over a longer follow-up time to increase confidence in the durability of response expected from the use of axicabtagene ciloleucel in Canada.

Studies Addressing Gaps in the Systematic Review Evidence

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Objectives for the Summary of Other Relevant Evidence

The ZUMA-5 trial is a single-arm trial and therefore does not provide evidence of efficacy against standard of care for patients with r/r FL who have received 2 or more lines of therapy. Treatment choice for r/r FL is dependent on a variety of factors, including prior therapies, duration of remission, patient-related factors such as age, and clinician/patient preferences. As such, the comparator patients receive can vary considerably. The sponsor submitted evidence of relative efficacy of axicabtagene ciloleucel against standard of care therapies in patients with r/r FL who have received 2 or more lines of therapy.

Description of Other Relevant Evidence

The relative efficacy of axicabtagene ciloleucel versus standard of care was estimated in the ZUMA-5 population using propensity scores with SMR weights.[19] SMR weighting estimates the treatment effect in a population with an equal distribution of risk factors to that of the treatment study participants only.[58] SCHOLAR-5, the standard of care cohort, is a retrospective, observational, multicentre, database study of patients with r/r FL (grades 1, 2, or 3a) who have received 2 or more systemic therapies. The SCHOLAR-5 cohort was derived from 3 international cohorts: IQVIA, Vanderbilt, and DELTA. The IQVIA and Vanderbilt cohorts were created from electronic medical records, while the DELTA cohort represented patients from the DELTA clinical trial (NCT01282424) who proceeded to receive therapy after idelalisib treatment. The DELTA cohort was added to increase statistical power for OS, TTNT, and response outcomes. However, the DELTA cohort was not used to inform PFS as tumour assessment dates were not provided for the line of therapy subsequent to idelalisib (i.e., the index line of therapy). The index line of therapy was chosen at random from all lines of therapy received by a patient after they met all the eligibility criteria for the study. The index date for the primary analysis was defined as the initiation date of the patient's index line. A summary of the SCHOLAR-5 study is provided in Table 20.

Table 20: Study Selection Criteria and Methods for Other Relevant Evidence Submitted by the Sponsor

Characteristics	Indirect comparison
Population	Patients with r/r grade 1, 2, or 3a FL after 2 or more systemic therapies
Interventions	Any therapy used for r/r grade 1, 2, or 3a FL in the third- and later-line treatment setting
Comparator	Standard of care therapies: • Anti-CD20 agent + alkylating chemotherapy • Alkylating chemotherapy • Allo-SCT or auto-SCT • Experimental therapy • Bruton tyrosine kinase inhibitor • PI3K inhibitor • Immunomodulatory agent • Fludarabine • Radioimmunotherapy
Outcome	• OS: time from index date to death. • PFS: time from index date until earliest date of progression or death from any cause. • TTNT: time from index date to initiation of next therapy or death. • DOR: time from first objective response within the line of therapy until disease progression or death due to any cause, whichever comes first. DOR is only defined for patients with a PR or CR. • ORR: proportion of patients achieving either a CR or PR as indicated by direct documentation in the patient's medical record since the index date.
Study designs	Retrospective, observational study
Data used	Data on file
Inclusion criteria	• Patients aged ≥ 18 years • Patients with histologically confirmed diagnosis of iNHL, with histological subtype limited to FL grade 1, 2, or 3a, based on criteria established by the WHO 2016 classification • Patients with r/r disease starting third or later line of therapy on or after July 23, 2014[a]
Exclusion criteria	• Transformed FL[b] • FL histological grade 3b • Prior CAR T-cell therapy or other genetically modified T-cell therapy • Eligible within 12 months before the last updated version of the database • ECOG PS score > 1 • CNS involvement

allo-SCT = allogeneic stem cell transplant; auto-SCT = autologous stem cell transplant; CNS = central nervous system; CR = complete response; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphoinositide 3-kinase; PR = partial response; r/r = relapsed or refractory; TTNT = time to next treatment.

[a]Eligibility criteria were not restricted by date for patients from the DELTA clinical trial.

[b]Patients who pass all other inclusion/exclusion criteria but transform at a later date were eligible until transformation.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: Sponsor-provided analysis report.[19]

Analysis Methods

Patient-level data for the ZUMA-5 and SCHOLAR-5 studies were used to inform a comparative analysis. Propensity scores were calculated for each patient in the pooled analysis set to account for differences in baseline characteristics across populations. These calculated scores were then used to apply SMR weighting, with differences required to be less than 0.1. All ZUMA-5 patients were included in the analysis. Selection of variables for the propensity score model was determined in a hierarchal manner and based on the advice of investigators or clinical experts, with the goal of minimizing the imbalance in prognostically important covariates. For high and medium priority rank variables with less than 40% missing data, multiple imputation was performed.

The variables included in the propensity score model were:

- POD24
- number of lines of prior therapy
- r/r to prior line of therapy
- prior SCT (yes/no)
- tumour bulk
- time since last treatment
- response to prior line of therapy
- age
- prior anti-CD20 + alkylator combination treatment.

Weighted logistic regression was used to estimate ORs of the ORR and CRR across cohorts. A weighted KM estimator of the risk probabilities and 95% CIs for OS, PFS, TTNT, and DOR were estimated at 3-month intervals.[19] Time-to-event outcomes were summarized via hazard ratios, estimated using a Cox proportional hazard model. Statistical sensitivity analyses of ORR and OS were conducted to support the robustness of the findings. Additional sensitivity analyses performed for all outcomes included: exclusion of DELTA trial patients from the SCHOLAR-5 cohort, using the date of axicabtagene ciloleucel infusion as the start point for time-to-event variables, and using the safety and inferential analysis sets. Prespecified subgroup analyses included investigations on patient disease status and prior therapies. A summary of the methods is shown in Table 21.

Table 21: Analysis Methods

Methods	Description
Balancing methodology	Propensity score weighting: A logistic regression model was used to estimate propensity scores. Weights, assigned in the SMR method, were calculated for individuals in the SCHOLAR-5 cohort as: propensity score / (1–propensity score). PSM: Performed as a sensitivity analysis, patients in the ZUMA-5 trial were matched with a patient in the SCHOLAR-5 study exhibiting the nearest propensity score.
Propensity score specification	Propensity scores were specified by patient characteristics in a hierarchal order of importance, based on investigator and clinical advice.

Methods	Description
Covariates included	• POD24 after initiation of first-line anti-CD20 chemotherapy combination therapy • Number of lines of prior therapy • Relapsed vs. refractory at index • Prior SCT • Time from last treatment • Best response to last line of therapy • Tumour bulk (diameter of largest lesion) • Age • Prior anti-CD20 + alkylating agent
Multiple imputation	Multiple imputation was applied for variables with missing data (< 40%) that were specified as part of the propensity score model. Little's test of missing completely at random was performed, which provided a significance value of P < 0.001. Variables that required imputation were: • tumour bulk • time since last treatment • CR or PR to prior line of therapy.
Outcomes	• ORR • OS (date of leukapheresis as start point) • PFS (date of leukapheresis as start point) • TTNT (date of leukapheresis as start point) • DOR (date of first objective response as start point) • Best overall response (CR, PR, stable disease)
Follow-up time points	ZUMA-5: 36-month FAS; the SCHOLAR-5 study is retrospective study where at least 12 months of follow-up was required
Model estimation	Two-sided CI was utilized, and all tests were performed on the 5% alpha level. For time-to-event variables, HRs of the outcome between groups were estimated using a Cox proportional hazard model.
Sensitivity analyses	For ORR, the robustness of findings was tested using 3 types of bootstrap CI (computed using the percentile method, normal distribution method, and bias-corrected method) and the robust Wald assessment. Additional sensitivity analyses were performed using inverse probability of treatment weights for doubly robust analysis and nullification analysis for assessment of unmeasured confounders and their association with the outcome. For OS, a statistical sensitivity analysis was prespecified via the parametric g-formula to assess differences between the ZUMA-5 and SCHOLAR-5 groups. For all outcomes, additional sensitivity analyses included: • PSM analysis (as opposed to PS weighting) • Propensity score unweighted analysis (as opposed to propensity score weighting) • Exclusion of DELTA trial patients from the SCHOLAR-5 cohort. This sensitivity analysis was performed to account for the involvement of DELTA trial patients in a clinical trial, which was not the case for SCHOLAR-5 patients • Analysis using the ZUMA-5 safety and inferential analysis sets • Date of axicabtagene ciloleucel infusion as the start point for time-to-event variables (PFS, OS, TTNT), as opposed to date of leukapheresis.

Methods	Description
Subgroup analysis	The comparative effectiveness of axicabtagene ciloleucel vs. standard of care was assessed in prespecified subgroups of interest as follows: • Patients with POD24 after initiation of first-line anti-CD20 chemotherapy combination therapy • Patients who were refractory at index date • Patients who had failed 3 or more lines of therapy.

CI = confidence interval; CR = complete response; DOR = duration of response; FAS = full analysis set; HR = hazard ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; POD24 = progression of disease within 24 months; PR = partial response; PS = propensity score; PSM = propensity score matching; SCT = stem cell transplant; SMR = standardized mortality ratio; TTNT = time to next treatment; vs. = versus.

Note: Low priority variables were not included in the propensity score weighting.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: Sponsor-provided analysis report.[19]

Results

Summary of Included Studies

The comparative analysis contrasted 2 populations, those in the ZUMA-5 and SCHOLAR-5 studies, to derive estimates of relative efficacy for axicabtagene ciloleucel and standard of care. The ZUMA-5 trial is a single-arm, phase II study evaluating the efficacy and safety of axicabtagene ciloleucel in patients with r/r grade 1, 2, or 3a FL (n = 127). The SCHOLAR-5 cohort was constructed retrospectively from 3 international observational cohorts: IQVIA, Vanderbilt, and DELTA. The DELTA cohort included patients from the DELTA clinical trial (NCT01282424) who proceeded to receive therapy after idelalisib treatment. The DELTA cohort in the SCHOLAR-5 trial did not report progression assessment dates and had to be removed from the PFS and DOR analysis. Table 22 summarizes the assessment of homogeneity between the ZUMA-5 trial and the SCHOLAR-5 cohort.

Table 22: Assessment of Homogeneity

Characteristics	Description and handling of potential effect modifiers
Disease severity	Disease severity was similar across the SCHOLAR-5 and ZUMA-5 studies as both studies required patients to have a confirmed diagnosis of FL (grade 1, 2, or 3a) with r/r disease and starting their third (or later) line of treatment. Prior to weighting, the proportion of patients in the SCHOLAR-5 study with POD24 was smaller (35.7%) than the proportion of patients in the ZUMA-5 trial with POD24 (55.1%).
Treatment history	Patients in the SCHOLAR-5 study had fewer lines of prior therapy (mean of [redacted]) compared to patients in the ZUMA-5 trial ([redacted]).
Eligibility criteria	Eligibility criteria for the SCHOLAR-5 study was aligned with ZUMA-5 criteria. Patients in both studies were ≥ 18 years and had histologically confirmed iNHL limited to FL (grade 1, 2, or 3a) based on WHO 2016 classification.[48] Eligible patients also had r/r disease and were starting their third (or later) line of therapy. Patients were excluded if they had transformed FL or FL histological grade 3b. Additional exclusion criteria were prior CAR T-cell therapy or other genetically modified T-cell therapy, ECOG PS score > 1, and involvement of the CNS. A subset of eligible patients from the DELTA clinical trial were included to increase statistical power for OS, TTNT, and response rates.

Characteristics	Description and handling of potential effect modifiers
Dosing of comparators	In the ZUMA-5 study, patients received 2 × 10^6 anti-CD19 CAR T cells/kg body weight. The SCHOLAR-5 study involved patients who received any available treatment for r/r FL, including approved and experimental therapies, and autologous and allogeneic transplant. The index LOT for SCHOLAR-5 participants was randomly selected from eligible LOTs. For the subset of patients derived from the DELTA trial, the index LOT was the treatment received after idelalisib. Ineligible index treatments for the SCHOLAR-5 study included single-agent anti-CD20 therapy, surgery, and radiotherapy alone. CAR T-cell therapy and other cellular therapies were also ineligible index treatments.
Definitions of end points	The SCHOLAR-5 study defined ORR as the proportion of patients achieving either CR or PR, as indicated by direct documentation in the patient's medical record since the index date. OS, PFS, and TTNT were defined as the time from index date to death (in the case of OS), progression or death (in the case of PFS), or initiation of next therapy or death (in the case of TTNT). In the ZUMA-5 trial, the start point date for these time-to-event outcomes was date of leukapheresis. DOR was defined as the time from first objective response within the line of therapy until disease progression or death.
Timing of end point evaluation	Efficacy end points as described above were measured at the 36-month follow-up analysis in the ZUMA-5 trial. The SCHOLAR-5 study is a retrospective study where at least 12 months of follow-up was required. Time-to-event end points (OS, PFS, TTNT, DOR) were also compared at 3-month intervals.
Clinical trial setting	The SCHOLAR-5 cohort was generated from database records provided by IQVIA and Vanderbilt University Medical Center. The SCHOLAR-5 study also included eligible patients from the DELTA clinical trial. Data from the ZUMA-5 trial came from patients who were assessed at 17 investigative sites across the US and France.
Study design	The ZUMA-5 trial is a single-arm, open-label, phase II study. The SCHOLAR-5 study is a retrospective database study, acquiring data from multiple centres and from the DELTA clinical trial.

CAR = chimeric antigen receptor; CNS = central nervous system; CR = complete response; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; iNHL = indolent non-Hodgkin lymphoma; FL = follicular lymphoma; LOT = line of therapy; ORR = ; OS = overall survival; PFS = progression-free survival; POD24 = progression of disease within 24 months; PR = partial response; r/r = relapsed or refractory; TTNT = time to next treatment.

Details included in this table are from the sponsor's Summary of Clinical Evidence.[59]

Source: Sponsor-provided analysis report.[19]

Table 23 summarizes the index treatment patterns in the SCHOLAR-5 cohort before propensity score weighting. The most common index treatments, in descending order, were anti-CD20 agent plus bendamustine (16.8%), experimental therapy (16.1%), immunomodulatory agent (12.6%), PI3K inhibitor (9.8%), auto-SCT (8.4%), anti-CD20 agent plus other chemotherapy (8.4%), and other chemotherapy (8.4%).

A full description of the ZUMA-5 trial can be found in the Systematic Review section of this report.

Table 23: Index Treatment Patterns for the SCHOLAR-5 (n = 143) Sample of Patients With 2 or More Lines of Prior Therapy

Treatment	Frequency, n (%)
Alkylating chemotherapy	1 (0.7)
Allo-SCT	4 (2.8)
Auto-SCT	12 (8.4)
Bruton tyrosine kinase inhibitor	1 (0.7)
Anti-CD20 agent + alkylating chemotherapy	5 (3.5)
Anti-CD20 agent + bendamustine	24 (16.8)
Anti-CD20 agent + CHOP-like chemotherapy	7 (4.9)
Anti-CD20 agent + fludarabine-based chemotherapy	3 (2.1)
Anti-CD20 agent + immunomodulatory agent	1 (0.7)
Anti-CD20 agent + platinum-based chemotherapy	1 (0.7)
Anti-CD20 agent + other chemotherapy	12 (8.4)
Other chemotherapy	12 (8.4)
Experimental therapy	23 (16.1)
Fludarabine	1 (0.7)
Immunomodulatory agent	18 (12.6)
PI3K inhibitor	14 (9.8)
Radioimmunotherapy	2 (1.4)
SCT (other)	2 (1.4)

allo-SCT = allogeneic stem cell transplant; auto-SCT = autologous stem cell transplant; CHOP = cyclophosphamide + doxorubicin-vincristine-prednisone; PI3K = phosphoinositide 3-kinase; SCT = stem cell transplant.

Source: Sponsor-provided analysis report.[19]

Results — Propensity Score Weighting

The SCHOLAR-5 cohort was reweighted using the propensity scores to further align with the ZUMA-5 patient population. After propensity score weighting, the SCHOLAR-5 effective sample size was reduced from 143 patients to 128 patients. The largest difference between cohorts was in time from last treatment; after weighting the average was reduced from the original [redacted] months in the full SCHOLAR-5 population to [redacted] months, and the proportion of patients with POD24 increased from 35.7% in the unadjusted population to 57.1% in the propensity score–weighted population. After propensity score weighting, variables were mostly similar to the ZUMA-5 population. The removal of the DELTA cohort from the SCHOLAR-5 cohort also resulted in relatively balanced variables; however, the proportion of patients with POD24 and the proportion who were refractory to their most recent treatment were both lower.

A summary of the patient characteristics not included in the propensity score model for both the ZUMA-5 and SCHOLAR-5 trials before and after weighting is shown in Table 25. The largest differences between the post-weighting SCHOLAR-5 and ZUMA-5 trials are in the proportion of patients with an ECOG PS score of

0, that is, 32.6% versus 62.2%, respectively. Other large differences between the SCHOLAR-5 and ZUMA-5 trials are in the proportion of patients who are double refractory (versus , respectively) and have bone marrow involvement (versus , respectively).

Table 24: Propensity Score Variables in the ZUMA-5 and SCHOLAR-5 Trials

Propensity score variables	SCHOLAR-5		ZUMA-5 (N = 127)	P value	SMD
	Before weighting (N = 143)	After weighting (N = 128)			
POD24, n (%)	51 (35.7)	73 (57.1)	70 (55.1)	0.789	0.039
Number of lines of prior therapy, mean (SD)					
Relapsed or refractory to prior line of therapy, n (%)					
Relapsed	57 (39.5)	36 (25.5)	40 (31.5)	0.560	0.083
Refractory	86 (60.5)	93 (72.3)	87 (68.5)		
Prior SCT, n (%)	31 (21.7)	33 (25.5)	30 (23.6)	0.783	0.043
Tumour bulk (cm), mean (SD)					
Time since last treatment (months), mean (SD)					
Response to prior line of therapy, n (%)					
CR					
PR					
Stable disease					
Progressive disease					
Age, mean (SD)					
Prior anti-CD20 + alkylator combination treatment, n (%)					
Propensity score variables, after weighting (removal of DELTA cohort)					
N (%)	NA				
POD24, n (%)	NA				
Number of lines of prior therapy, mean (SD)	NA				
Relapsed or refractory to prior line of therapy, n (%)					
Relapsed	NA				
Refractory	NA				
Prior SCT, n (%)	NA				
Tumour bulk (cm), mean (SD)	NA				
Time since last treatment (months), mean (SD)	NA				
Response to prior line of therapy, n (%)					

Propensity score variables	SCHOLAR-5		ZUMA-5 (N = 127)	P value	SMD
	Before weighting (N = 143)	After weighting (N = 128)			
CR	NA	[redacted]	[redacted]	[redacted]	[redacted]
PR	NA	[redacted]	[redacted]		
Stable disease	NA	[redacted]	[redacted]		
Progressive disease	NA	[redacted]	[redacted]		
Age, mean (SD)	NA	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-CD20 + alkylator combination treatment, n (%)	NA	[redacted]	[redacted]	[redacted]	[redacted]

CR = complete response; POD24 = progression of disease within 24 months; PR = partial response; SCT = stem cell transplant; SD = standard deviation; SMD = standardized mean difference.

Source: Sponsor-provided analysis report.[19]

Table 25: Patient Characteristics not Included in the Propensity Score Model in the ZUMA-5 and SCHOLAR-5 Trials

Propensity score variables	SCHOLAR-5		ZUMA-5 (N = 127)	P value	SMD
	Before weighting (N = 143)	After weighting (N = 128)			
FL subtype, n (%)					
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]		
Grade 3a	[redacted]	[redacted]	[redacted]		
Missing	[redacted]	[redacted]	[redacted]		
ECOG PS, n (%)					
0	39 (33.1)	35 (32.6)	79 (62.2)	< 0.001	0.621
1	79 (66.9)	72 (67.4)	48 (37.8)		
Missing	[redacted]	[redacted]	[redacted]		
Double refractory, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior alkylating monotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-CD20 monotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior lenalidomide, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior PI3K inhibitor, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow involvement, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Propensity score variables	SCHOLAR-5		ZUMA-5 (N = 127)	P value	SMD
	Before weighting (N = 143)	After weighting (N = 128)			
FLIPI, n (%)					
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]		
2	[redacted]	[redacted]	[redacted]		
3	[redacted]	[redacted]	[redacted]		
4	[redacted]	[redacted]	[redacted]		
5	[redacted]	[redacted]	[redacted]		
Missing	[redacted]	[redacted]	[redacted]		
Hemoglobin (g/dL), mean (SD)	[redacted]	[redacted]	12.60 (1.92)	0.027	0.363

ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; FLIPI = Follicular Lymphoma Internal Prognostic Index; PI3K = phosphoinositide 3-kinase; SD = standard deviation; SMD = standardized mean difference.

Source: Sponsor-provided analysis report.[19]

A summary of the estimated relative efficacy is provided in Table 26. The ORR in the ZUMA-5 population was 93.7% compared to 54.0% in the propensity score–weighted SCHOLAR-5 population (OR = 12.66; 95% CI, 5.24 to 30.57; P < 0.001). The CRR in the ZUMA-5 population was 78.7% compared to 34.9% in the propensity score–weighted SCHOLAR-5 population (OR = 6.90; 95% CI, 3.62 to 13.18; P < 0.001).

The median PFS in the ZUMA-5 population was 40.21 months (95% CI, 28.94 months to NE) compared to 12.97 months (95% CI, 7.75 months to 15.47 months) in the propensity score–weighted SCHOLAR-5 population, with HR of 0.27 (95% CI, 0.18 to 0.41; P < 0.0001. The KM curve for the PFS analysis is shown in Figure 4. The median OS in the ZUMA-5 population was NE (95% CI, NE to NE) compared to NE (95% CI, 38.40 months to NE) in the propensity score–weighted SCHOLAR-5 population (HR = 0.56; 95% CI, 0.33 to 0.95; P = 0.0303). The KM curve for the OS analysis is shown in Figure 5. The median TTNT in the ZUMA-5 population was NE (95% CI, 37.85 months to NE) compared to 26.61 months (95% CI, 12.65 months to NE) in the propensity score–weighted SCHOLAR-5 population (HR = 0.25; 95% CI, 0.15 to 0.41; P < 0.0001).

The median DOR in the ZUMA-5 population was 38.64 months (95% CI, 29.04 months to NE) compared to [redacted] in the propensity score–weighted SCHOLAR-5 population, with HR of [redacted]; P [redacted].

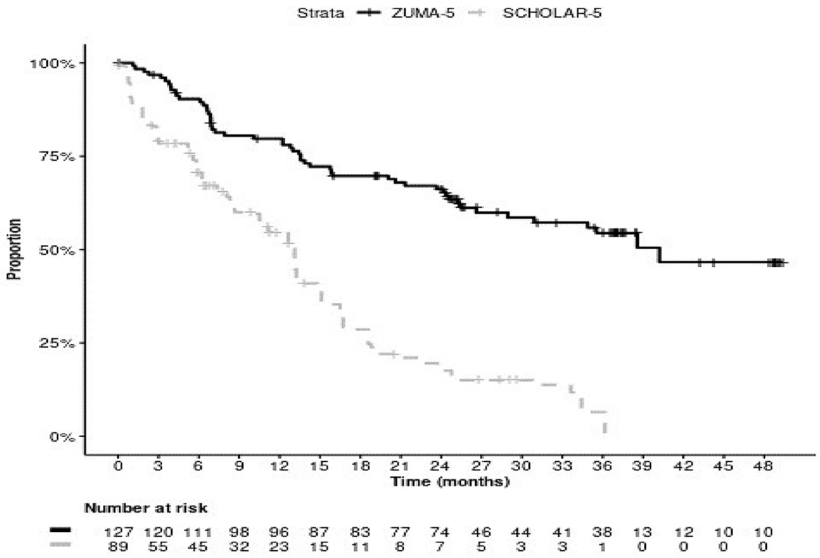
Table 26: Summary of Estimated Relative Efficacy in r/r FL

Measure	Propensity score–weighted analysis	
	SCHOLAR-5 (N = 128)	ZUMA-5 36-month analysis (N = 127)
ORR		
n (%)	69 (54.0)	119 (93.7)
OR (95% CI)	12.66 (5.24 to 30.57)	
P value	< 0.001	
CRR		
n (%)	45 (34.9)	100 (78.7)
OR (95% CI)	6.90 (3.62 to 13.18)	
P value	< 0.001	
OS		
n	128	127
OS time (months), median (95% CI)	NE (38.40 to NE)	NE (NE to NE)
Cox model HR (95% CI)	0.56 (0.33 to 0.95)	
P value	0.0303	
G-estimation HR (95% CI)	[redacted]	
P value	[redacted]	
PFS		
n	89	127
PFS time (months), median (95% CI)	12.97 (7.75 to 15.47)	40.21 (28.94 to NE)
Cox model HR (95% CI)	0.27 (0.18 to 0.41)	
P value	< 0.0001	
TTNT		
n	128	127
TTNT time (months), median (95% CI)	26.61 (12.65 to NE)	NE (37.85 to NE)
Cox model HR (95% CI)	0.60 (0.39 to 0.93)	
P value	0.0223	
DOR		
n	[redacted]	[redacted]
DOR time (months), median (95% CI)	[redacted]	38.64 (29.04 to NE)
Cox model HR (95% CI)	[redacted]	
P value	[redacted]	

CI = confidence interval; CRR = complete response rate; DOR = duration of response; HR = hazard ratio; NE = not evaluable; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTNT = time to next treatment.

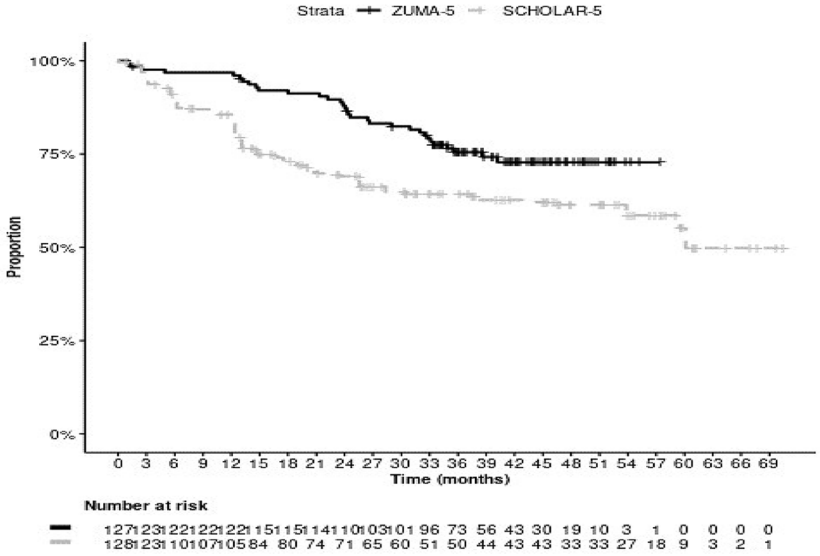
Note: OR > 1 and HR < 1 demonstrate a relative benefit of axicabtagene ciloleucel vs. the comparator basket.
Source: Sponsor-provided analysis report.[19]

Figure 4: PFS in the ZUMA-5 Trial (36-Month FAS) Compared to the SCHOLAR-5 Study (Propensity Score Weighted)



FAS = full analysis set; PFS = progression-free survival.
Source: Sponsor-provided analysis report.[19]

Figure 5: OS in the ZUMA-5 Trial (36-Month FAS) Compared to the SCHOLAR-5 Trial (Propensity Score Weighted)



FAS = full analysis set; OS = overall survival.
Source: Sponsor-provided analysis report.[19]

Critical Appraisal of Other Relevant Evidence

Internal Validity

The submitted comparative analysis provides an estimate of relative efficacy of axicabtagene ciloleucel, using evidence from the ZUMA-5 clinical trial, against a basket of therapies representing standard of care, using evidence from the SCHOLAR-5 cohort, a combination of retrospective real-world evidence and a subset of the DELTA clinical trial.

Due to differences between the ZUMA-5 and SCHOLAR-5 cohorts in treatment allocation, it is possible that the treatment effect estimate is confounded by imbalances in prognostic covariates across populations. The sponsor identified and adjusted for several important variables, resulting in a suitable balance of these characteristics across both populations. However, characteristics deemed critical by the clinical experts — FLIPI score, ECOG PS score, and double refractory status — were omitted; FL grade was also omitted. Of the variables collected in both cohorts, there were observed imbalances across treatment groups even after reweighting the populations. The variables were acknowledged by the sponsor, but were omitted due to concerns regarding missing data. The clinical experts consulted by CADTH suggested that differences in ECOG PS scores and the proportion of patients who are double refractory could affect how patients would be expected to respond to treatment. The direction of this impact is uncertain, with some differences potentially favouring axicabtagene ciloleucel over the SCHOLAR-5 comparator. There is additional uncertainty in the results because of the low effective sample sizes in both the ZUMA-5 trial and the SCHOLAR-5 cohort. The removal of the DELTA cohort resulted in a statistically significant change in the mean number of lines of prior therapy, that is, [redacted] in the SCHOLAR-5 study compared to [redacted] in the ZUMA-5 trial. Differences between populations in the number of lines of prior therapy have a particularly large impact when determining how patients would be expected to respond to treatment. The proportion of patients with POD24 and the proportion of patients who were refractory to their most recent treatment were also both reduced with the exclusion of the DELTA cohort, indicating that the removal of this cohort results in a population with a lower risk prognosis. The ZUMA-5 trial and the SCHOLAR-5 study had different follow-up time requirements: the ZUMA-5 cohort used a 36-month follow-up, while the SCHOLAR-5 cohort required at least 12 months of follow-up. It is possible that individuals' characteristics or issues with treatment adherence determined patients' decisions to exit the cohort early and introduced informative censoring, which bias the results.

External Validity

The clinical experts confirmed that the distribution of therapies in the SCHOLAR-5 cohort were representative of the standard of care for patients in Canada; however, it is unclear how this distribution was affected by the propensity score weighting or the exclusion of the DELTA cohort, as the comparator therapies used were not reported in the post-weighting population. The inclusion and exclusion criteria for the SCHOLAR-5 cohort was similar to the ZUMA-5 trial, although it is uncertain if the results can be generalized beyond this selected group of patients.

Future Planned Studies

Contents within this section have been informed by materials submitted by the sponsor. The following have been summarized and validated by the CADTH review team.

Table 27: Summary of Gaps in the Systematic Review Evidence

Evidence gap	Studies that address gaps	
	ZUMA-22	Summary of key results
• Patients with POD24 were not included in the ZUMA-5 trial. • HRQoL was not assessed in the pivotal study.	A prospective, interventional, open-label, randomized, phase III study assessing the efficacy and safety of axicabtagene ciloleucel vs. standard of care in patients with r/r FL after 2 or more lines of systemic therapy, or r/r FL after first-line chemoimmunotherapy in patients with POD24.	NA

FL = follicular lymphoma; HRQoL = health-related quality of life; NA = not applicable; POD24 = progression of disease within 24 months; r/r = relapsed or refractory.
Source: Sponsor's Summary of Clinical Evidence.[59]

Description of Studies

The ZUMA-22 trial[56] is a prospective, interventional, open-label, randomized, phase III study assessing the efficacy and safety of axicabtagene ciloleucel versus standard of care in patients with r/r FL after 2 or more lines of systemic therapy or r/r FL after first-line chemoimmunotherapy in patients with POD24. The study began in September 2022 and is actively recruiting participants. Final study results of the ZUMA-22 trial are expected by Health Canada in [redacted] as a requirement for the issued Notice of Compliance for adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy.

Discussion

Summary of Available Evidence

One clinical trial was included in the systematic review conducted by the sponsor. The ZUMA-5 study is a phase II, open-label, single-arm study that evaluated the efficacy and safety of axicabtagene ciloleucel in patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. The primary end point was ORR per central assessment in the inferential analysis set at the 18-month time point. Secondary end points included CRR, OS, PFS, DOR, and TTNT. A total of 127 patients with r/r FL were enrolled, with 86 included in the 18-month primary analysis. Data for the full analysis up to the 36-month time point were available at the time of this review (the data cut-off was March 31, 2022). The median age in the FAS was 60 years (range, 34 years to 79 years). More males (59%) were enrolled than females (41%). Most patients had an ECOG PS score of 0 (62%), and the most common number of prior therapies was 2 ([redacted]). The proportion of patients with POD24 was 55%.

The sponsor provided an additional study in which patient-level data from the retrospective SCHOLAR-5 study were reweighted using propensity scores to be comparable with the ZUMA-5 populations. Given that the ZUMA-5 trial is a single-arm noncomparative study, adjusting the SCHOLAR-5 patient population to be more similar to the ZUMA-5 population allows for an estimate of comparative efficacy against standard of care within the ZUMA-5 population. The outcomes analyzed were ORR, CRR, DOR, OS, PFS, and TTNT. The

treatments that made up the basket of therapies in the SCHOLAR-5 study were any available treatment for r/r FL, including approved and experimental therapies, and autologous and allogeneic transplant.

Interpretation of Results

Efficacy

In the ZUMA-5 trial, based on the primary end point ORR, 94% (95% CI, 88% to 97%) of patients achieved a partial response to axicabtagene ciloleucel treatment 36 months following infusion, and based on the secondary end point CRR, 79% (95% CI, NE to NE) of patients achieved a complete response to treatment. The results of subgroup analyses were consistent with those of the FAS. The clinical experts consulted by CADTH indicated that the ORR and CRR results were clinically important and acceptable surrogates for survival outcomes (PFS and OS) based on their clinical experience in treating patients with r/r FL where extended survival is common, and therefore trials with mature survival follow-up are rare.

Survival outcomes were identified by CADTH with input from patient groups and clinicians as the most important efficacy outcomes to assess treatment effect in patients with r/r FL. Prolonged survival may be correlated with high response rates (e.g., ORR and CRR). In a meta-analysis evaluating the relationship between response rates and median PFS in patients with NHL (including FL, which accounted for 23% of the study population), strong correlation between response rates and PFS was found, the coefficient of determination (R^2) was 0.78 for ORR versus median PFS and 0.74 for CRR versus median PFS. The results were similar in the subgroup of patients with r/r FL and treatment-naive FL.[60] In another meta-analysis examining the correlation between response and survival outcomes, a moderate correlation was observed between CRR and median PFS in patients with FL (R^2 = 0.69). In this study, the authors noted that since the median OS was usually not reached in clinical trials of NHL, none of the median OS-related correlation analysis results were evaluable due to the limited data.[61] The clinical experts supported the use of surrogate outcomes by noting that, in their experience, patients who achieve complete remission after CAR T-cell therapy have better prognosis (e.g., more favourable survival) compared to those who do not respond well, but this is not always the case.

At the 36-month analysis time point in the ZUMA-5 trial, the survival probability for patients treated with axicabtagene ciloleucel was 75.5% (95% CI, 66.9% to 82.2%) and the median OS had not been reached. PFS was measured from the time of leukapheresis to the date of disease progression or death due to any cause. The proportion of patients who were progression free at the 36-month time point was 54.4% (95% CI, 44.2% to 63.5%), the median PFS was 40.2 months (95% CI, 28.9 months to NE). According to the clinical experts consulted by CADTH, the survival results from the ZUMA-5 trial are consistent with the expected clinical benefit; however, it must be noted that due to the slowly progressing nature of r/r FL, the OS and PFS data are immature and therefore the effect on long-term survival is uncertain. Results from a retrospective analysis conducted in a single centre in the US showed that median OS was 11.7 years, 8.8 years, and 5.3 years for patients who received second-line, third-line, and fourth-line treatments, respectively. In this study, recurrent uses of single-agent rituximab (9% to 31%), alkylator-based chemotherapy (22% to 26%), and radiotherapy (alone or radioimmunotherapy, 10% to 18%) were common in second- to sixth-line treatment therapy. Ten percent of the treated patients received SCT during their course of therapy (auto-SCT 6%; allo-SCT 4%).

Investigational therapies (not specified, and unclear whether CAR T-cell products were used) ranged from 8% to 22% when second or later lines of therapy were required.[62] Furthermore, when considering the long survival periods in r/r FL, it is important to take into account the impact of any beneficial therapies that could be introduced in the future and the impact that they may have on the long-term survival of patients who received axicabtagene ciloleucel in the ZUMA-5 trial.

HRQoL was identified by patient groups and clinicians as an important outcome. The ZUMA-5 trial did not include any HRQoL end points, and therefore the effects of axicabtagene ciloleucel on HRQoL in patients with r/r FL is unknown.

Given the single-arm design of the ZUMA-5 trial, there is no head-to-head evidence against standard of care for patients with r/r FL. A comparison of axicabtagene ciloleucel against an external standard of care control arm from the retrospective SCHOLAR-5 cohort found that axicabtagene ciloleucel is associated with improved OS and PFS. The interpretation of the comparative efficacy estimates is limited by the potential for selection bias when accepting patients into the ZUMA-5 clinical trial, and residual imbalances in important prognostic and effect-modifying patient characteristics, despite propensity score weighting.

It is also noted that tisagenlecleucel is another CAR T-cell therapy currently under review at CADTH for use in patients with r/r FL after 2 or more lines of therapy.[63] No comparative evidence between axicabtagene and tisagenlecleucel was identified, and therefore the comparative efficacy is unknown.

Harms

At the 36-month time point, [redacted] of patients in the ZUMA-5 trial had reported at least 1 AE. The most common were pyrexia ([redacted]), hypotension ([redacted]), headache ([redacted]), and fatigue ([redacted]). SAEs were reported in [redacted] of patients, with the most common being pyrexia ([redacted]). It was also noted that given that axicabtagene ciloleucel is administered as a 1-time infusion, the ZUMA-5 trial follow-up is sufficient to characterize the safety profile. The clinical experts highlighted the adverse events of special interest, specifically CRS that occurred in [redacted] of patients ([redacted] at grade ≥ 3) and neurologic events that occurred in [redacted] of patients ([redacted] at grade ≥ 3). The clinical experts noted that it appears that patients have different rates of CRS and immune effector cell–associated neurotoxicity syndrome. The experts indicated that patients' characteristics, such as performance status and comorbidities that might predict their ability to tolerate an episode of CRS or immune effector cell–associated neurotoxicity syndrome, might influence the choice of product. However, given the lack of head-to-head evidence or an indirect treatment comparison, the comparative safety profiles are unknown.

The SCHOLAR-5 comparison did not include safety as an end point, and therefore the safety profile of axicabtagene ciloleucel compared to standard of care is unknown. The clinical experts consulted by CADTH considered the safety profile of axicabtagene ciloleucel to be as expected given the mechanism of action and prior experience in other indications; therefore, side effects are expected to be manageable with proper monitoring.

Conclusion

Evidence from a single-arm study (ZUMA-5) suggests that treatment with axicabtagene ciloleucel affects clinically important tumour responses, including complete remission, in adult patients with r/r FL after 2 or more lines of systemic therapies. Due to the single-arm design of the trial and limited duration of follow-up, there is insufficient evidence to determine the magnitude of the effect of axicabtagene ciloleucel on OS and PFS. HRQoL outcomes were not included in the ZUMA-5 trial and therefore the impact of axicabtagene ciloleucel on patients' HRQoL is unknown. The harms associated with the axicabtagene infusion are as expected given the mechanism of action and prior experience in other indications. The comparison of the ZUMA-5 trial to the retrospective SCHOLAR-5 external control was limited by heterogeneity across study designs and populations. Specifically, the inability to adjust for ECOG PS and double refractory status can introduce bias to the estimation procedure within the comparative populations. Generalizability to individuals who do not meet the ZUMA-5 trial criteria is also in question. Therefore, the magnitude of the comparative efficacy estimates for axicabtagene ciloleucel against standard of care in the Canadian setting is uncertain.

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Pharmacoeconomic Review

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Abbreviations

AE	adverse event
allo-SCT	allogeneic stem cell transplant
auto-SCT	autologous stem cell transplant
axi-cel	axicabtagene ciloleucel
CAR	chimeric antigen receptor
CRS	cytokine release syndrome
FL	follicular lymphoma
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
KM	Kaplan-Meier
OCCI	Ontario Case Costing Initiative
OS	overall survival
PD	progressed disease
PFS	progression-free survival
QALY	quality-adjusted life-year
R2	lenalidomide plus rituximab
r/r	relapsed or refractory
SCT	stem cell transplant
SOC	standard of care
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Axicabtagene ciloleucel (Yescarta), cell suspension of CAR-positive viable T-cells, for IV infusion.
Submitted price	Axicabtagene ciloleucel, cell suspension of 2×10^6 CAR T cells/kg body weight, to a maximum of 2×10^8 CAR T cells: $485,021 per 1-time infusion.
Indication	Adult patients with relapsed or refractory grade (r/r) grade 1, 2, or 3a follicular lymphoma (FL) after two or more lines of systemic therapy.
Health Canada approval status	NOC/c
Health Canada review pathway	Standard review
NOC date	September 28, 2022
Reimbursement request	As per indication
Sponsor	Gilead Sciences Canada Inc.
Submission history	Previously reviewed: Yes Indication: Treatment of adult patients with DLBCL or HGBL that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Recommendation date: February 3, 2023 Recommendation: Reimburse with clinical criteria and conditions Indication: Treatment of adult patients with r/r LBCL after 2 or more lines of systemic therapy. Recommendation date: August 15, 2019 Recommendation: Recommended with clinical criteria and conditions[a]

CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBL = high-grade B-cell lymphoma; LBCL = large B-cell lymphoma; NOC = Notice of Compliance; NOC/c = Notice of Compliance with conditions; r/r = relapsed or refractory.

[a]This review of axicabtagene ciloleucel went through the interim review process for CAR T-cell therapies, in which recommendations were issued by the CADTH Health Technology Expert Review Panel.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with r/r grade 1, 2, or 3a FL after ≥ 2 lines of systemic therapy
Treatment	Axicabtagene ciloleucel
Comparator	SOC is composed of chemotherapy (50%), SCT (12%), idelalisib (5%), and clinical trials (33%). Chemotherapy includes 6 different regimens: • rituximab plus bendamustine • CHOP

Component	Description
	• CVP • obinutuzumab plus bendamustine • GDP • R-CVP
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (50 years)
Key data source	• Axi-cel: single-arm, phase II ZUMA-5 trial (36-month data cut-off: March 31, 2022) • SOC: SCHOLAR-5 retrospective cohort study (patients who initiated third or higher line of therapy on or after July 2014) • Comparative efficacy data were informed from the indirect treatment comparison of SCHOLAR-5 and ZUMA-5 studies through propensity score weighting on prespecified prognostic factors using standardized mortality ratios.
Submitted results	ICER = $115,543 per QALY gained compared with SOC (incremental costs = $505,565; incremental QALYs = 4.38).
Key limitations	• The sponsor implemented a cure model that assumed that 40% of patients receiving axi-cel who remain progression-free for 5 years would be considered clinically cured. CADTH noted that it is premature to determine the fraction and time point upon which patients would achieve long-term remission given that (1) follow-up in the ZUMA-5 trial is limited; (2) long remissions are common among patients with FL; and (3) permanence of CAR T-cell treatment efficacy is uncertain. • The magnitude and durability of the survival benefit with axi-cel is highly uncertain in the absence of more robust head-to-head evidence. Clinical experts indicated that it is plausible that the OS due to axi-cel treatment could converge with that of SOC within the model's lifetime horizon, that is, for axi-cel's treatment effect to wane within patients' lifetimes. • The parametric distribution selected by the sponsor to model long-term OS for patients receiving SOC in the economic model underestimated both the KM estimates informed by the sponsor-submitted SCHOLAR-5 retrospective cohort study and the median OS derived from real-world evidence. • The sponsor failed to consider the upfront costs associated with assessment of CAR T-cell therapy eligibility. In addition, the sponsor underestimated the pretreatment costs of leukapheresis for patients receiving CAR T-cell therapy. • The sponsor assigned different utility estimates to be accrued by patients with PD according to subsequent treatment status. Clinical experts indicated that quality of life is not expected to differ between those who are on subsequent treatment and those who are off subsequent treatment. • The sponsor omitted the R2 regimen from the analysis despite evidence that the therapy is used off-label in current Canadian clinical practice.
CADTH reanalysis results	• CADTH reanalyses were derived by making changes to the following model parameters: using standard parametric models based on KM data from the ZUMA-5 trial to extrapolate the OS and PFS of axi-cel for the entire duration of the model; using alternative parametric models to extrapolate the OS of SOC and axi-cel; and including a CAR T-cell therapy eligibility assessment cost and updating the pretreatment cost associated with leukapheresis. Given the magnitude of uncertainty of the effect of axi-cel treatment on OS, its comparative efficacy against SOC, and the durability of such a benefit, CADTH

Component	Description
	conducted separate analyses involving different parametric assumptions for OS. • In CADTH reanalysis A, the OS for axi-cel was modelled using the exponential distribution (assuming treatment effect for 15.3 years postinfusion before waning). Axi-cel was associated with an ICER of $544,875 per QALY gained compared to SOC (incremental costs: $505,223; incremental QALYs: 0.93). A price reduction of 95% would be required for axi-cel to be cost-effective at a WTP threshold of $50,000 per QALY gained. • In CADTH reanalysis B, the OS for axi-cel was modelled using the log-normal distribution (assuming treatment effect would be maintained for the entire time horizon of the model). Axi-cel was associated with an ICER of $243,879 per QALY gained compared to SOC (incremental costs: $505,885; incremental QALYs: 2.07). Under this reanalysis, a price reduction of 82% would be required for axi-cel to be cost-effective at a WTP threshold of $50,000 per QALY gained.

axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone; FL = follicular lymphoma; GDP = gemcitabine, dexamethasone, and cisplatin; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; PD = progressed disease; PFS = progression-free survival; QALY = quality-adjusted life-year; R2 = lenalidomide plus rituximab; R-CVP = rituximab plus cyclophosphamide, vincristine, and prednisone; r/r = relapsed or refractory; SOC = standard of care; SCT = stem cell transplant; WTP = willingness to pay.

Conclusions

Evidence from the ZUMA-5 single-arm trial suggests that treatment with axi-cel may be associated with clinically important tumour responses, including complete remission, in adult patients with relapsed or refractory (r/r) FL after 2 or more lines of systemic therapies. However, there is insufficient evidence — due to the single-arm design of the trial as well as limited follow-up duration — to determine the effects of axi-cel on overall survival (OS) and progression-free survival (PFS). In addition, the CADTH clinical assessment identified limitations with the sponsor's comparison of the ZUMA-5 trial to the SCHOLAR-5 trial, which substantially restricted the ability to interpret the treatment effects of axi-cel relative to that of SOC. Overall, the Clinical Review concluded that there is a high degree of uncertainty around the comparative treatment effects of axi-cel relative to SOC.

Given the magnitude of uncertainty to do with the effect of axi-cel treatment on OS, its comparative efficacy against SOC, and the durability of such a benefit, CADTH was unable to derive a robust base-case estimate of cost-effectiveness. Moreover, given the duration of the ZUMA-5 trial (36 months) in contrast to the model's time horizon (50 years), it is important to note that the majority of the quality-adjusted life-year (QALY) benefit was derived from the time period beyond which there are observed trial data (i.e., extrapolated period). To address this, CADTH conducted separate reanalyses involving different parametric assumptions of treatment effect waning for OS: (A) using the exponential distribution that assumes 15.3 years of treatment effect postinfusion before waning; and (B) using the log-normal distribution that assumes sustained treatment effect for the entire time horizon of the model.

In CADTH reanalysis A (assuming 15.3 years of treatment effect postinfusion before waning), axi-cel was associated with 0.93 incremental QALYs gained and additional costs of $505,223 relative to SOC, resulting in an incremental cost-effectiveness ratio (ICER) of $544,875 per QALY gained. In CADTH reanalysis B (assuming that treatment effect would be maintained for the entire time horizon of the model), axi-cel was associated with 2.07 incremental QALYs gained and additional costs of $505,885 relative to SOC, resulting in an ICER of $243,879 per QALY gained. The estimated ICERs were higher than the sponsor's

base-case value, driven primarily by removing the cure assumption. In line with clinical expert advice, these reanalyses achieved more plausible OS curves in the absence of robust long-term evidence, while still conferring a benefit with axi-cel. CADTH noted that both reanalyses assume life expectancy increases for patients receiving axi-cel relative to current SOC (2.68 and 1.10 years of life gained in reanalysis A and B, respectively). However, the true impact of axi-cel on OS relative to SOC remains uncertain in the absence of evidence from randomized studies. The CADTH reanalyses assume that the impacts of residual confounding that could influence the nonrandomized comparison of the ZUMA-5 and SCHOLAR-5 studies are limited and that their findings could be replicated in real-world clinical practice. Both assumptions are highly uncertain. Given the available evidence, the estimates presented within the CADTH reanalyses may represent the upper bounds of the incremental gains that may be realized from this therapy.

Assuming OS and PFS outcomes from the nonrandomized comparison of the ZUMA-5 and SCHOLAR-5 studies can be replicated in real-world settings and extensions in lifespan occur relative to current SOC, a price reduction of between 82% and 95% would be required for axi-cel to be cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained. This would reduce the 1-time price of axi-cel from $485,021 to $86,334 (an 82% price reduction) or $26,676 (a 95% price reduction). This range reflects the uncertainty around long-term survival extrapolation as analyzed in CADTH reanalyses A and B.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

One patient group, Lymphoma Canada, provided input through data collected via an online survey. The survey, conducted from April 2022 to April 2023, included 143 patients with lymphoma (of whom 34% were diagnosed with follicular lymphoma [FL] and 86% lived in Canada). Of note, 3 respondents reported having experience with axicabtagene ciloleucel (axi-cel). The most important outcomes, according to the respondents, included delaying disease progression and achieving long-term remission, with the ultimate objective of improving survival; reducing side effects from treatments; preserving independence to minimize the burden on caregivers; and maintaining quality of life. Based on survey responses, 49% of patients underwent a period of “watchful waiting” before starting treatment. The majority of the patients surveyed (43%) had received 1 line of therapy, while 20% had received 2 and 16% had received 3, where chemoimmunotherapy was the most commonly prescribed treatment. The majority of patients surveyed received 2 regimens: rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), and prednisone; and cyclophosphamide, vincristine, and prednisone. Important side effects of chemotherapy included fatigue, low activity level, and hair loss. The patients emphasized the need for therapies that can be administered at a hospital located near home to minimize travel time and burden on caregivers, as well as improve quality of life by keeping patients close to their support systems. Patients who had experience with axi-cel accessed this therapy via enrolment in a clinical trial. They reported travelling out of province to receive treatment and being away from home for up to 3 months to do so. Patients who

received axi-cel experienced side effects that included cytokine release syndrome (CRS), neutropenia, febrile neutropenia, thrombocytopenia, constipation, and swelling.

Registered clinician input was received from Ontario Health-Cancer Care Ontario Hematology Cancer Drug Advisory Committee. According to the clinicians, the current pathway of care for patients with r/r FL after 2 or more lines of systemic therapy is chemoimmunotherapy and autologous stem cell transplant (auto-SCT). The clinicians noted that in select patients for whom the treatment goal is mostly palliative; allogeneic stem cell transplant (allo-SCT) and radiotherapy may also be considered. The clinicians suggested chemoimmunotherapy would likely be less efficacious among re-treated patients, thus pointing to the need for additional therapy options. The clinicians suggested that axi-cel may shift the current treatment paradigm by replacing chemoimmunotherapy in third line, but will likely not replace auto-SCT among eligible patients. Although it is uncertain whether axi-cel could replace auto-SCT in third line, the clinicians noted the potential for axi-cel to be prescribed in advance of auto-SCT among patients who are refractory to chemotherapy. Furthermore, it was noted that axi-cel should only be considered in relatively fit patients without significant comorbidities. Patients with uncontrolled infections, severe organ dysfunction, and poor performance status should be excluded. Clinician input further noted that axi-cel should be considered in select patients who had received prior CD19-directed therapy or allo-SCT, despite their exclusion from the pivotal trial.

Participating drug plans noted concerns that the existing capacity may not be able to meet the anticipated demand in Canada. Given the requirement for specialized and accredited treatment centres where the therapy can be administered, access may require interprovincial travel and, without full coverage of interprovincial reimbursement, may impact equitable access across Canada. Finally, drug plans queried whether, and how, potential manufacturing delays may impact the clinical effectiveness of axi-cel.

Several of these concerns were addressed in the sponsor's model:

- The impact of disease and treatment on a patient's quality of life was captured with utility values. Adverse events (AEs) were incorporated as disutilities within the analyses.
- The standard of care (SOC) modelled by the sponsor reflected the current treatments available to patients with r/r FL.

In addition, CADTH addressed some of these concerns as follows:

- Noting that r/r FL is a disease that can have extended periods of survival when treated with current SOC, CADTH revised the sponsor's long-term extrapolation of OS for patients receiving SOC in line with real-world evidence and clinical plausibility.
- In line with clinicians' expectations that axi-cel will likely shift the current treatment paradigm by replacing chemoimmunotherapy as a new preferred treatment for patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy, CADTH revised the sponsor's projected market share in the budget impact analysis (BIA).

CADTH was unable to address the following concerns raised from stakeholder input:

- Capacity is not explicitly considered in the model. The sponsor assumes all patients with r/r FL have access to axi-cel if required and that the manufacturing time is similar to that observed in the trial.

- Accessing axi-cel may require interprovincial travel. These costs were not considered in the analysis given heterogeneity across provinces in terms of their policy for interprovincial billings. Furthermore, given the public payer perspective, patient-borne interprovincial travel costs were not included as it was considered outside the scope of this review's perspective.

Economic Review

The current review is for axi-cel (Yescarta) for adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of axi-cel compared with SOC. Aligned with Health Canada's indicated population, the modelled population comprised adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy.[1]

Axi-cel is a CD19-directed genetically modified autologous T-cell immunotherapy individually prepared from a patient's peripheral blood mononuclear cells.[1] It is available as a cell suspension for infusion containing a target dose of 2×10^6 chimeric antigen receptor (CAR) T-cells/kg body weight (range, 1×10^6 cells/kg to 2.4×10^6 cells/kg), to a maximum of 2×10^8 CAR T cells for patients weighing 100 kg or more.[2] It is provided as a single-dose, 1-time infusion. The sponsor's submitted price for axi-cel is $485,021 per infusion,[1] not including costs associated with pretreatment (i.e., leukapheresis, bridging chemotherapy, and lymphodepleting chemotherapy), hospitalization related to inpatient administration, and postinfusion stay in an intensive care unit (ICU) stay.

SOC, the comparator for this analysis, encompassed a basket of therapies commonly used in Canadian clinical practice. SOC was composed of 50% chemotherapy, 12% SCT, 5% phosphoinositide 3-kinase inhibitors (i.e., idelalisib), and 33% investigational therapies offered though clinical trials.[1] The treatment cost associated with chemotherapy was estimated as a weighted average of 6 chemotherapy regimens: rituximab plus bendamustine; cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; cyclophosphamide, vincristine, and prednisone; obinutuzumab plus bendamustine; gemcitabine, dexamethasone, and cisplatin; rituximab plus cyclophosphamide, vincristine, and prednisone.[1]

Based on clinician-informed proportions of patients on each chemotherapy regimen and average number of cycles per regimen, the sponsor estimated the total weighted drug cost of chemotherapy to be $15,650.[1] The sponsor estimated the cost of auto-SCT and allo-SCT to be $70,434 and $91,992, respectively, which incorporated the cost of stem cell transplant (SCT) procedures (including high-dose chemotherapy, stem cell harvest, and infusion), as well as the cost of inpatient stay associated with administration.[1] The SOC composite cost was estimated as a weighted average of the drug acquisition and administration costs

associated with chemotherapy, SCT, phosphoinositide 3-kinase inhibitors, and investigational therapies accessed through clinical trials ($32,073).[1] Vial-sharing was not incorporated by the sponsor.

The clinical outcomes modelled were PFS and OS.[1] The economic outcomes of interest were QALYs and life-years. The economic evaluation was conducted over a lifetime time horizon (50 years), from the perspective of the Canadian public health care payer. Costs and outcomes were discounted at 1.5% per annum.[1]

Model Structure

The sponsor used a partitioned survival model to capture all costs and outcomes associated with axi-cel and SOC. The model included 3 health states: progression-free, progressed disease (PD), and death, with transitions between health states occurred on a monthly cycle length (Figure 1). The proportion of patients in progression-free, PD, and death states was estimated over time based on OS and PFS curves, which were informed by the ZUMA-5 single-arm trial, as well as the SCHOLAR-5 retrospective cohort study. The proportion of patients with PD (i.e., post-progression state) was estimated as the difference between the proportion of living patients (estimated from the OS curve) and the proportion of progression-free patients (estimated from the PFS curve). PFS was defined as the time from the date of enrolment to the date of first documented progression or death due to any cause. Patients began in the progression-free health state and, over time, could transition to either the PD health state or the death state. Patients in the PD health state could remain either in this health state or transition to the death state (i.e., patients could not return to the progression-free health state).

Model Inputs

Baseline patient characteristics were derived from the ZUMA-5 trial, a phase II, single-arm, multicentre trial investigating the efficacy and safety of axi-cel among patients with r/r grade 1, 2, or 3a FL (n = 127).[1] The typical patient in the modelled cohort, which the sponsor assumed reflected the patient population in Canada, was aged [redacted] years and weighed [redacted] kg, and was more likely to be male (59%).[1] These characteristics were those of the patient population enrolled in the ZUMA-5 trial and were used to inform the drug dosage regimens and the age- and sex-specific distribution of the general population mortality risk.[1]

Clinical efficacy parameters used to characterize axi-cel and SOC, including OS and PFS, were derived from various data sources. For axi-cel, inputs were based on the 36-month follow-up analysis of the ZUMA-5 single-arm trial (data cut-off: March 31, 2022). For SOC, inputs were informed by the SCHOLAR-5 study, a multicentre, international, observational, retrospective study that constructed a historical control cohort of patients with r/r FL treated with 2 or more prior lines of usual therapies in routine practice (n = 128). The SCHOLAR-5 cohort was derived from 3 international cohorts: IQVIA, Vanderbilt, and DELTA. The IQVIA and Vanderbilt cohorts were created from electronic medical records, while the DELTA cohort represented patients from the DELTA clinical trial who proceeded to receive therapy subsequent to idelalisib. The DELTA cohort was added to increase statistical power for OS. In the absence of head-to-head evidence, the sponsor conducted an indirect treatment comparison to assess the relative efficacy of axi-cel versus SOC therapies. Propensity score methods, specifically standardized mortality ratio weighting, were applied to account for the imbalance of confounders between the ZUMA-5 trial and the SCHOLAR-5 external control cohort.[3] Specifically, the OS and PFS for axi-cel and SOC were estimated using a weighted Kaplan-Meier (KM)

estimator, whereby patients from the SCHOLAR-5 external cohort were weighted to be comparable with the ZUMA-5 trial population across baseline covariates using propensity score matching.[3]

Survival data from the indirect comparison of the ZUMA-5 and SCHOLAR-5 study results were extrapolated to derive the long-term survival estimates of OS and PFS informing the economic model.[1] Standard parametric models were fit independently to the individual patient data from the ZUMA-5 and SCHOLAR-5 studies. Under the assumption that axi-cel was curative, the sponsor derived piecewise cure models to estimate OS and PFS, which accounted for the proportion of patients receiving axi-cel who may experience long-term survival. The piecewise cure models estimated a likelihood of cure (i.e., "statistically cured" fraction), wherein the survival outcomes for the "cured" group, relative to the "uncured" group, which does not achieve long-term remission, are assumed to be better. Cured patients experience a slightly worse survival than the general population (hazard ratio = 1.09),[4] while uncured patients experience poorer survival outcomes relative to cancer-free individuals of the same age and sex. In the submitted base case, 40% of patients receiving axi-cel were expected to achieve long-term remission (i.e., the cure fraction), with long-term survival applied 5 years from the start of the model (i.e., the cure time point). Hence, in the sponsor's piecewise cure model, (1) standard parametric extrapolations for OS and PFS were applied until the 5-year cure time point; and (2) OS and PFS were calculated thereafter as the weighted product of background survival (for the cured population) and cancer-specific survival (for the uncured fraction). For patients receiving axi-cel, the sponsor used a piecewise cure model based on the exponential distribution to model OS, and a piecewise cure model based on the log-normal distribution to model PFS. Given that the sponsor did not extend the assumption of cure to patients receiving SOC therapies, the sponsor selected the standard exponential distribution to model both the OS and PFS of SOC. Survival distributions were selected based on Akaike information criterion and Bayesian information criterion, as well as visual inspection.[1]

As health-related quality of life data were not collected in the ZUMA-5 trial, health state utility values were obtained from the literature. Utility values were derived from 2 sources that reported health state utilities for indolent non-Hodgkin lymphoma using the EQ-5D results of 222 patients in the UK. The sponsor sourced utility values of 0.805 for the progression-free state, 0.620 for the PD on-treatment state, and 0.736 for the PD off-treatment state. Utility values were adjusted using age-related utility decrements based on an algorithm developed by Ara et al. (2010)[5] to account for the natural decline in quality of life associated with age. The model incorporated disutilities associated with AEs categorized as grade 3 or greater in any of the treatments considered.[1] Disutilities were applied as a 1-time decrement to the first model cycle; thus, it was assumed that AEs would have no further impact on costs beyond the initial hospitalization period. For axi-cel, AE rates were derived from those occurring in at least 5% of patients in the ZUMA-5 trial (36-month data cut-off);[6] while for SOC, rates were calculated as a weighted average of AEs reported in clinical trials of SOC regimens.[7-9]

Costs captured in the model included pretreatment cost (i.e., drug acquisition and drug administration associated with pretreatment), treatment cost (i.e., drug acquisition, drug administration, and hospitalization associated with treatment), follow-up medical costs before progression (i.e., physician visits, PET/CT scans, and laboratory tests), subsequent treatment costs in fourth line, follow-up medical costs in postprogression, AE management costs, and terminal care costs.[1] Drug acquisition costs for axi-cel were based on the

sponsor's submitted price.[1] The dosing modelled for axi-cel is consistent with that described in the overview section. Drug acquisition costs were sourced from the Ontario Drug Benefit Formulary,[10] with dosing schedules based on the chemotherapy regimen monographs from Ontario Health-Cancer Care Ontario.[11]

Prior to infusion, patients receiving axi-cel underwent leukapheresis, bridging chemotherapy, and conditioning chemotherapy. Given that data from the ZUMA-5 trial were used to determine the proportion of patients that would receive each phase of treatment, weighted costs were modelled for axi-cel. Pretreatment costs were applied in the first cycle of the model. The cost of leukapheresis ($2,688) was applied to all patients receiving axi-cel.[12] The cost of bridging chemotherapy ($25) was estimated as the weighted 1-cycle cost of the following therapies: 60% dexamethasone ($3); 10% radiotherapy ($157); and 30% gemcitabine, dexamethasone, and cisplatin regimen ($652). This cost was applied to 3.1% of patients receiving axi-cel.[1] Moreover, all patients receiving axi-cel were assumed to receive fludarabine plus cyclophosphamide administered daily for 3 days as conditioning chemotherapy ($2,300).[1] Hospitalization and ICU inputs for axi-cel were estimated based on the average length of stay ([redacted]) and proportion of patients in ICU ([redacted]) observed in the ZUMA trial as these were assumed to be reflective of Canadian clinical practice. Costs typically associated with the ongoing monitoring were obtained from the Canadian Institute for Health Information's Patient Cost Estimator for an inpatient hospitalization for malignant lymphoma.[13]

For patients receiving SOC, treatment costs included chemotherapy (50%), SCT (12%), idelalisib (5%), and clinical trials (33%), based on a review of Canadian clinical practice guidelines and clinical expert opinion. The treatment costs associated with the SOC basket of therapies were as previously described. All regimens were assumed to be given in an outpatient setting, except for SCT. The cost of outpatient administration was based on the cost of complex chemotherapy administration from the Ontario Schedule of Benefits for Physician Services,[14] and the cost associated with chair time was estimated based on the CCO regimen monographs.[11] SCT procedure costs were obtained from the Interprovincial Health Insurance Agreements Coordinating Committee,[15] and the Ontario Case Costing Initiative (OCCI).[16]

The total weighted costs of subsequent therapy differed by prior treatment (i.e., those who received CAR T cells versus SOC as third-line therapy) and were applied as a one-off cost in the first model cycle after progression. The weighted cost associated with subsequent therapy among patients receiving axi-cel and SOC in third line was estimated to be $14,714 and $6,871, respectively. Treatment monitoring costs and health care resource use costs were sourced from the Ontario Ministry of Health Schedule of Benefits for Laboratory and Physician Services.[17] Treatment-emergent AE costs were estimated based on the data from the OCCI and applied as a 1-time cost in the first model cycle. All patients who transitioned to the death state were assumed to incur terminal care costs ($68,703) in the last cycle before death, based on the average cost for patients with terminal lymphoma in the Ontario Cancer Registry.[19]

Summary of Sponsor's Economic Evaluation Results

The sponsor conducted the base case via a probabilistic sensitivity analysis with 1,000 simulations. The deterministic and probabilistic results were similar. The probabilistic findings are presented below.[1]

Base-Case Results

Compared with SOC, axi-cel was associated with an incremental QALY gain of 4.38 and an incremental cost of $505,565, resulting in an ICER of $115,543 per QALY (Table 3).[1] Notably, the sponsor's analysis predicted that axi-cel was associated with a longer duration of life than SOC (i.e., incremental life-years: 5.83).

Given the duration of the ZUMA-5 trial (i.e., 36 months) in contrast to the model's time horizon (i.e., 50 years), it is important to note that the majority of the QALY and life-year benefit (96% and 97%, respectively) realized by patients receiving axi-cel was derived from the time period beyond which there are observed trial data (i.e., extrapolated period). Most of the QALYs gained by patients receiving axi-cel were realized in the progression-free state (78%), whereas patients receiving SOC realized most of their QALY gains in the PD state (78%). The key cost driver among patients receiving axi-cel was the cost of drug acquisition, accounting for 81% of the total cost incurred by patients. The main cost driver among patients receiving SOC was end-of-life care, which accounted for 55% of the total estimated cost.

Axi-cel was not cost-effective at a WTP threshold of $50,000 per QALY in any of the iterations when compared to SOC. The sponsor's submitted analysis is based on the publicly available prices for all drug treatments. Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. SOC ($/QALY)
SOC	$111,964	Reference	4.90	Reference	Reference
Axi-cel	$617,528	$505,565	9.28	4.38	$115,543

axi-cel = axicabtagene ciloleucel; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

The sponsor assessed several model parameters and assumptions in probabilistic scenario analyses. These included: applying a shorter model time horizon; using another analysis set from the ZUMA-5 trial; applying different health state utility values; assessing the impact of different cure fractions; applying alternative parametric distributions to model the OS and PFS of axi-cel and SOC; and aligning the axi-cel re-treatment proportion with that observed in the ZUMA-5 trial. The parameters with the greatest influence were other assumptions regarding efficacy, particularly selection of OS extrapolations and cure fraction, as well as shorter time horizons. When applying a 10% cure fraction for axi-cel, the ICER increased to $168,794 per QALY gained. Moreover, when applying a 10-year time horizon, the ICER increased to $375,698 per QALY gained. All other scenarios resulted in ICERs ranging between $92,912 and $162,936 per QALY gained.[1]

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Assumption of cure of patients with FL is inappropriate:** The sponsor derived piecewise cure models to extrapolate the OS and PFS for axi-cel beyond the ZUMA-5 trial period based on the assumption that a proportion of the population receiving axi-cel would be cured. Specifically, in the submitted base case, 40% of patients receiving axi-cel were expected to achieve long-term remission (i.e., the cure fraction), with long-term survival applied 5 years from the start of the model (i.e., the cure time point). The sponsor suggested that a cure model would be better suited to capture the expected long-term survival of patient populations receiving CAR T-cell therapies with curative intent. CADTH noted that due to the limited duration of follow-up in the ZUMA-5 trial (36 months), there is a great deal of uncertainty as to whether there truly is a statistically cured fraction. CADTH additionally noted that both the cure fraction and cure time point used in the submitted model were sourced from a single-centre trial with a relatively small number of patients with FL (n = 14), for whom the median duration of response had not been reached.[20] Given this small sample size, CADTH noted that the evidence sourced by the sponsor to inform relevant cure input parameters is uncertain and subject to imprecision. This is a concern in view of the fact that estimating survival (and whether this includes a statistically cured fraction) plays a key role in determining the cost-effectiveness of axi-cel relative to that of SOC. Moreover, the clinical expert panel convened by CADTH during the review process noted that long remissions are common for patients with FL, and it would thus be premature to determine the fraction of patients and the time point when patients with r/r FL who remain progression-free are considered clinically cured. The clinical panel highlighted that the evidence submitted by the sponsor does not support a proportion of patients being cured; moreover, it was noted that cure in this disease area is rare. CADTH further noted that clinical expert opinion is aligned with the emerging scientific literature on the uncertainty around the permanence of CAR T-cell treatment efficacy among patients with hematologic malignancies; lack of permanence, in turn, can result in late relapse.[21] In alignment with clinical expert advice, CADTH noted that the assumption of cure of patients with r/r FL remains uncertain given the available evidence.
    - CADTH conducted reanalyses using standard parametric models based on KM data from the ZUMA-5 trial to extrapolate the OS and PFS of axi-cel for the entire duration of the model.
- **Impact of axi-cel on long-term OS is highly uncertain:** The sponsor's base case predicted a survival advantage with axi-cel compared to SOC (incremental life-years: 5.83), of which, 96% were accrued in the time period beyond which there are observed trial data. At the 36-month follow-up analysis of the ZUMA-5 trial reviewed by the CADTH clinical team (data cut-off: March 31, 2022), the OS data for axi-cel were immature as both the median OS and the upper bound of the 95% confidence interval had not been reached.[22] The clinical experts consulted by CADTH noted that r/r FL is a disease that can have extended periods of survival, suggesting that the duration of follow-up may not be sufficiently long to capture the effects of axi-cel on OS. As noted by the CADTH Clinical Review, in addition to the duration of the ZUMA-5 trial and the noncomparative design, the prevalence of

subsequent therapy complicates the interpretation of the OS findings. Following axi-cel infusion, [redacted] of patients received at least 1 subsequent antineoplastic medication (of whom [redacted] received SCT). Hence, the trial's OS results should be considered in the context of subsequent therapies, given that it may be difficult to distinguish which treatment (primary, or subsequent) had greater impact on survival. This is especially relevant considering the lack of comparative data in the ZUMA-5 trial. Furthermore, as the ZUMA-5 trial is ongoing, the data analyzed at the aforementioned cut-off date represent an interim analysis. Evidence suggests that the clinical benefit of cancer agents demonstrated in primary publications is often different from updated mature data. A recent study comparing the predicted survival of parametric extrapolations with observed survival based on updated data of 32 trials identified through US FDA oncology approvals revealed that extrapolations based on initial KM curves had low precision compared with updated KM curves.[23] Therefore, CADTH contends that, in the absence of mature OS data and in tandem with the noncomparative design of the ZUMA-5 trial, the extent to which the parametric distributions of OS for axi-cel overestimate or underestimate the true incremental life-years is uncertain.

CADTH also noted that there is uncertainty regarding the expected OS benefit of axi-cel to a broader population beyond the select patient population recruited for the clinical trial. The ZUMA-5 trial consisted exclusively of patients with an Eastern Cooperative Oncology Group Performance Status of less than or equal to 1 and with a mean age of [redacted] years. According to the clinical experts consulted by CADTH, the ZUMA-5 study population is generally representative of patients in the Canadian population with r/r FL who would receive axi-cel. However, the clinical experts noted that patients seen in clinical practice would also include those with poorer performance status, prior experience with CD19-targeted therapy, and higher prevalence of comorbidities. The clinical experts also noted that the average age of patients with r/r FL is expected to be higher. A Canadian real-world population-based study of a cancer registry estimated the median age of patients with incident FL to be 64 and 61 years in women and men, respectively.[24] As such, if axi-cel were to become available in clinical practice, where patients are likely to have more diverse clinical and demographic profiles than in a clinical trial, there remains uncertainty regarding the expected presence and magnitude of the OS benefit in the real-world setting.

The sponsor selected parametric distributions based on goodness-of-fit criteria, visual inspection, and clinical plausibility. CADTH agrees that appropriate models should be compared based on their statistical fit to the observed trial data, as well as based on their ability to generate clinically plausible long-term extrapolations.[25] However, statistical fit pertains only to the observed trial period, not to the extrapolation period. The weight given to the comparative fit of alternative parametric models to the observed data depends on the extent to which extrapolation is required and the degree of censoring present. Given the length of time required for extrapolation and the size of the censored population in the ZUMA-5 trial, the clinical plausibility of the extrapolated portion of alternative models is of greater importance than the statistical fit to the observed data.[25] According to the clinical experts consulted by CADTH for this review, although the ZUMA-5 trial findings appeared favourable and clinically important (and a survival benefit with axi-cel was deemed plausible), the magnitude and durability of such a benefit was highly uncertain in the absence of longer-term or head-to-head evidence. Clinical

experts indicated that given the degree of uncertainty to do with the durability of the treatment effect of axi-cel relative to SOC, it is clinically plausible for the OS curve of axi-cel to converge with that of SOC within the model's lifetime horizon.

  - Considering these limitations, CADTH conducted 2 reanalyses with different assumptions of treatment effect durability for axi-cel, which sought to address the uncertainty in long-term clinical outcomes.
  - In reanalysis A, the OS of patients receiving axi-cel was modelled using the exponential distribution; as such, the OS for axi-cel was capped by the OS for SOC at 15.3 years, where the survival curves would have otherwise crossed.
  - In reanalysis B, the OS of patients receiving axi-cel was modelled using the log-normal distribution; as such, it was assumed that the treatment effect of axi-cel, relative to that of SOC, would be maintained for the entire model time horizon. The log-normal distribution was maintained for the PFS extrapolation of axi-cel in each reanalysis. In line with clinical expert advice, these reanalyses achieved more plausible OS curves in the absence of long-term evidence, while still conferring a benefit with axi-cel.

- **Impact of SOC on long-term OS is underestimated:** The sponsor derived clinical efficacy data used to characterize SOC from the SCHOLAR-5 study, a retrospective study that constructed a historical control cohort of patients with r/r FL treated with 2 or more prior lines of usual therapies in routine practice. In the absence of head-to-head evidence, the SCHOLAR-5 data used to extrapolate OS for SOC were weighted to be comparable with the ZUMA-5 trial population across baseline covariates. The sponsor selected the exponential distribution based on the weighted KM data from the SCHOLAR-5 trial to model the long-term OS for patients receiving SOC. CADTH noted that the 5-year OS estimate predicted by the exponential distribution for SOC (49.8%) underestimated the observed 5-year survival rate informed by KM data from the SCHOLAR-5 trial ([redacted]).[3] CADTH further noted that a recent retrospective analysis conducted by Batlevi et al. (2020)[26] in a single centre in the US reported a median OS of 8.8 years for patients with r/r FL treated with third-line SOC therapies. In this study, usage of single-agent rituximab (22.4%), rituximab plus alkylator chemotherapy (16.7%), rituximab plus anthracycline chemotherapy (11.7%), investigational therapy (10.0%), SCT (8.3%), and radioimmunotherapy (8.0%) were common in the third-line setting.[26] Therefore, the exponential distribution selected by the sponsor to extrapolate long-term survival for SOC underestimated the 9-year OS by 20.8 percentage points (29.2% versus 50%). Hence, the parametric distribution selected by the sponsor to model long-term OS for patients receiving SOC in the economic model underestimated both the KM estimates informed by the sponsor-submitted SCHOLAR-5 control cohort and the median OS derived from real-world evidence.

  According to clinical expert judgment, the OS curve for SOC generated with the exponential distribution produced 10-, 20-, and 30-year extrapolations that were misaligned with the expectation of survival in current clinical practice. The clinical experts consulted by CADTH reiterated that although long-term survival evidence for SOC therapies is not yet obtainable, clinically plausible extrapolations of OS for patients receiving SOC should align with the available real-world evidence.

Therefore, the clinical experts noted, the log-logistic distribution was likely the most appropriate way to extrapolate the OS for SOC given that: midterm projections were within range of the survival estimates observed in the SCHOLAR-5 trial and by Batlevi et al. (2020); and 10-year, 20-year, and 30-year long-term extrapolations were aligned with clinical plausibility.

  - CADTH conducted a reanalysis using the log-logistic parametric model to extrapolate the OS of SOC.

- **Exclusion of costs related to CAR T-cell therapy:** In the sponsor's base case, costs related to CAR T-cell therapy eligibility assessment were excluded. Feedback from the clinical experts consulted by CADTH noted that the upfront costs of assessment of CAR T-cell therapy eligibility would include those associated with MRIs, PET scans, bone marrow transplants, lumbar punctures, and bloodwork. Should axi-cel be reimbursed, this assessment cost would be incurred by all adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy regardless of whether they would go on to receive CAR T-cell therapy. In addition, the pretreatment cost of leukapheresis considered by the sponsor ($2,688) for patients receiving CAR T-cell therapy was underestimated. CADTH consulted the OCCI and was informed that the cost of stem cell apheresis (code 1.LZ.58.HX; data not available for leukapheresis specifically due to limited number of events) was $5,426.[16] This underestimation of the costs incurred by patients receiving axi-cel relative to their receiving SOC biased the results of the economic analysis in favour of the drug under review.
  - CADTH conducted a reanalysis that included the additional CAR T-cell therapy eligibility assessment cost and the updated cost associated with apheresis.
- **Health state utility estimates are uncertain.** Given that health-related quality of life data were not collected in the ZUMA-5 trial, the sponsor sourced health state utility values from the accrued literature. Values were derived from 2 sources that reported health state utilities for 222 patients with indolent non-Hodgkin lymphoma in the UK using the EQ-5D questionnaire.[27,28] CADTH noted that the utility values adopted in the economic analysis should reflect the preferences of the general population in Canada. The sponsor sourced utility values of 0.805 for the progression-free state, 0.620 for the PD on-treatment state, and 0.736 for the PD off-treatment state. CADTH noted that these estimates were applied without distinguishing which interventions were received (i.e., axi-cel, SOC). The clinical experts consulted by CADTH indicated that, while declining utility in the PD state, relative to the progression-free state, appeared reasonable, the difference between on- and off-treatment utilities accrued in the PD state did not align with their experiences in current clinical practice. In fact, the clinical experts noted that patients treated with currently available subsequent therapies (compared with those available in 2007, as per Pettengell et al., 2008) are unlikely to experience substantial differences in quality of life resulting from treatment status. As such, clinical experts reiterated that, for patients with r/r FL who have PD, quality of life is not expected to differ between those who are on subsequent treatment and those who are off subsequent treatment.
  - CADTH conducted a scenario analysis assuming that the utility value for patients with PD would not differ according to treatment status.

- **Selection of comparators is not supported by current clinical practice.** The sponsor omitted the lenalidomide plus rituximab (R2) regimen, from the base-case analysis, despite evidence that this therapy is prescribed by some oncologists in current Canadian clinical practice.[29] During the review process, both the participating drug plans and the clinical expert panel convened by CADTH indicated that the R2 regimen is used off-label for the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy in Canada. According to CADTH's Reimbursement Review procedures, the base case must comprise all relevant comparators, including (1) treatments currently reimbursed by at least 1 participating drug plan for the indication under review; (2) reimbursed treatments that are currently used off-label in Canadian practice; or (3) treatments that have previously received a recommendation in favour of reimbursement from CADTH for the indication under review. CADTH noted that the off-label use of the R2 regimen for this indication is infrequent, and, as such, it is unlikely that its omission impacted the cost-effectiveness results.
    - CADTH was unable to address this limitation as the relevant evidence for the R2 regimen was not incorporated in the economic model submitted by the sponsor.
- **Poor modelling practices were employed.** The sponsor's submitted model included numerous "IFERROR" statements, resulting in situations where the parameter value was overwritten with another value without alerting the user to the automatized overwriting. The systematic use of IFERROR statements rendered thorough auditing of the sponsor's model impractical, as it remains unclear whether the model ran inappropriately by overriding errors. In addition, CADTH noted that selecting the generalized gamma parametric distribution to extrapolate the OS for axi-cel within a prespecified dropdown list yielded calculation errors across several iterations, which complicated the validation process.
    - CADTH was unable to address this limitation, noting that a thorough validation of the submitted model was not possible.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (See Table 5).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
AEs qualified as grade ≥ 3 were incorporated in the model with an associated cost and disutility, because they were observed in ≥ 5% of patients in the ZUMA-5 trial. These were only applied to patients during the first cycle of the model, as it was assumed that AEs would have no further impact on costs and quality of life beyond the initial hospitalization period.	Not appropriate. This approach would be appropriate if all treatment-emergent AEs grade ≥ 3 occurred within the first month of treatment with axi-cel. However, patients in the ZUMA-5 trial experienced AEs beyond the first month of therapy. This is unlikely to be a key source of uncertainty.
Given that all eligible lines of treatment for each patient were included in the SCHOLAR-5 analysis set, the sponsor opted to randomly select the index line of therapy for patients with ≥ 2 prior lines of therapy. As such, the index treatment patterns for the SCHOLAR-5 cohort are not the same as the basket of	Reasonable. CADTH noted that there is a misalignment between the third-line basket of therapies used by the SCHOLAR-5 patients (whose outcomes are used to derive the OS and PFS for SOC) and the third-line SOC therapy usage assumed by the sponsor in the model. While it was possible to alter the distribution of SOC

Sponsor's key assumption	CADTH comment
therapies that patients receive as SOC in the third-line setting in the economic model.	therapies in line with Canadian clinical practice, doing so only impacted the cost of SOC and not the underlying OS estimates for SOC. Given that there are no established clinical practice guidelines for treating r/r FL in Canada (particularly after second-line therapy), the SOC options tend to be variable and dependent on what patients may have failed on previously. However, the SOC therapies included in the economic model were among the most prevalent in the SCHOLAR-5 analysis set. CADTH further noted that although simplifying assumptions were made, in general, these assumptions are reasonable. This is unlikely to be a key source of uncertainty.

AE = adverse event; axi-cel = axicabtagene ciloleucel; FL = follicular lymphoma; OS = overall survival; PFS = progression-free survival; r/r = relapsed or refractory; SOC = standard of care.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses were derived by making changes to model parameter values and assumptions, in consultation with clinical experts. The following changes were made to address several limitations within the economic model: using standard parametric models based on KM data from the ZUMA-5 trial to extrapolate the OS and PFS of axi-cel for the entire duration of the model; using alternative parametric models to extrapolate the OS of SOC and axi-cel; and including a CAR T-cell therapy eligibility assessment cost and updating the pretreatment cost associated with apheresis. However, given the magnitude of uncertainty to do with the comparative clinical efficacy and durability of treatment effect of axi-cel relative to SOC, CADTH was unable to derive a robust base-case estimate of cost-effectiveness. CADTH conducted separate reanalyses involving different parametric assumptions of treatment effect for axi-cel. In reanalysis A, the treatment effect of axi-cel on OS was modelled using the exponential distribution; in reanalysis B, the treatment effect of axi-cel on OS was modelled using the log-normal distribution. These changes are summarized in Table 5.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
1. Assumption of cure of patients with FL is inappropriate	Piecewise cure models selected to extrapolate the OS and PFS for axi-cel	Standard parametric models selected to extrapolate the OS and PFS for axi-cel.
2. Impact of SOC on long-term OS is underestimated	OS for SOC was modelled using the exponential distribution.	OS for SOC was modelled using the log-logistic distribution.
3. Exclusion of CAR T-cell–related costs	• Excluded CAR T-cell therapy eligibility assessment cost. • Cost associated with apheresis ($2,688) is underestimated.	• Included CAR T-cell therapy eligibility assessment cost ($3,000). • Updated cost associated with apheresis ($5,426).
4. Impact of axi-cel on long-term OS is uncertain[a]	OS for axi-cel was modelled using a piecewise cure model based on the exponential distribution.	OS for axi-cel was modelled using the exponential distribution.

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
5. Impact of axi-cel on long-term OS is uncertain[a]	OS for axi-cel was modelled using a piecewise cure model based on the exponential distribution.	OS for axi-cel was modelled using the log-normal distribution.
CADTH reanalysis A	Reanalyses 1 + 2 + 3 + 4	
CADTH reanalysis B	Reanalyses 1 + 2 + 3 + 5	

axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; OS = overall survival; PFS = progression-free survival; SOC = standard of care.

[a]CADTH reanalyses 4 and 5 (which change the axi-cel parametric distribution of OS to exponential and log-normal, respectively), require that reanalyses 1 and 2 be performed concurrently, that is, the axi-cel extrapolation method must be standard parametric (reanalysis 1) and the OS for SOC modelled using the log-logistic distribution (reanalysis 2).

Results from CADTH reanalyses A and B were generally aligned: axi-cel is not cost-effective at a $50,000 WTP threshold compared to SOC. In CADTH reanalysis A (assuming 15.3 years of treatment effect postinfusion before waning), axi-cel was associated with an ICER of $544,875 per QALY gained compared to SOC (incremental costs: $505,223; incremental QALYs: 0.93). In CADTH reanalysis B (assuming that treatment effect would be maintained for the entire model time horizon), axi-cel was associated with an ICER of $243,879 per QALY gained compared to SOC (incremental costs: $505,885; incremental QALYs: 2.07). The probability that axi-cel was cost-effective at a WTP threshold of $50,000 per QALY was 0% in both reanalyses A and B.

The estimated ICERs were higher than the sponsor's base-case value, driven primarily by the use of standard parametric models based on KM data from the ZUMA-5 trial to extrapolate the OS and PFS of axi-cel (i.e., rejecting the assumption of a statistically cured fraction). In line with clinical expert advice, these reanalyses achieved more plausible OS curves in the absence of long-term evidence, while still conferring a survival benefit with axi-cel. In both reanalyses, most incremental QALYs were due to improvements in life-years. Furthermore, 76% (reanalysis A) and 89% (reanalysis B) of QALYs gained by patients receiving axi-cel were derived from the extrapolated period in which there are no observed trial data. The majority of the total cost among patients receiving axi-cel was associated with drug acquisition costs (78%), while the key cost driver among patients receiving SOC was related to terminal care costs (51%).

CADTH reanalyses are based on the publicly available prices for all drug treatments. Full results are available in Appendix 4.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case (deterministic)	SOC	$111,947	4.87	Reference
	Axi-cel	$617,582	9.26	$115,232
CADTH reanalysis 1: cure assumption	SOC	$111,947	4.87	Reference
	Axi-cel	$615,331	7.50	$190,994
CADTH reanalysis 2: SOC OS (log-logistic)	SOC	$113,102	6.96	Reference
	Axi-cel	$617,582	9.26	$220,155

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH reanalysis 3: CAR T-cell costs	SOC	$114,947	4.87	Reference
	Axi-cel	$623,320	9.26	$115,855
CADTH reanalysis 4: axi-cel OS (exponential)	SOC	$113,102	6.96	Reference
	Axi-cel	$615,594	7.90	$536,574
CADTH reanalysis 5: axi-cel OS (log-normal)	SOC	$113,102	6.96	Reference
	Axi-cel	$616,285	9.11	$235,080
CADTH reanalysis A: (1 + 2 + 3 + 4)	SOC	$116,102	6.96	Reference
	Axi-cel	$621,332	7.90	$539,497
CADTH reanalysis B: (1 + 2 + 3 + 5)	SOC	$116,102	6.96	Reference
	Axi-cel	$622,022	9.11	$236,359
CADTH reanalysis A: probabilistic	**SOC**	**$116,105**	**6.97**	**Reference**
	Axi-cel	**$621,329**	**7.90**	**$544,875**
CADTH reanalysis B: probabilistic	**SOC**	**$116,105**	**6.97**	**Reference**
	Axi-cel	**$621,991**	**9.05**	**$243,879**

axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life-year; SOC = standard of care.

Scenario Analysis Results

CADTH undertook price reduction analyses based on the sponsor's results and CADTH's reanalyses. Results of CADTH reanalysis A suggested a price reduction of 95% would be required to achieve cost-effectiveness of axi-cel relative to SOC at a $50,000 per QALY threshold. In CADTH reanalysis B, a price reduction of 82% would be required (Table 7).

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for axi-cel vs. SOC		
Price reduction	**Sponsor base case**	**CADTH reanalysis A**	**CADTH reanalysis B**
No price reduction	$115,231	$539,487	$236,356
10%	$104,178	$487,696	$213,697
20%	$93,125	$435,906	$191,038
30%	$82,071	$384,115	$168,378
40%	$71,018	$332,324	$145,719
50%	$59,965	$280,533	$123,060
60%	$48,911	$228,742	$100,401
70%	$37,858	$176,951	$77,741
80%	$26,805	$125,161	$55,082
90%	$15,751	$73,370	$32,423

Analysis	ICERs for axi-cel vs. SOC		
100%	$4,698	$21,579	$9,764

axi-cel = axicabtagene ciloleucel; ICER = incremental cost-effectiveness ratio; SOC = standard of care; vs. = versus.

CADTH undertook 1 scenario analysis on each of the CADTH reanalyses. In line with clinical expert advice, CADTH assumed that for patients with r/r FL who have PD, quality of life would not differ according to subsequent treatment status. Specifically, CADTH assumed utility equivalence between patients who are on and off subsequent treatment (0.736). In reanalysis A, the ICER increased to $564,126 (incremental costs: $505,223; incremental QALYs: 0.90). In reanalysis B, the ICER increased to $246,379 (incremental costs: $505,885; incremental QALYs: 2.05).

The results of this analysis are presented in Table 14.

Issues for Consideration

- **Travel-associated costs:** Travel costs and the requirement for time spent away from work were not taken into account in the economic model. The sponsor's implementation plan indicated that not all provinces and territories will have a site to provide axi-cel within the next 3 years.[30] Patients in jurisdictions that do not currently have a site for providing axi-cel will need to travel out of province for treatment. Furthermore, the clinical experts noted that some provinces do not have capacity to assess patients' eligibility for CAR T-cell therapy. The implementation plan suggests that the sponsor will coordinate travel and lodging for the patient and their caregiver, who need to remain close to the qualified treatment centre following infusion.[30] The sponsor stated that the program is intended to support adherence to axi-cel's monitoring requirements by providing financial support to cover transportation-related expenses and lodging costs for the patient and their caregiver during the pretreatment and treatment periods when they are required to stay close to the qualified treatment centre. The sponsor also noted that, for the patient to be eligible for support, their primary residence must be at least 2 hours or 200 km away from the authorized treatment centre. If this patient support program is not operationalizable and travel expenses (e.g., travel, lodging, food) are absorbed by the patient or public payer, this may impact access to axi-cel. Disparities in funding and treatment access may vary depending on the province or territory. Hence, the requirement for access to a tertiary care centre for delivery of axi-cel may have equity of access implications, which were not substantively considered in the economic submission.
- **Manufacturing delays:** The sponsor's implementation plan indicated that, in the ZUMA-5 trial, the median time from leukapheresis collection to release from the manufacturing site was [redacted], and the median time to final product delivery (i.e., time axi-cel is ready to be infused back into the patient) was observed to be 17 days.[22] The sponsor further noted that comparable findings were demonstrated in a retrospective analysis of the manufacturing and supply experience in Canada, where the median time between leukapheresis and product delivery was reported to be 21 days.[31] Moreover, a recent real-world study conducted in the US based on 3 commercial claims databases revealed that the median time from leukapheresis to CAR T-cell infusion was 26 to 27 days.[32] However, CADTH clinical expert feedback noted the potential for greater variability in manufacturing time in the real-world

setting given apheresis collection would be conducted across a broad network of pan-Canadian sites with manufacturing conducted across the border in the US.[30] Clinical expert feedback emphasized that manufacturing delays are a significant clinical problem, especially among patients who progress relatively fast and have a higher disease burden. In the context of manufacturing delays, axi-cel would not be as effective among fast-progressors as it would among patients who do not have disease progression.

- **Manufacturing failures:** Issues pertaining to manufacturing are important to the successful delivery of CAR T-cell therapies. Manufacturing failure may occur due to inadequate number of T-cells in the apheresed product, poor selection of T-cells on day 0 of manufacturing, or irreversibly impaired T-cells (i.e., no response to stimulation in culture), microbial contamination, equipment-related cell loss, high endotoxin levels, and accidents. The sponsor noted that the axi-cel manufacturing success rate in the ZUMA-5 trial was 100%; hence, the impact of manufacturing failure was not considered in the submitted economic model. However, manufacturing failure of CAR T-cell therapies is not uncommon and has been observed in trials for axi-cel[33] and other CAR T-cell products.[34] There may be additional costs associated with manufacturing failure including increased hospital stay while a second sample is prepared, if at all possible. In addition, manufacturing failure may impact patient outcomes due to treatment delays or compromised doses.
- **Re-treatment with axi-cel:** In ZUMA-5, patients who achieved a partial response at the 3-month assessment and subsequently experienced disease progression were eligible for an optional course of re-treatment with conditioning chemotherapy and axi-cel. Hence, 10.2% of enrolled patients were eligible for re-treatment (n = 13 in the 36-month full analysis set). Aligned with the ZUMA-5 trial, the sponsor conducted a scenario assuming that 10.2% of patients receiving axi-cel would be eligible for an optional course of re-treatment. Of note, in the economic model, the sponsor assumed that re-treated patients would not incur the additional drug acquisition cost of axi-cel and leukapheresis. CADTH noted that the sponsor had not offered additional information in the implementation plan regarding the potential costs associated with re-treatment with axi-cel (i.e., neither confirming nor denying that drug acquisition costs for axi-cel would be incurred only once in the event of re-treatment). The clinical expert panel convened by CADTH indicated that it is unlikely that axi-cel would be eligible for use in re-treatment of patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy in Canada, as there is no evidence to support re-treatment in this population. CADTH noted that the cost-effectiveness of re-treatment with axi-cel in patients with r/r FL is unknown.
- **Capacity constraints:** The sponsor's implementation plan indicated the capacity for annual production of axi-cel for patients in Canada. The sponsor stated that it currently has the capacity to produce therapy for 4,500 patients per year, with capacity increasing to 7,100 patients per year by December 2023.[30] The sponsor did not take into account potential capacity constraints in the submitted economic evaluation (i.e., additional costs arising from treatment delays and/or adverse clinical outcomes due to capacity issues).

- **Long-term clinical impacts:** The evidence for the effectiveness of CAR T-cell therapy is still in its early stages. In addition, evidence about the rate of late treatment-related toxicities, duration of treatment effect, and what comprises follow-up for patients receiving CAR T-cell therapy in Canada is emerging. Furthermore, if axi-cel is curative as claimed, patients with r/r FL would be expected to live a longer life, and as such, the health care system may incur additional costs.
- **High resource and administrative burden:** To be able to treat patients with axi-cel, personnel at specialized treatment centres need to be trained and the centres accredited by the manufacturer. Both obtaining and maintaining this accreditation process, including the development of various protocols and supporting yearly audits, can result in a high resource burden. There is also the added complexity of needing to coordinate patient care and product preparation with an external manufacturer. Since there will likely be multiple CAR T-cell therapies administered by the specialized treatment centres, various protocols for preparation will need to be managed along with delivery of each product type, which would increase the overall administrative burden.
- **Shortage of drugs to manage CRS:** CRS tends to be managed with tocilizumab, which is in relatively short supply in Canada. Tocilizumab has been on the Drug Shortages Canada website list because of its use in the treatment of COVID-19 treatment. Health Canada has previously declared a "Tier 3" shortage of tocilizumab, a designation reserved for shortages with the greatest potential impact on Canada's health care system.[35] The use of siltuximab has been considered by some clinicians if there is a severe shortage of tocilizumab, but this treatment is currently only publicly funded via the Alberta drug formulary.[36] Shortage of treatments for CRS may impact axi-cel use because of the risk of CRS associated with CAR T-cell therapy. This is especially relevant as 78% of patients in the ZUMA-5 trial experienced CRS.
- **Future treatments:** Clinical experts indicated that Canadian hospitals are in the midst of expanding their capacity to manufacture CAR T-cell products in the future. In particular, British Columbia's BC Cancer Immunotherapy Program has developed in-house expertise and infrastructure to manufacture CAR T cells for the treatment of blood cancers. More than 50 patients with end-stage leukemia and lymphoma in British Columbia and Ontario have received CAR T-cell therapy manufactured by the BC Cancer Immunotherapy Program as part of the CLIC-01 clinical trial, a phase I/II pan-Canadian clinical trial.[37] Clinical expert feedback noted that the price of CAR T-cell therapy produced in this setting would be substantially lower than the CAR T-cell therapy developed by the pharmaceutical industry.

Overall Conclusions

Evidence from the ZUMA-5 single-arm trial suggests that treatment with axi-cel may be associated with clinically important tumour responses, including complete remission, in adult patients with r/r FL after 2 or more lines of systemic therapies. However, there is insufficient evidence — due to the single-arm design of the trial as well as limited follow-up duration — to determine the effects of axi-cel on OS and PFS. The CADTH clinical assessment identified limitations with the sponsor's comparison of the ZUMA-5 trial to the SCHOLAR-5 study, which substantially restricted the ability to interpret the relative treatment effects of axi-cel and SOC. Overall, the CADTH Clinical Review concluded that there is a high degree of uncertainty around the treatment effects of axi-cel relative to SOC.

Given the magnitude of uncertainty to do with the effect of axi-cel treatment on OS, axi-cel's efficacy compared to SOC, and the durability of any benefit, CADTH was unable to derive a robust base-case estimate of cost-effectiveness. Moreover, given the duration of the ZUMA-5 trial (36 months) in contrast to the model's time horizon (50 years), it is important to note that the majority of the QALY benefit realized by patients receiving axi-cel was derived from the time period beyond which there are observed trial data (i.e., extrapolated period). To address this, CADTH conducted separate reanalyses involving different parametric assumptions of treatment effect: in reanalysis A, the OS of patients receiving axi-cel was modelled using the exponential distribution (thus, assuming 15.3 years of treatment effect postinfusion before waning); and in reanalysis B, the OS of patients receiving axi-cel was modelled using the log-normal distribution (thus, assuming that the treatment effect of axi-cel, relative to SOC, would be maintained for the entire time horizon of the model). In addition, the following changes were made consistently across reanalyses A and B to address limitations within the economic model: using standard parametric models based on KM data from the ZUMA-5 trial to extrapolate the OS and PFS of axi-cel for the entire duration of the model; using alternative parametric models to extrapolate the OS of SOC and axi-cel; and including a CAR T-cell eligibility assessment cost and updating the pretreatment cost associated with apheresis.

Results from CADTH reanalyses A and B were generally aligned: axi-cel is not cost-effective at a $50,000 WTP threshold compared to SOC. In CADTH reanalysis A (assuming 15.3 years of treatment effect postinfusion before waning), axi-cel was associated with an ICER of $544,875 per QALY gained compared to SOC (incremental costs: $505,223; incremental QALYs: 0.93). In CADTH reanalysis B (assuming that treatment effect would be maintained for the entire time horizon of the model), axi-cel was associated with an ICER of $243,879 per QALY gained compared to SOC (incremental costs: $505,885; incremental QALYs: 2.07). The estimated ICERs were higher than the sponsor's base-case value, driven primarily by the use of standard parametric models based on KM data from the ZUMA-5 trial to extrapolate the OS and PFS of axi-cel (i.e., rejecting the assumption of a statistically cured fraction). In line with clinical expert advice, these reanalyses achieved more plausible OS curves in the absence of robust long-term evidence, while still conferring a benefit with axi-cel. CADTH noted that both reanalyses assume life expectancy increases for patients receiving axi-cel relative to current SOC (2.68 and 1.10 years of life gained in reanalysis A and B, respectively). However, the true impact of axi-cel on OS relative to SOC remains uncertain in the absence of evidence from randomized trials. The CADTH reanalyses assume that the impacts of residual confounding that could influence the nonrandomized comparison of the ZUMA-5 and SCHOLAR-5 studies are limited and that their findings could be replicated in real-world clinical practice. Both assumptions are highly uncertain. Hence, given the available evidence, the estimates presented in the CADTH reanalyses likely represent the upper bounds of the incremental gains that may be realized from this therapy.

A price reduction of 95% or 82% would be required for axi-cel to be cost-effective at a WTP threshold of $50,000 per QALY gained, conditional on axi-cel's long-term impact on OS relative to SOC. This would mean a reduction in the 1-time price of axi-cel from $485,021 to $86,334 (an 82% price reduction) or $26,676 (a 95% price reduction). This range reflects the uncertainty around long-term survival extrapolation as analyzed in CADTH reanalyses A and B. Finally, CADTH undertook 1 scenario analysis on each of the CADTH reanalyses. In line with clinical expert advice, CADTH assumed that among patients with r/r FL who have PD, quality

of life would not differ according to subsequent treatment status. In reanalysis A, the ICER increased to $564,126 (incremental costs: $505,223; incremental QALYs: 0.90). In reanalysis B, the ICER increased to $246,379 (incremental costs: $505,885; incremental QALYs: 2.05).

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for r/r Grade 1, 2, or 3a FL After 2 or More Lines of Systemic Therapy (Gene Therapy)

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
CAR T-cell therapy						
Axicabtagene ciloleucel (Yescarta)	Refer to dosage	Suspension for IV infusion	485,021.0000[a]	Target of 2×10^6 anti-CD19 CAR T cells/kg body weight (range, 1×10^6 to 2.4×10^6 cells/kg) to a maximum of 2×10^8 anti-CD19 CAR T cells (1-time infusion)	485,021	NA

CAR = chimeric antigen receptor; FL = follicular lymphoma; NA = not applicable; r/r = relapsed or refractory.

Table 9: CADTH Cost Comparison Table for r/r Grade 1, 2, or 3a FL After 2 or More Lines of Systemic Therapy (Chemotherapy, SCT)

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
Chemotherapy						
BR						
Bendamustine (generic)	5 mg/mL	25 mg vial 100 mg vial with powder for solution	296.8800 1,062.5000	28-day cycles: 90 mg/m^2 days 1 and 2[c]	3,906	3,906
Rituximab (biosimilar)	10 mg/mL	100 mg vial for IV infusion	297.0000[b]	28-day cycles: 375 mg/m^2 on day 1[c]	2,079	2,079
BR regimen cost (21-day cycle)					5,985	5,985
CHOP						
Cyclophos-phamide (Procytox)	20 mg/mL	500 mg vial 1,000 mg vial	93.1400 168.8300 310.6000	21-day cycles: 750 mg/m^2 IV on day 1[c]	262	349

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
		2,000 mg vial for IV infusion				
Doxorubicin (generic)	2 mg/mL	10 mg vial 50 mg vial for IV infusion	50.0000 250.0000	21-day cycles: 50 mg/m^2 IV on Day 1[c]	455	607
Vincristine (generic)	1 mg/mL	1 mg vial 2 mg vial 5 mg vial for IV infusion	30.6000 62.0000 153.0000	21-day cycles: 1.4 mg/m^2 IV (max 2 mg) on day 1[c]	62	83
Prednisone (generic)	50 mg	Tablet	0.1735	21-day cycles: 100 mg orally on days 1 to 5[c]	2	2
CHOP regimen cost (21-day cycle)					781	1,041
CVP						
Cyclophos-phamide (Procytox)	20 mg/mL	500 mg vial 1,000 mg vial 2000 mg vial for IV infusion	93.1400 168.8300 310.6000	21-day cycles: 750 mg/m^2 IV on day 1[c]	262	349
Vincristine (generic)	1 mg/mL	1 mg vial 2 mg vial 5 mg vial for IV infusion	30.6000 62.0000 153.0000	21-day cycles: 1.4 mg/m^2 IV (max 2 mg) on day 1[c]	62	83
Prednisone (generic)	50 mg	Tablet	0.1735	21-day cycles: 100 mg PO on days 1 to 5[c]	2	2
CVP regimen cost (21-day cycle)					326	434
GB						
Obinutuzumab	10 mg/mL	100 mg vial for IV infusion	297.0000[b]	28-day cycles: 1,000 mg IV on days 1, 8, and 15 in cycle 1, and on day 1 on each cycle thereafter[c]	Induction: 15,827 Maintenance: 5,276	Induction: 15,827 Maintenance: 5,276
Bendamustine (generic)	5 mg/mL	25 mg vial 100 mg vial with powder for solution	296.8800 1,062.5000	28-day cycles: 90 mg/m^2 days 1 and 2[c]	3,906	3,906
GB induction regimen cost (21-day cycle)					19,733	19,733
GB maintenance regimen cost (21-day cycle)					9,182	9,182

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
GDP						
Gemcitabine (generic)	40 mg/mL	1,000 mg vial 2,000 mg vial with lyophilized powder for infusion	270.0000 540.0000	21-day cycles: 1,000 mg/m^2 days 1 and 8[c]	1,080	1,440
Dexamethasone (generic)	4 mg	Tablet	0.3046	21-day cycles: 40 mg days 1 to 4[c]	12	16
Cisplatin (generic)	1 mg/mL	50 mg vial 100 mg vial with solution for injection	135.0000 270.0000	21-day cycles: 75 mg/m^2 on day 1[c]	405	540
GDP regimen cost (21-day cycle)					1,497	1,996
R-CVP						
Rituximab (biosimilar)	10 mg/mL	100 mg vial for IV infusion	297.0000[b]	21-day cycles: 375 mg/m^2 on day 1[c]	2,079	2,772
Cyclophos-phamide (Procytox)	20 mg/mL	500 mg vial 1,000 mg vial 2,000 mg vial for IV infusion	93.1400 168.8300 310.6000	21-day cycles: 750 mg/m^2 IV on day 1[c]	262	349
Vincristine (generic)	1 mg/mL	1 mg vial 2 mg vial 5 mg vial for IV infusion	30.6000 62.0000 153.0000	21-day cycles: 1.4 mg/m^2 IV (max 2 mg) on day 1[c]	62	83
Prednisone (generic)	50 mg	Tablet	0.1735	21-day cycles: 100 mg orally daily[c]	7	10
R-CVP regimen cost (21-day cycle)					2,410	3,214
PI3K inhibitor						
Idelalisib (Zydelig)	100 mg 150 mg	Tablet	85.35 85.35	150 mg twice daily	NA	4,780
SCT						
Autologous SCT (< 72 hours)	Adult autologous stem cell transplant (< 72 hours); includes all facility costs including inpatient and diagnostic costs				36,645[d] per transplant	NA
Autologous SCT (> 72 hours)	Adult autologous stem cell transplant (> 72 hours); includes all facility costs including inpatient and diagnostic costs				77,956[e] per transplant	NA

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
Allogeneic SCT (non-MUD patients)	Adult allogeneic stem cell transplant; includes all facility costs including inpatient and diagnostic costs; excludes MUD patients				179,392[d] per transplant	NA
Allogeneic SCT (MUD patients)	Adult allogeneic stem cell transplant; includes all facility costs including inpatient and diagnostic costs; MUD patients				216,542[d] per transplant	NA

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone; FL = follicular lymphoma; GDP = gemcitabine, dexamethasone, and cisplatin; MUD = matched unrelated donor; PI3K = phosphoinositide 3 kinase; R2 = lenalidomide plus rituximab; R-CVP = rituximab plus cyclophosphamide, vincristine, and prednisone; SCT = stem cell transplant.

Note: All prices are wholesale from IQVIA Delta PA (accessed May 2023), unless otherwise indicated, and do not include dispensing fees. Calculations assume a patient body weight of 75 kg and a body surface area of 1.8 m^2.

[a]Sponsor's submitted price.[1]

[b]Ontario Drug Benefit Formulary or Exceptional Access Program list price[10] (accessed May 2023).

[c]Cancer Care Ontario Formulary: Regimens database.[38]

[d]Interprovincial Billing Rates for Designated High Cost Transplants Effective for Discharges on or after April 1, 2022.[15] The cost includes all facility costs associated with a single transplant episode including inpatient and diagnostic costs.|

[e]Interprovincial Billing Rates for Designated High Cost Transplants Effective for Discharges on or after April 1, 2022.[15] The cost includes all facility costs associated with a single transplant episode including inpatient and diagnostic costs, with a maximum length of stay of 16 days.

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

Table 10: Submission Quality

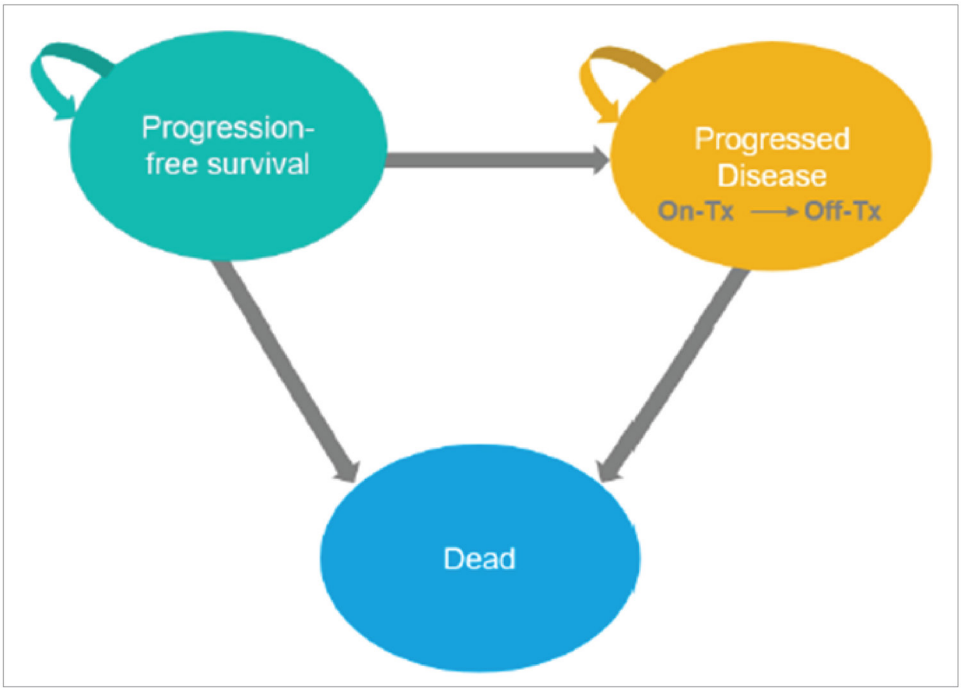
Description	Yes or no	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing.	No	The sponsor excluded the R2 regimen (lenalidomide + rituximab) from the base-case analysis, despite the fact that the therapy is used off-label for the treatment of adult patients with r/r grade 1, 2, or 3a FL after ≥ 2 lines of systemic therapy in Canada.
Model has been adequately programmed and has sufficient face validity.	No	The sponsor's model was not thoroughly debugged. For instance, CADTH remarks that when selecting the generalized gamma parametric distribution to extrapolate the OS for axi-cel within a prespecified dropdown list, the probabilistic analysis could not be properly conducted as it would yield calculation errors across several iterations, which complicated the validation process.
Model structure is adequate for decision problem.	No	The PSM further introduces structural assumptions about the relationship between PFS and OS (i.e., non–mutually exclusive curves), which is potentially problematic since they are likely dependent outcomes. Clinical expert opinion suggested that survival is linked to the occurrence of progressive disease and thus the transition probability to death should vary for patients within the progression-free state compared to those in the progressive disease state.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	Yes	No comment.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	Yes	No comment.

FL = follicular lymphoma; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; R2 = lenalidomide + rituximab.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



Tx = treatment.

Source: Sponsor's pharmacoeconomic submission.[1]

Detailed Results of the Sponsor's Base Case

Table 11: Disaggregated Summary of the Sponsor's Base Case

Parameter	Axi-cel	SOC	Incremental
Discounted LYs			
Total	**12.39**	**6.54**	**5.85**
Pre-progression	9.69	1.37	8.33
Post-progression	2.70	5.18	−2.48
Discounted QALYs			
Total	**9.26**	**4.87**	**4.39**
Pre-progression	7.32	1.09	6.23
Post-progression	1.97	3.78	−1.81

Parameter	Axi-cel	SOC	Incremental
AE Disutility	−0.03	0.00	−0.03
Discounted costs ($)			
Total	**$617,582**	**$111,947**	**$505,635**
Pre-progression	$544,097	$34,950	$509,146
Drug costs	$487,347	$28,765	$458,581
Administration costs	$36,134	$3,308	$32,826
HCRU costs	$20,616	$1,998	$18,618
AE costs	$0	$879	−$879
Post-progression	$17,451	$14,983	$2,468
Drug costs	$12,592	$6,731	$5,861
Administration costs	$1,015	$875	$140
HCRU costs	$3,844	$7,377	−$3,533
Terminal care	$56,034	$62,013	−$5,979
ICER ($/QALY)	**$115,232**		

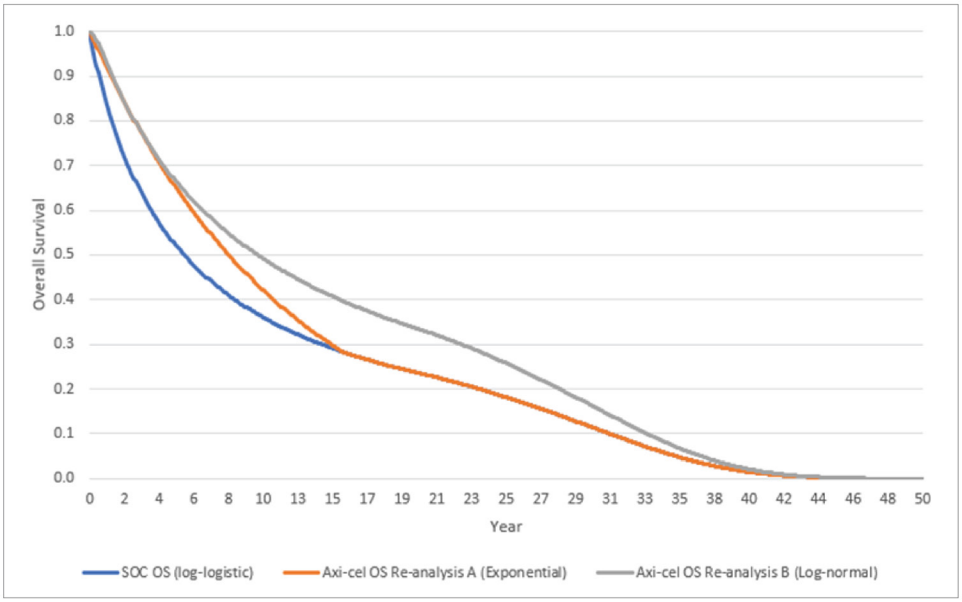
AE = adverse event; axi-cel = axicabtagene ciloleucel; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Figure 2: OS for SOC and Axi-Cel in CADTH Reanalyses A and B



Axi-cel; axicabtagene ciloleucel; OS = overall survival; SOC = standard of care.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 12: Disaggregated Summary of CADTH's Reanalysis A

Parameter	Axi-cel	SOC	Incremental
Discounted LYs			
Total	**10.53**	**9.42**	**1.12**
Pre-progression	7.03	1.37	5.66
Post-progression	3.51	8.05	−4.54
Discounted QALYs			
Total	**7.90**	**6.96**	**0.94**
Pre-progression	5.37	1.09	4.28
Post-progression	2.56	5.87	−3.31
AE Disutility	−0.03	0.00	−0.03

Parameter	Axi-cel	SOC	Incremental
Discounted costs ($)			
Total	**$621,332**	**$116,102**	**$505,230**
Pre-progression	$544,162	$37,950	$506,212
Drug costs	$487,347	$28,765	$458,581
Administration costs	$41,872	$6,308	$35,564
HCRU costs	$14,944	$1,998	$12,946
AE costs	$0	$879	−$879
Post-progression	$19,237	$19,079	$158
Drug costs	$13,176	$6,731	$6,445
Administration costs	$1,062	$875	$187
HCRU costs	$4,999	$11,473	−$6,473
Terminal care	$57,932	$59,073	−$1,141
ICER ($/QALY)	**$539,497**		

AE = adverse event; axi-cel = axicabtagene ciloleucel; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care.

Table 13: Disaggregated Summary of CADTH's Reanalysis B

Parameter	Axi-cel	SOC	Incremental
Discounted LYs			
Total	**12.19**	**9.42**	**2.77**
Pre-progression	7.08	1.37	5.71
Post-progression	5.11	8.05	−2.94
Discounted QALYs			
Total	**9.11**	**6.96**	**2.14**
Pre-progression	5.41	1.09	4.31
Post-progression	3.73	5.87	−2.14
AE Disutility	−0.03	0.00	−0.03
Discounted costs ($)			
Total	**$622,022**	**$116,102**	**$505,920**
Pre-progression	$544,274	$37,950	$506,323
Drug costs	$487,347	$28,765	$458,581
Administration costs	$41,872	$6,308	$35,564
HCRU costs	$15,055	$1,998	$13,057
AE costs	$0	$879	−$879
Post-progression	$21,513	$19,079	$2,434

Parameter	Axi-cel	SOC	Incremental
Drug costs	$13,164	$6,731	$6,433
Administration costs	$1,061	$875	$186
HCRU costs	$7,287	$11,473	−$4,185
Terminal care	$56,236	$59,073	−$2,837
ICER ($/QALY)	**$236,359**		

AE = adverse event; axi-cel = axicabtagene ciloleucel; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care.

Scenario Analyses

Table 14: Scenario Analysis Conducted on CADTH Reanalyses A and B

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH reanalysis A: Exponential OS for axi-cel	SOC	$116,105	6.97	Reference
	Axi-cel	$621,329	7.90	$544,875
CADTH reanalysis A, scenario 1: Progressed disease utility	SOC	$116,105	7.03	Reference
	Axi-cel	$621,329	7.92	$564,126
CADTH reanalysis B: Log-normal OS for axi-cel	SOC	$116,105	6.97	Reference
	Axi-cel	$621,991	9.05	$243,879
CADTH reanalysis B, scenario 1: Progressed disease utility	SOC	$116,105	7.03	Reference
	Axi-cel	$621,991	9.08	$246,379

Axi-cel = axicabtagene ciloleucel; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life-year.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 15: Summary of Key Take-Aways

Key take-aways of the BIA
• CADTH identified the following limitations in the sponsor's base case: the projected market share of axi-cel is underestimated, the proportion of patients who receive second-line therapy is underestimated, the proportion of patients who receive active therapy in third-line therapy is underestimated, and CAR T-cell pretreatment costs are underestimated. • CADTH conducted reanalyses of the BIA by adjusting the projected share of axi-cel and increasing the proportion of patients with FL who would relapse and continue with treatment in second-line. • Based on the CADTH base case, the estimated budget impact associated with the reimbursement of axi-cel for the treatment of r/r grade 1, 2, or 3a FL after ≥ 2 lines of systemic therapy is expected to be $36,353,386 in year 1, $74,624,909 in year 2, and $99,608,235 in year 3, with a 3-year total of $210,586,531, under the drug plan perspective. When considering a health care system perspective, the CADTH base case estimated a budgetary impact of $38,924,621 in year 1, $79,905,269 in year 2, and $106,624,743 in year 3, for a 3-year cumulative total of $225,454,632. • Under the drug plan perspective, a scenario analysis based on the assumption that 80% of patients with r/r FL would receive active therapy in third line resulted in an increase of axi-cel's estimated 3-year budget impact to $280,782,041. This indicates that the budget impact is highly sensitive to the estimation of the patient population that is likely to seek treatment. • Under a health care system perspective, a scenario analysis that applied CAR T-cell therapy eligibility assessment costs uniformly across all patients starting treatment in third line resulted in an increase of axi-cel's estimated 3-year budget impact to $232,487,999.

Summary of Sponsor's BIA

The sponsor submitted a BIA to estimate the incremental 3-year budget impact of reimbursing axi-cel for the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy, as per its Health Canada indication. The analysis was performed from the perspective of the Canadian public drug plan formulary, with a scenario analysis based on the health care system perspective. The sponsor estimated the budget impact by comparing 2 scenarios: a reference scenario that estimated the total costs associated with SOC for the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy; and a new drug scenario, where axi-cel is funded in the third-line setting. SOC was composed of 50% chemoimmunotherapy (i.e., BR, CHOP, CVP, GB, GDP, and R-CVP); 12% SCT; 5% phosphoinositide 3-kinase inhibitors (i.e., idelalisib); and 33% investigational therapies offered though clinical trials. The sponsor estimated the eligible population using an epidemiology-based approach, leveraging data from multiple sources in the scientific literature[39-41] and assumptions based on clinical expert input. Under the drug plan perspective, the sponsor included drug acquisition costs, as well as costs associated with pretreatment pertaining to CAR T-cell therapy (i.e., bridging and lymphodepleting therapies). In addition, the sponsor included drug administration costs (i.e., leukapheresis, hospitalization, chair time) and resource use costs in a scenario that assessed the broader budgetary impact of funding axi-cel on the health care system. The dosing modelled for axi-cel reflected the product monograph. Key inputs to the BIA are documented in Table 15.

Table 16: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate)
Target population	
At-risk population[a]	30,410,851
Incidence of FL[39-41]	0.00721%
Patients with r/r FL in third line[b]	30.95%
Population of interest (intention-to-treat)	100%
Patients receiving active therapy[b]	60%
Number of patients eligible for axi-cel	423 / 440 / 457
Market uptake (3 years)	
Uptake (reference scenario) SOC	 100% / 100% / 100%
Uptake (new drug scenario) Axi-cel SOC	 [redacted] [redacted]
Cost of treatment (per patient)	
Axi-cel (one-time) Acquisition Leukapheresis[c] Bridging therapy (weighted) Conditioning chemotherapy (weighted)	 $485,021 $2,688 $25 $2,300
SOC Chemotherapy (weighted) auto-SCT (weighted) Allo-SCT (weighted) Idelalisib (weighted) Clinical trial (weighted)	 $15,650 $4,226 $5,520 $3,370 $0

allo-SCT = allogeneic stem cell transplant; auto-SCT = autologous stem cell transplant; axi-cel = axicabtagene ciloleucel; FL = follicular lymphoma; SOC = standard of care.

[a]The at-risk population represents the pan-Canadian population and excludes Quebec, Northwest Territories, Yukon, and Nunavut.

[b]Assumption based on clinical expert opinion.

[c]Leukapheresis is included in a scenario analysis under the broader health care system perspective.

Key assumptions made by the sponsor include:

- 31% of patients with FL would relapse in second line and receive treatment in third line.
- 60% of patients with r/r grade 1, 2, or 3a FL would receive active therapy after 2 or more lines of systemic therapy.
- 33% of patients in the eligible population would seek treatment through clinical trials for investigational therapies in third line (at no additional cost to drug plans).

- Treatment regimens and the proportion of patients receiving each phase of treatment before axi-cel infusion (i.e., leukapheresis, bridging chemotherapy, conditioning chemotherapy) were based on the ZUMA-5[22] clinical trial and assumed reflective of Canadian clinical practice.
- Lymphodepleting chemotherapy regimens received by patients before CAR T-cell therapy infusion were based on the ZUMA-5[22] trial protocol and assumed reflective of Canadian clinical practice.

Summary of the Sponsor's BIA Results

Results of the sponsor's base-case BIA suggest that the incremental expenditures associated with the reimbursement of axi-cel for the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy would be $10,507,766 in year 1, $21,577,008 in year 2, and $28,629,038 in year 3, for a 3-year cumulative total of $60,713,811, under the drug plan perspective. When considering a broader health care system perspective, the sponsor's base case estimated a budgetary impact of $11,251,024 in year 1, $23,103,865 in year 2, and $30,645,989 in year 3, for a 3-year cumulative total of $65,000,877.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA.

- **Projected market share of axi-cel is underestimated:** The sponsor assumed that axi-cel would have a market share of [redacted] in years 1, 2, and 3, respectively. Clinical expert feedback emphasized that the sponsor's market share projections were substantially lower than they would anticipate in practice if a therapy like axi-cel were to be funded in the third line. This aligned with the feedback received from registered clinician groups in Canada who noted that axi-cel was expected to shift the current treatment paradigm by replacing chemoimmunotherapy as a new preferred treatment for patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. Clinical experts indicated that given the expectation of a potential paradigm shift, the future market uptake for axi-cel is likely to be twice that assumed by the sponsor.
    - CADTH conducted a reanalysis by adjusting the projected market share of axi-cel to 10.3%, 20.3%, and 26.2% in Years 1, 2, and 3, respectively, based on feedback sought from clinical experts.
- **Proportion of patients who receive second-line therapy is underestimated:** The sponsor assumed that 31% of patients with FL would relapse and continue with subsequent treatment in the second-line setting. Clinical expert feedback highlighted that there is uncertainty associated with this estimate and that it may be substantively higher in real-world clinical practice. Clinical experts indicated that, in Canada, the majority of patients with FL are likely to relapse and continue with subsequent therapy.
    - CADTH conducted a reanalysis by assuming that 55% of patients with FL would relapse and continue with subsequent treatment in the second-line setting based on feedback sought from clinical experts.

- **Proportion of patients who receive active therapy in third line is underestimated.** The sponsor assumed that 60% of patients with r/r FL would receive active therapy in third line. Clinical expert feedback highlighted that there is uncertainty associated with this estimate and that it may be substantively higher in real-world clinical practice. CADTH notes that a recent Canadian real-world population-based study of a cancer registry estimated the median age of patients with incident FL to be 64 years in women and 61 in men.[24] The clinical experts consulted by CADTH confirmed that given the demographic profile of the average patient with FL that relapses or is refractory to second-line therapy in Canada, it is reasonable to assume that a higher proportion of eligible patients would decide to continue treatment in third line.
    - CADTH conducted a scenario analysis by assuming that 80% of patients with r/r FL would receive active therapy in the third-line setting based on feedback sought from clinical experts.
- **Exclusion of CAR T-cell therapy related costs:** The pretreatment cost of leukapheresis considered by the sponsor ($2,688) for patients receiving CAR T-cell therapy was underestimated. CADTH consulted the OCCI for apheresis costs and obtained a cost of $5,426 for stem cell apheresis (code 1.LZ.58.HX).[42] In addition, the sponsor failed to consider the upfront costs of assessment of CAR T-cell therapy eligibility, which would include costs associated with MRIs, PET scans, bone marrow transplants, lumbar punctures, and bloodwork. Should axi-cel be reimbursed, this assessment cost would be incurred by all adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy (regardless of whether they would go on to receive CAR T-cell therapy).
    - CADTH conducted a scenario analysis undertaken from the health care system perspective that included updated costs associated with leukapheresis.
    - As CAR T-cell therapy eligibility assessment costs are non-negligible and would be applied uniformly across all patients starting treatment in the third-line setting, CADTH included them in a scenario analysis undertaken from the health care system perspective.

CADTH Reanalyses of the BIA

CADTH conducted reanalyses of the BIA by adjusting the projected share of axi-cel and increasing the proportion of patients with FL who would relapse and continue with treatment in second line, in line with clinical expert advice.

The results of the CADTH step-wise reanalysis are presented in summary format in Table 18 and a more detailed breakdown is presented in Table 19. Based on the CADTH base case, the estimated budget impact associated with the reimbursement of axi-cel for the treatment of r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy is expected to be $36,353,386 in year 1, $74,624,909 in year 2, and $99,608,235 in year 3, with a 3-year total of $210,586,531.

Table 17: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None.	—	—
Changes to derive the CADTH base case		
1. Projected market share of axi-cel	Year 1: [redacted] Year 2: [redacted] Year 3: [redacted]	Year 1: 10.3% Year 2: 20.3% Year 3: 26.2%
2. Proportion of patients with FL who would relapse and continue with treatment in 2L	31%	55%
CADTH base case	Reanalyses 1 + 2	

2L = second line; axi-cel = axicabtagene ciloleucel; BIA = budget impact analysis; FL = follicular lymphoma.

Table 18: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total
Submitted base case	$60,713,811
CADTH reanalysis 1	$118,502,784
CADTH reanalysis 2	$107,892,072
CADTH base case	$210,586,531

BIA = budget impact analysis.

CADTH conducted the following additional scenario analyses to address remaining uncertainty, using the CADTH base case. Results are provided in Table 19.

1. Assuming that 80% of patients with r/r FL would receive active therapy in the third-line setting.
2. Exploring the budget impact associated with the reimbursement of axi-cel from a broader health care system perspective.
3. Revising the cost associated with leukapheresis within a scenario analysis undertaken from a health care system perspective.
4. Applying CAR T-cell therapy eligibility assessment costs uniformly across all patients starting treatment in third line within a scenario analysis undertaken from a health care system perspective.
5. Assuming 31% of patients with FL would relapse and continue with 2L treatment (the sponsor's original assumption).

Table 19: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	$11,712,343	$12,573,023	$13,483,021	$14,008,858	$40,064,902
	New drug	$11,712,343	$23,080,789	$35,060,028	$42,637,896	$100,778,713
	Budget impact	$0	$10,507,766	$21,577,008	$28,629,038	$60,713,811
CADTH base case	Reference	$20,813,534	$22,343,013	$23,960,134	$24,894,579	$71,197,726
	New drug	$20,813,534	$58,696,399	$98,585,043	$124,502,814	$281,784,256
	Budget impact	$0	$36,353,386	$74,624,909	$99,608,235	$210,586,531
CADTH scenario analysis 1: Assuming 80% of patients receive active therapy in 3L	Reference	$27,751,379	$29,790,684	$31,946,845	$33,192,772	$94,930,301
	New drug	$27,751,379	$78,261,865	$131,446,724	$166,003,752	$375,712,341
	Budget impact	$0	$48,471,181	$99,499,879	$132,810,980	$280,782,041
CADTH scenario analysis 2: Health care system perspective[a]	Reference	$25,012,715	$27,148,712	$29,756,795	$31,597,782	$88,503,289
	New drug	$25,012,715	$66,073,333	$109,662,063	$138,222,525	$313,957,921
	Budget impact	$0	$38,924,621	$79,905,269	$106,624,743	$225,454,632
CADTH scenario analysis 3: Revision of leukapheresis cost (health care perspective)	Reference	$25,012,715	$27,148,712	$29,756,795	$31,597,782	$88,503,289
	New drug	$25,012,715	$66,289,618	$110,105,609	$138,812,845	$315,208,072
	Budget impact	$0	$39,140,906	$80,348,814	$107,215,063	$226,704,783
CADTH scenario analysis 4: Inclusion of CAR T-cell therapy eligibility cost (health care perspective)	Reference	$25,012,715	$27,148,712	$29,756,795	$31,597,782	$88,503,289
	New drug	$25,012,715	$68,328,686	$112,005,375	$140,657,227	$320,991,288
	Budget impact	$0	$41,179,974	$82,248,581	$109,059,444	$232,487,999
CADTH scenario analysis 5: 31% of patients relapse	Reference	$11,712,343	$12,573,023	$13,483,021	$14,008,858	$40,064,902
	New drug	$11,712,343	$33,030,064	$55,476,492	$70,061,129	$158,567,686
	Budget impact	$0	$20,457,042	$41,993,472	$56,052,271	$118,502,784
CADTH scenario analysis 6: 95% price reduction	Reference	$20,813,534	$22,343,013	$23,960,134	$24,894,579	$71,197,726
	New drug	$20,813,534	$22,485,789	$24,326,282	$25,670,907	$72,482,978
	Budget impact	$0	$142,776	$366,148	$776,328	$1,285,253
CADTH scenario analysis 7: 82% price reduction	Reference	$20,813,534	$22,343,013	$23,960,134	$24,894,579	$71,197,726
	New drug	$20,813,534	$27,198,916	$33,991,708	$38,534,743	$99,725,367
	Budget impact	$0	$4,855,903	$10,031,574	$13,640,164	$28,527,641

3L = third line; BIA = budget impact analysis; CAR = chimeric antigen receptor.

[a]Health care perspective includes drug administration costs in third line (e.g., hospitalization, chair time, leukapheresis), adverse event costs, and resource use costs.

Ethics Review

Abbreviations

ALL	acute lymphoblastic leukemia
CAR	chimeric antigen receptor
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
ECOG PS	Eastern Cooperative Oncology Group performance status
FL	follicular lymphoma
ICU	intensive care unit
ICANS	immune effector cell-associated neurotoxicity syndrome
MCL	mantle cell lymphoma
MM	multiple myeloma
r/r	relapsed or refractory
SCT	stem cell transplant
SOC	standard of care

Supplementary Ethical Considerations: Axicabtagene Ciloleucel for Follicular Lymphoma

Ethical considerations relevant to all chimeric antigen receptor (CAR) T-cell therapies in the treatment of hematological cancers are described in the *Summary Report: Ethical Considerations in the Use of CAR T-Cell Therapies for Hematological Cancers*. Ethical considerations specific to the use of axicabtagene ciloleucel (Yescarta) for the treatment of adult patients with relapsed or refractory (r/r) grade 1, 2, or 3a follicular lymphoma (FL) after 2 or more lines of systemic therapy have also been identified from a review of patient and clinician group and drug program input, as well as consultation with clinical experts engaged by CADTH for this review and CADTH clinical and economic reviewers:

- **Patient experiences and treatment options for FL:** As described in detail in the CADTH Clinical Review report, FL is a subtype of non-Hodgkin, B-cell lymphoma that presents as an indolent (or slow-growing) cancer. As a result, many patients with FL are asymptomatic and may not require intervention beyond surveillance for many years following diagnosis. However, most patients with FL will eventually develop increasingly resistant or refractory disease characterized by recurrent disease progressions, shorter remission periods, and decreased survival. Patients with r/r FL have limited third-line therapeutic options, especially if they are ineligible for stem cell transplant (SCT), and have a need for therapies with fewer toxicities and more durable response. Patients who become chemoimmunotherapy refractory have no remaining standard of care (SOC) therapeutic options available and thus have an unmet need for treatment that can delay disease progression and maintain or improve quality of life.
- **Clinical decision-making for r/r FL:** Clinical experts consulted by CADTH during this Reimbursement Review noted that, owing to the heterogeneity of FL and availability of other third-line therapies, the decision to recommend axicabtagene ciloleucel for the treatment of FL would include taking into account all available third-line therapeutic options, including other CAR T-cell therapies, as well as a patient's individual presentation of the disease and circumstances. They noted that, as a disease, FL presents heterogeneously with respect to symptoms and severity of disease, which creates challenges for clinicians tasked with determining the best therapeutic course of action. For example, while many patients present with indolent FL or have long remission periods between treatments, others may present with a more aggressive form of the disease requiring immediate therapeutic intervention or becoming chemotherapy refractory. Shared decision-making may be part of this process, given the range of therapies available and individualized risk-benefit decisions.
- **Evidentiary uncertainties related to axicabtagene ciloleucel for FL:** The safety and efficacy of axicabtagene ciloleucel in the treatment of adult patients with r/r FL after 2 or more lines of systemic therapy was evaluated in the pivotal phase II, open-label, single-arm ZUMA-5 trial. As noted in the CADTH Clinical Review report, treatment with axicabtagene ciloleucel is associated with clinically important tumour responses, including complete remission, but the ZUMA-5 trial did not yield long-term safety and efficacy data or comparative effectiveness data. The sponsor submitted a comparison of ZUMA-5 trial results to SOC from the retrospective, observational SCHOLAR-5

external control. However, the CADTH clinical assessment identified methodological limitations with the comparison of the ZUMA-5 study to the SCHOLAR-5 study (including small sample sizes, heterogeneity across study designs and populations, and the inability to adjust for all potential effect modifiers and prognostic variables), which limited the ability to interpret the magnitude of the relative treatment effects observed between axicabtagene ciloleucel and SOC in Canada. Clinical experts noted the need for long-term safety and efficacy outcomes and comparative effectiveness data with other CAR T-cell therapies, emerging therapeutic options, or SOC collected from a phase III trial to address this evidentiary uncertainty and inform clinical and health systems decision-making with respect to axicabtagene ciloleucel in Canada. They emphasized the importance of having comparative effectiveness data, as well as information on feasibility and costs, given the availability of alternative treatments for FL, and the fact that CAR T-cell therapy is very costly, resource intensive, and administratively burdensome, presenting significant opportunity costs for publicly funded oncology and nononcology drug budgets and health systems. Moreover, the clinical experts noted the value of having a robust analysis of real-world evidence to understand which patients might benefit the most from axicabtagene ciloleucel treatment in practice, given the heterogeneity of FL and associated limitations of relying on a mean or median result to inform therapeutic decisions for patients with FL. In addition, and as discussed in the CADTH Economic Report for this review, the clinical experts also noted that there is currently insufficient long-term evidence to support the sponsor's assumed 40% cure rate at 5 years following treatment with axicabtagene ciloleucel, and thus it is premature to determine whether axicabtagene ciloleucel was curative for FL, including due to the indolent and heterogeneous nature of the disease.

- **Implications of capacity constraints and outpatient delivery for the use of CAR T-cell therapies for FL:** Clinical experts emphasized that offering CAR T-cell therapies for FL would require increasing delivery capacity in Canada, given the resource-, personnel-, and infrastructure-intensive nature of these therapies. The ethical, equity, and access challenges arising from existing limitations in manufacturing and delivery capacity for CAR T-cell therapy are detailed further in the Summary Report that follows. Where delivery constraints exist, clinical experts noted that CAR T-cell therapy would likely be prioritized for the treatment of patients with other, more aggressive hematological cancers, rather than patients with FL. Moreover, clinical experts noted that some centres were shifting to outpatient delivery of therapies, unless patients were deemed to be at high risk of serious adverse events (e.g., cytokine release syndrome [CRS] or immune effector cell-associated neurotoxicity syndrome [ICANS]), to expand treatment capacity. However, they discussed how capacity constraints and the resulting shift to outpatient delivery could have implications for choice of CAR-T product for FL, since clinicians may prioritize using a product based on its safety profile to minimize the risk of hospital admission (e.g., selecting a product with a lower risk of neurotoxicity) rather than primarily its efficacy.
- **Jurisdictional inequities:** Clinical experts also noted that variability in funding for FL treatment, and oncological drugs more broadly, across Canadian jurisdictions could result in inequities in access to axicabtagene ciloleucel, were it reimbursed in a piecemeal manner across Canada. The Summary Report that follows discusses additional inequities and barriers to accessing CAR T-cell therapies

that patients may face due to their geographic location, socioeconomic status, race or ethnicity, or physician referral patterns, even when a therapy is reimbursed, because CAR T-cell therapies are administered through a limited number of tertiary treatment centres in Canada.

Summary Report: Ethical Considerations in the Use of CAR T-Cell Therapies for Hematological Cancers

Summary

- Normative and empirical literature on CAR T-cell therapies, as well as past CADTH ethics reports of CAR T-cell therapies for hematological cancers, were reviewed to summarize the ethical considerations associated with the use of CAR T-cell therapies for the treatment of hematological cancers.
- Ethical considerations arising in the context of hematological cancers include the unmet need for durable, life-prolonging treatment for patients with r/r disease, as well as disparities in the incidence, diagnosis, treatment, and outcomes in hematological cancers, especially the way these affect patients from racialized, marginalized, and low socioeconomic groups, and those residing in rural areas.
- Ethical considerations arising in the evidence used to evaluate CAR T-cell therapies indicate limitations in the representativeness of clinical trial populations, the absence of long-term safety and efficacy data, and the absence of comparative effectiveness data. Uncertainty about the magnitude of clinical benefit presents challenges for the pharmacoeconomic assessment of CAR T-cell therapies and the assessment of opportunity costs, and may expose payers to greater financial risks. Budget forecasting may underestimate the overall budget impact of reimbursing CAR T-cell therapies if they are implemented fairly and as needed.
- Ethical considerations arise with respect to the potential benefits and harms related to the use and delivery of CAR T-cell therapies. Several access considerations arise in the context of CAR T-cell therapies in Canada, including those related to geographical access, especially as they may disproportionately impact racialized, marginalized, and low socioeconomic groups and those lacking caregiver support, as well as inequities that may arise during referral or treatment. Considerations related to privacy and culturally sensitive practices also arise in the context of cell and tissue ownership, as do considerations related to informed consent, shared decision-making, and balanced communication related to CAR T-cell therapies.
- Ethical considerations for health systems include challenges associated with the capacity to manufacture and deliver CAR T-cell therapy and scale CAR T-cell centres across Canada due to the complex infrastructure and personnel requirements. Fair priority-setting criteria are required if demand for therapy exceeds manufacturing or delivery capacity. The reimbursement of high-cost, resource-intensive therapies such as CAR T-cell therapies presents opportunity costs for health systems within and beyond the hematological-oncological cancer space. Resources for health

information infrastructure may be required to support post-market surveillance, the collection of real-world evidence, and the implementation of alternative pricing or financing models.

Objectives

This report summarizes the ethical considerations common to the use of CAR T-cell therapies for the treatment of children and adults with hematological cancers in Canada, as identified in the normative and empirical literature on CAR T-cell therapies and informed by previous CADTH ethics reports of CAR T-cell therapies for hematological cancers. These reports addressed ethical considerations related to CAR T-cell therapies in the context of acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), FL, mantle cell lymphoma (MCL), and multiple myeloma (MM).[1-8] Past CADTH reports drew upon published literature, consultation with clinical experts, consideration of input from patient groups, clinician groups, and drug programs, and collaboration with clinical and pharmacoeconomic review teams at CADTH. Domains of interest in this Summary Report include ethical considerations related to the therapeutic context of hematological cancers, the evidentiary basis and use of CAR T-cell therapies, and health systems. In the context of this report, any reference to CAR T-cell therapy refers to CAR T-cell therapies used to treat hematological cancers.

Key Ethical Considerations

Therapeutic Context: Hematological Cancers

Patient and caregiver experiences, as well as diagnostic and treatment pathways, vary across the different hematological cancers for which CAR T-cell therapies are available or are under development (e.g., ALL, DLBCL, FL, MCL, and MM). Nonetheless, common ethical considerations are reported across indications, including those related to the high unmet needs of the patient population and equity issues related to disparities in diagnosis, treatment, and outcomes of these cancers. Presently, CAR T-cell therapies are reimbursed, or are under consideration for reimbursement, as second-line, third-line, and fourth-line therapies for patients with r/r disease, for whom there are few or no available alternative treatments or for whom alternative treatments have failed. As a result, patients eligible for CAR T-cell therapy are usually characterized as having a high unmet need for durable, life-prolonging therapy.

Published literature, which is largely reported from the US, indicates that there are disparities in diagnosis, treatment, and outcomes across hematological cancers, especially for racialized, marginalized, and low socioeconomic groups and those residing in rural areas or far from tertiary care centres, and sometimes across age groups.[1,2,5-8] Published literature concerning the distribution, incidence, treatment, and outcomes of hematological cancers in Canada is more limited, in part due to gaps in the collection of age-, sex-, and race-related demographic data in Canadian health information databases.[9,10] This may limit a contextualized understanding of cancer-related disparities observed in Canada and its subnational jurisdictions.[1]

The clinical experts consulted during previous CADTH reimbursement reviews indicated that geography (residence in rural areas and/or far from tertiary centres) and socioeconomic status could impact the distribution of diagnosis, treatment, and outcomes for hematological cancers in Canada.[1,2] They noted that disparities are more likely to be observed in access to primary care before diagnosis than once a patient is

actively followed in the cancer care system. However, even in cancer care, requirements to travel and leave one's support system and costs associated with travel, time off work, or childcare, as well as inconsistent funding and support across Canadian jurisdictions, can differentially impact patients' and caregivers' decision-making about treatment and care, including for CAR T-cell therapies, as will be discussed later. Disparities in outcomes between age groups have also been reported in Canada, as adults older than 70 years may have fewer therapeutic options if they are considered ineligible for common second-line or third-line treatments for hematological cancers, including allogenic SCT and autologous SCT.[2]

Evidence and Evaluation of CAR T-Cell Therapies

Ethical Considerations in Clinical Trial Data

During reimbursement review, CAR T-cell therapies have usually been evaluated with phase I/II or II, single-arm, open-label trials that offer only limited certainty about short-term therapeutic safety and efficacy and lack head-to-head comparative effectiveness and long-term safety, efficacy, and survival data.[1-8] Uncertainty about the magnitude and duration of clinical benefit presents challenges for the assessment of clinical benefits and harms.[11] Clinical experts consulted during previous CADTH reimbursement reviews of CAR T-cell therapies noted that the risks associated with evidentiary uncertainty for particular therapies are partially mitigated by the growing body of evidence on CAR T-cell therapies as a therapeutic class, which facilitates earlier identification and response to adverse events.[1,2] Evidence-generating measures, such as active post-market surveillance, are required to better understand the risk-benefit profile and cost-effectiveness of CAR T-cell therapies in practice,[12] and to inform the clinical and policy decision-making that serves the interests of patients and the public.[11,13,14]

The extent to which participants in CAR T-cell therapy trials are representative of patients in clinical practice in Canada varies. CAR T-cell therapy trials have generally tended to exclude patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) greater than 1, which may not be reflective of clinical practice.[1,2,6] Further, trials tend to include patients with a median age lower than that observed in practice, which may present challenges for the applicability of results to patients who are older and exclude patients with HIV or hepatitis B.[1,6] CAR T-cell therapy trials also tend to include disproportionately higher rates of patients who are white than from other racial or ethnic groups, irrespective of disease incidence within the patient population.[1,2,6] Indeed, racial and socioeconomic disparities in access to, and inclusion in, clinical trials have been reported in clinical trials for CAR T-cell therapies in the US (where most CAR T-cell trials are conducted).[15,16] For example, participants who are African American or Black were underrepresented in clinical trials of 5 CAR T-cell products across 7 indications for hematological cancers, and are often underrepresented in clinical trials for cancer therapies across hematological indications more generally.[1,6-8,15] This may potentially exacerbate existing health disparities observed in these populations[15] and lead to a limited understanding of, and hinder efforts to eliminate, the racial and ethnic disparities observed in disease outcomes for these populations.[17]

The underrepresentation of racial, ethnic, and other marginalized groups, as well as women, in clinical trials has been identified as a common issue in clinical trials more generally. Underrepresentation in trial participation is ethically concerning, as diverse clinical trial participation contributes to building trust

in medical research and institutions (which can impact a patient's willingness to pursue treatment), promotes fairness for potential participants and their communities, and produces higher quality biomedical knowledge.[18] Clinical experts consulted by CADTH in a previous reimbursement review were uncertain about the clinical implications of the underrepresentation of racial or ethnic groups in CAR T-cell trials.[1] However, demographically representative clinical trial data for CAR T-cell therapies may help to determine whether therapeutic efficacy varies between subgroups and whether nontherapeutic factors (such as caregiver support or socioeconomic status) have an impact on effectiveness and clinical outcomes in the real world.[1,19] Greater support is required to facilitate equitable access to clinical trial participation and to CAR T-cell treatment centres,[15,18] and it is important to consider how trial participant selection may privilege certain groups and disadvantage others where demand for CAR T-cell therapy and trial participation exceed supply.[11,20]

Ethical Considerations in Economic Models

The lack of long-term safety, efficacy, and survival data, as well as head-to-head comparative effectiveness data, at the time of a reimbursement review has implications for the pharmacoeconomic assessment of CAR T-cell therapies, as it limits the ability to accurately model and assess cost-effectiveness.[1,21,22] Uncertainty about pharmacoeconomic assessments, which are used to support the ethical principles of stewardship and public accountability in resource allocation,[3] has implications for resource allocation at a health systems level, because it hinders assessments of opportunity costs (or forgone benefits) associated with the reimbursement and resourcing of CAR T-cell therapies over other resources.[1,6,23] Data collection for long-term safety, efficacy, and comparative effectiveness may support more the robust pharmacoeconomic assessments used to inform reimbursement recommendations and decisions.[23]

Concerns about evidentiary limitations in pharmacoeconomic assessments and health-system sustainability have prompted consideration of alternative pricing and reimbursement models (e.g., value-based agreements, outcome-based pricing) as potential risk-sharing mechanisms that could possibly help mitigate the risks that payers face when reimbursing high-cost therapies, including CAR T-cell therapies, based on uncertain clinical and pharmacoeconomic evidence.[6,23-28] Although not currently used in Canada for the reimbursement of CAR T-cell therapies, risk-sharing payment models have been used in other jurisdictions (especially in Europe).[24] However, the way such financial arrangements are designed has ethical implications for the distribution of their potential benefits and burdens (e.g., for patients, the public, patients, payers, and manufacturers).[28] For example, the way the value of a drug is defined, such as which surrogate outcomes are selected to evaluate efficacy, impacts how financial risks are distributed between manufacturers and payers.

The budget impact of implementing a CAR T-cell therapy may be underestimated if the estimated uptake does not reflect expected demand by patients and clinicians. In the absence of challenges related to manufacturing and delivery capacity, which will be discussed later, CAR T-cell therapies that are reimbursed are expected to be widely adopted by clinicians and patients, resulting in a high expected budget impacted.[1] Higher budget impacts may present challenges for health systems with respect to the consideration of opportunity costs and fair resource allocation within and beyond the reimbursement of hematological-oncological therapies.[6]

Use of CAR T-Cell Therapies

Potential Benefits and Harms in the Use and Delivery of CAR T-Cell Therapies

CAR T-cell therapies have the potential to expand access to therapeutic options for patients without alternative options, including those who are ineligible for SCT (e.g., patients who are still sufficiently healthy to receive CAR T-cell therapy but not to undergo SCT, patients who could not find a suitable match for allogeneic SCT, and patients who exceed the age cut-offs for SCT). As a result, CAR T-cell therapies may offer equity-related advantages by expanding therapeutic options for older patients and for patients who are Black, Indigenous, and racialized, who may be underrepresented in SCT registries and thus unable to find adequate matches for allogeneic SCT in a timely manner.[2,29] CAR T-cell therapies may offer additional practical advantages over existing therapies, especially for patients residing in rural or remote regions or with mobility issues, as they require a single infusion and treatment period, and as a durable therapy, may offer the first treatment-free window for patients with some cancers (e.g., MM).[1,30,31]

Nonetheless, most CAR T-cell therapies lack long-term safety and efficacy data at the time of reimbursement review, which limits the assessment of clinical benefits and harms. In practice, the balance of potential risks and benefits associated with CAR T-cell therapy is assessed relative to available alternative therapeutic options and to a patient's condition (which, in the case of r/r cancer, may have a poor prognosis).[1,11,32,33] CAR T-cell therapies bear the risk of severe toxicities, including CRS and other adverse events. Moreover, shortages or inconsistent availability of treatments (e.g., tocilizumab) used to treat patients who develop adverse events (e.g., CRS) after CAR T-cell therapy could impact the safe administration of these therapies.[4]

Although the long-term safety of CAR T-cell therapies remains uncertain, clinical experts consulted in previous reimbursement reviews noted that the safety of CAR T-cell therapies has improved as clinicians have become more experienced at administering treatment and identifying and responding to adverse events.[1,2] This suggests that the safety of CAR T-cell therapies is context-dependent, where safety and efficacy may be impacted by the level of experience of the treating team and centre and the availability of supportive resources.[12] The collection of post-market data and real-world evidence related to the use of novel CAR T-cell therapies could contribute to a more robust understanding of the real-world safety and efficacy of CAR T-cell therapies, and the balance of risks and benefits, in diverse clinical practice settings and communities.

Equitable Access to CAR T-Cell Therapies

The safe and effective administration of CAR T-cell therapies presently requires administration in a limited number of accredited treatment centres equipped with specialized infrastructure and highly trained providers, which are currently localized in large urban centres in Canada. As a result, access to CAR T-cell therapies may be moderated by geographic and financial barriers. Patients residing far from treatment centres (including in other provinces or territories) must travel to access treatment and spend more than a month near the treatment centre for pre-infusion and post-infusion treatment and care.[1-3] The financial and psychosocial burdens resulting from geographic distance may impact patients' therapeutic decision-making (e.g., patients opting for noncurative or inferior treatments to avoid leaving their communities or spending an extended time in hospital).[1]

Disparities in access to CAR T-cell therapies have been widely reported in the US context, including across race, geography (residence), and socioeconomic status.[34,35] Geographic disparities in access to CAR T-cell therapies are especially salient in Canada, and especially for populations residing in rural and Northern communities or in provinces and territories without CAR T-cell centres, given Canada's vast geography and the limited number of established and proposed CAR T-cell centres.[1,2] In the Canadian context, race-based disparities in access should be considered, as they impact Indigenous people — especially in light of their disproportionately increased representation in rural and Northern communities — as well as other marginalized people or groups.[1,2] At the same time, CAR T-cell therapies may offer access-related advantages over, and be less burdensome than, existing treatments, as they only require a single treatment period.[1,31] Ensuring equitable access to high-quality care across Canada may also require considering what, if anything, might be owed to patients who are eligible for, but opt not to pursue, effective therapeutic options such as CAR T-cell therapy, due to geographic or other barriers.[1]

Presently in Canada, most jurisdictions provide some support for accommodation and/or food-related expenses for people who reside a certain distance from an infusion centre, whereas fewer provide support for travel costs.[1] CAR T-cell manufacturers may offer programs for financial and/or accommodation support for required travel, but often include distance-related eligibility cut-offs, which could leave gaps in coverage for some patients or provide insufficient support to cover all costs borne by patients and caregivers.[1,2,6,36] Adequate financial support for patients and caregivers may be important for facilitating equitable access to CAR T-cell therapies by mitigating cost-related barriers that are exacerbated by geography (e.g., costs associated with travel, accommodations, and lost income for patients and caregivers who reside outside of cities with CAR T-cell treatment facilities).[1,6]

Referral practices can also impact access to CAR T-cell therapies in Canada.[6,12,37,38] Not only do patients require access to primary care, to be referred for CAR T-cell therapy, physicians must be aware of available therapies and eligibility criteria, as well as the processes involved in making a referral to a treatment centre (which could be located in a different jurisdiction).[1,2] Providers less confident in their knowledge about CAR T-cell therapies may be less likely to refer,[37] and racial and ethnic disparities observed in the distribution of patients receiving CAR T-cell therapy may be, in part, explained by disparities in referral patterns in primary care rather than in treatment practices in cancer care.[38] Accordingly, it is important to have clear and equitable referral practices, educate clinicians about CAR T-cell therapies and referral processes, facilitate communication between clinicians and treatment centres, and provide systems-level supports for clinicians practising outside the large metropolitan centres where CAR T-cell centres are located.[1,2] Eligibility for CAR T-cell therapy presently requires patients to have already undergone and failed several lines of therapy, but not all patients may have had access to, or been eligible for, earlier lines of therapy for reasons outside of their or their providers' control; this may present a barrier to access to CAR T-cell therapy for a subset of patients.[1,31]

Cell Ownership

The collection and storage of patients' cells during CAR T-cell manufacturing may raise questions related to patient privacy and cell ownership, particularly when manufacturers are outside of Canadian jurisdictions.[1,6,39]

It is important to recognize that tissue and genetic materials are valued differently by different cultural groups (e.g., Indigenous groups internationally), and that informed consent processes need to clearly detail cell processing and ownership, as well as how remaining cells that are not infused will be handled or disposed of.[40] Consultation with diverse groups has been identified as essential to CAR T-cell research and implementation to ensure that cell handling and disposal practices, as well as educational and consent materials, are sensitive to the needs and values of diverse patients and communities.[6,39,40] In the Canadian context, attention should be paid to understanding Indigenous communities' values and practices with respect to cell and tissue ownership and governance (e.g., with reference to guidance such as the First Nations principles of OCAP [ownership, control, access, possession]).[41]

Considerations for Informed Consent

Processes should be in place to ensure that patients (and caregivers) are apprised of the unique risks of, and evidentiary uncertainties related to, CAR T-cell therapies to support robust and ongoing, iterative informed consent, including as patients transition between care settings.[6,42-45] Robust consent processes should recognize both the unique vulnerabilities of patients with cancer who have limited or no alternative therapeutic options, and who may be exposed to hype or the underreporting of treatment-related harms or uncertainties related to CAR T-cell therapies, as well as their autonomous decision-making capacity.[4,6,8] The term "cure" should be avoided in discussions to avoid misleading or promoting false hope for therapies for which long-term clinical effectiveness remains unknown.[46] The balance of potential risks and benefits associated with CAR T-cell therapy should be assessed in a process of shared decision-making by patients, providers, and caregivers. For CAR T-cell therapies approved for use in pediatric populations, it is important to recognize the unique vulnerability of children who are reliant on parents or caregivers for decision-making, as well as broader support. Depending on age or determined level of competency, minors may have a more active role in consent or assent to treatment, supported by age-appropriate educational materials about the potential benefits and harms of CAR T-cell therapy to facilitate family-based discussions.[43,45] Discussions related to the preservation of fertility may also be important for adolescents and young adults considering CAR T-cell therapy.[2] Studying and considering patient reported outcomes and patient experiences may better facilitate shared decision-making about the use of CAR T-cell therapies.[12] Additional resources, including the use of translators and the provision of age-appropriate and language-appropriate educational materials for patients and caregivers, may be required to support patient decision-making.[45]

Health Systems

Manufacturing and Health Systems Capacity

There are at least 2 challenges related to CAR T-cell therapy delivery in Canada: manufacturing and health systems capacity.[12] The first concerns the capacity to manufacture and supply CAR T-cell therapies, and for timely coordination between manufacturers and CAR T-cell centres for limited manufacturing slots and a multiweek preparatory and manufacturing period (e.g., stabilizing patients' conditions before apheresis, manufacturing and treatment, coordinating bridging therapy, apheresis, and the transport of cells). As each step in the complex sequence of manufacturing and delivery requirements for CAR T-cell therapy represents an opportunity for disruption or delay, it may be important to consider the development of contingency plans to ensure a stable supply.[1,47] Patients may be harmed by delays in access to therapy, because they have to be

in sufficiently stable and in good health to remain eligible for, and to be able to withstand, treatment.[1,31] The proliferation of CAR T-cell therapies also presents a growing administrative burden for centres, which must maintain resource-intensive accreditations and manage multiple protocols for the preparation and delivery of a growing number of therapies.[1] The possibility of domestic, local CAR T-cell manufacturer in hospital and research settings is currently under investigation in the CLIC-01 clinical trial in British Columbia.[48] Although still nascent, the potential use of a local CAR T-cell manufacturer in the future may expedite access to CAR T-cell therapies for patients (including eliminating the time required to transport cells to and from international manufacturing facilities) and is expected to be less costly and more cost-effective than CAR T-cell therapies produced by pharmaceutical manufacturers.[48]

The second challenge concerns the health systems capacity required to meet the therapeutic demand for CAR T-cell therapies in Canada due to the complex infrastructure and personnel requirements.[6,39] For example, implementation requires tertiary medical centres with specialized expertise; specialized training for staff; infrastructure modifications; close interactions among experienced inpatient, intensive care unit (ICU), outpatient, and emergency personnel and facilities; and the identification of and planning for patients before and after treatment. The implementation of an increasing number of CAR T-cell therapies for a growing number of indications may exacerbate existing health systems capacity challenges. Presently, there are a limited number of pediatric and adult CAR T-cell centres in Canada, which are localized in large urban centres in only some provinces. Although access in provinces and territories lacking CAR T-cell centres is managed through interjurisdictional agreements, the distribution of CAR T-cell centres in Canada could present a barrier for access to treatment for patients residing far from, or in jurisdictions without, CAR T-cell facilities. As a result, it is important to consider the allocation of CAR T-cell centres in a way that reflects regional, rural-urban, and sociodemographic equity.[6,49]

Although not currently used, outpatient delivery of CAR T-cell therapies has been suggested as a potential mechanism to address capacity limitations and expand access to a greater number of patients by circumventing limitations in inpatient capacity (e.g., health human resources, hospital beds, ICU capacity, apheresis facilities) and to reduce health systems costs.[1,49] However, outpatient delivery would increase the need for patients to have access to social supports and a reliable caregiver, because the responsibility for care would be shifted largely onto patients and caregivers and away from trained health care personnel and health systems.[1] Thus, a shift to outpatient delivery could potentially exacerbate burdens and the resulting inequities associated with accessing CAR T-cell therapies for patients and caregivers in lower socioeconomic strata and residing far from CAR T-cell centres, as is already observed in the context of SCTs.[1] Outpatient delivery would still require significant health systems resources to deliver safe follow-up care for patients presenting with severe side effects or requiring ongoing care, emphasizing the need to invest in the infrastructure required to implement CAR T-cell therapies.[6,39]

Resource Allocation in the Context of Capacity Limitations

Insufficient supply or capacity to deliver CAR T-cell therapies raises ethical questions related to distributive justice (e.g., *Who should be prioritized for access to a particular CAR-T-cell therapy, and why?*), as well as procedural justice (e.g., *Who should decide how to allocate limited resources and capacity? What constitutes*

a fair allocation process?).[1,3,20,47,50] Fair decision-making processes and priority-setting criteria are required to inform the prioritization of patients for access to CAR T-cell therapies within and across indications to facilitate the equitable allocation of limited resources in Canada.[1-8] Indeed, as multiple CAR T-cell therapies become available for single indications, criteria may also be required to determine whether to use 1 therapy over another,[31] or whether patients would be eligible (and if so, under what conditions) for re-treatment with CAR T-cell therapy. The development of pan-Canadian priority-setting criteria for prioritizing access to CAR T-cell therapies and/or pan-Canadian coordination could facilitate fair resource allocation processes, accountability in decision-making, equitable pan-Canadian access to CAR T-cell therapies, reduce decision-making burden for clinicians, and reduce inefficiencies as a result of duplicated efforts.[1,3,50] Consideration of manufacturing and health systems capacity implications may be required if CAR T-cell therapies demonstrate long-term curative potential, which could prompt the use of CAR T-cell therapy in earlier lines of treatment and, thus, for a greater number of patients.[11]

Funding, Opportunity Costs, and Data Infrastructure

The reimbursement and implementation of CAR T-cell therapies, which are highly expensive and resource intensive, raises concerns about the sustainability of the Canadian health care system[1,6,12] and stewardship, or the responsible use of health resources based on available evidence.[3] Reimbursing and implementing CAR T-cell therapies presents opportunity costs (or forgone benefits for other treatments or health care services) for fixed health care budgets in which not all services or therapies can be reimbursed, both within hematological and oncological therapies and in other therapeutic classes.[12,14,23,42,51,52] Additionally, it presents opportunity costs for health systems resources (e.g., hospital beds, ICU capacity, access to clinical specialists) due to the resource-intensive nature of CAR T-cell therapies.[1,3] As discussed previously, uncertainty in the clinical evidence and pharmacoeconomic models used to evaluate CAR T-cell therapies limits the ability to accurately assess the magnitude of benefit of CAR T-cell therapies relative to other treatments or services, and thus to inform an understanding of whether the benefits and burdens associated with funding some therapies or services but not others are distributed fairly.[23] Clear and transparent decisions about the expansion of access to CAR T-cell therapies in the context of existing systems constraints, competing health care priorities, and long-term health systems sustainability are required to support fair decision-making and sustain patient and public trust.[1,11,26,42] Although, as discussed previously, alternative pricing and reimbursement models may potentially help attenuate the risks faced by payers reimbursing therapies based on uncertain clinical and pharmacoeconomic evidence, it is still important to recognize that CAR T-cell therapies would still remain very expensive and resource intensive from a health systems perspective.[1]

From a health systems perspective, it is also important to consider the clinical and health informatics infrastructure and resources required to collect the data needed to implement novel funding models and post-market surveillance.[14,39]

Conclusion

CAR T-cell therapies are being introduced as second-line, third-line, and fourth-line therapies for the treatment of various hematological cancers (e.g., ALL, DLBCL, FL, MCL, MM). Published empirical and normative

literature, as well as past CADTH ethics reviews of CAR T-cell therapies, were reviewed to identify the ethical considerations relevant to the use of CAR T-cell therapies for the treatment of hematological cancers. Ethical considerations in the context of hematological cancers include the need for an effective, durable treatment that prolongs life, as well as existing disparities in the incidence, diagnosis, treatment, and outcomes for racialized, marginalized, and low socioeconomic groups, although more data are required to inform a greater understanding of disparities in the Canadian context. Clinical trials assessing CAR T-cell therapies may not be fully representative of the patient population in Canada (e.g., across race, age, and functional status) and lack long-term safety and efficacy data and comparative effectiveness data. The lack of long-term and comparative clinical data limits the certainty of pharmacoeconomic assessments, which poses challenges for the assessment of opportunity costs, and may expose payers to greater financial risks. The way alternate pricing or funding arrangements are designed has implications of the distribution of the potential benefits and risks associated with the reimbursement of high-cost therapies based on uncertain clinical and pharmacoeconomic evidence. Underestimates in the demand for CAR T-cell therapy can lead to underestimates in the total budget impact of reimbursing and implementing CAR T-cell therapies.

The implementation of CAR T-cell therapies to clinical practice raises several access-related considerations, given a limited delivery capacity and resulting geographic barriers to access; notably, barriers to access may disproportionately impact racialized, marginalized, and low socioeconomic groups, as well as those lacking caregiver support. The reimbursement and implementation of an increasing number of CAR T-cell therapies raises several ethical considerations for health systems, including challenges associated with scaling CAR T-cell delivery across Canada due to the complex and resource-intensive infrastructure and personnel requirements. A possible shift to outpatient delivery in the future may expand access to CAR T-cell therapies, but may also shift responsibility for care onto patients and caregivers, and may disproportionately burden patients without robust caregiver support. The development of fair, consistent criteria to prioritize access to CAR T-cell therapy would facilitate equitable access across Canada, especially if demand exceeds manufacturing or delivery capacity (e.g., the growing number of CAR T-cell therapies and use in earlier lines of therapy if CAR T-cell therapies demonstrate curative potential may exacerbate demand). Additionally, the high cost of implementing CAR T-cell therapies presents a challenge for health care budgets and raises questions about the systems-level opportunity costs (both within and beyond the oncological space) of reimbursing CAR T-cell therapies.

The absence of long-term and comparative evidence for the safety and efficacy of CAR T-cell therapies necessitates robust post-market surveillance to better understand the risk-benefit profile, as well as cost-effectiveness, of CAR T-cell therapies in practice. Moreover, where possible, post-market surveillance and the use of real-world evidence may contribute to a better understanding of how the safety and efficacy of CAR T-cell therapies in clinical practice may be impacted by nonclinical factors, and whether this has an impact on how the benefits and burdens associated with the use of this therapy are distributed fairly across diverse demographic subgroups of patients with hematological cancers in Canada.

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Stakeholder Input

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Patient Input

Lymphoma Canada

About Lymphoma Canada

Lymphoma Canada (LC) is a national Canadian registered charity whose mission it is to empower patients and the lymphoma community through education, support, advocacy, and research. Based out of Mississauga (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and work together to find a cure.

Resources are provided in both English and French. www.lymphoma.ca

Information Gathering

The data presented in this submission was collected from an online anonymous patient survey, which Lymphoma Canada created and promoted between April 21, 2022, to April 3, 2023. This survey was originally created in 2022, but promotion was halted after being notified the submission timeline would be delayed. In 2023, the link was re-promoted via e-mail to patients registered in the LC national emailing list and made available via social media outlets, including Twitter, Instagram, and Facebook accounts. The survey had a combination of multiple-choice, rating, and open-ended questions. Skipping logic was built into the survey so that respondents were asked questions only relevant to them. Open-ended responses were noted in this report verbatim, to provide a deeper understanding of patient perspectives. 143 responses were collected, three patients reported having experience with axicabtagene ciloleucel (Yescarta).

A summary of the demographics for those that completed LC's survey can be found in Tables 1 to 4. The majority of patients lived in Canada (86%), are between the age of 55 and 64 (71%), female (64%), and were diagnosed with follicular lymphoma 3-5 years ago (34%).

Table 1: Country of Respondents From Lymphoma Canada Survey

Respondents	CAN	USA	International	Skipped	Total
Patients with follicular lymphoma	78	7	6	52	91

Table 2: Age Range of Respondents From Lymphoma Canada Survey

	Age (years old)						
Respondents	35-44	45-54	55-64	65-74	75-89	Skipped	Total
Patients with follicular lymphoma	9	11	31	27	13	52	44

Table 3: Gender of Respondents From Lymphoma Canada Survey

Respondents	Gender			
	Female	Male	Skipped	Total
Patients with follicular lymphoma	58	33	52	91

Table 4: Number of Years Ago Respondents Were Diagnosed With Follicular Lymphoma, From Lymphoma Canada Survey

Respondents	Years					Skipped	Total
	<1	1-2	3-5	5-8	9-10		
Patients with follicular lymphoma	16	16	42	16	34	19	124

Disease Experience

At Diagnosis

In Lymphoma Canada's survey, patients were asked to rate a list of physical symptoms on a scale of 1 (no impact) to 5 (significant impact) regarding their quality of life at diagnosis. The most common reported symptoms rated as a three or higher were fatigue (50%), bodily aches and pain (33%), enlarged lymph nodes (33%), indigestion (32%), and bodily swelling (21%). Common psychosocial symptoms which were present for survey respondents were anxiety/worry (84%), stress diagnosis (77%), fear of progression (70%), and difficulty sleeping (48%).

A few patient quotes are included below which capture symptoms and experiences of what it's like getting diagnosed with follicular lymphoma:

> "There is the initial shock of a serious illness and then always the fear of progression of disease and it is hard to adjust to. The watch and wait approach take time to come to terms with although good medical observation helps so much."
>
> "I have a 2-year-old and the fear of not being able to care for him broke my heart. Also, the fear of not seeing him grow up was the most stressful and hurtful. But I realize now that I will, and I will not let this take me down."
>
> "I had to quit my PhD program because the stress of the diagnosis was too much. It also triggered a flare of an autoimmune disease."
>
> "I did not know anything about Lymphoma and my doctor was so stressed - she was not able to give me any hope. I wish I had known more about FL and that it is possible to live well for a long time with the diagnosis."

Current Quality of Life

Follicular lymphoma patients were also asked in this survey to rate the physical symptoms which impact their current quality of life (on a scale of 1 = no impact, to 5 = significant impact). Symptoms rated as 3 or higher included fatigue (51%), bodily aches and pains (32%), indigestion (23%), and enlarged lymph nodes

(21%). Psychosocial which continue to impact follicular patients include fear of progression/relapse (67%), anxiety/worry (67%), stress of having cancer (64%), and difficulty sleeping (39%).

Daily Activities

From a list of nine factors, lymphoma patients indicated the following factors have impacted their life (at least a 3, on a scale of 1 to 5): the ability to travel (46%), ability to spend time with family & friends (41%), ability to exercise (37%), ability to concentrate (36%), and ability to work/school/volunteer (35%). When asked to include further information about these challenges, patients left the following comments:

> "It takes time to adjust to having a serious illness that changes everything about your life. Having good medical care has helped me to adjust to my new normal but I am constantly aware that my life could change at any moment."
>
> "I have been doing follow-up appointments for the past 13 years and it seems like the health care system has trouble with chronic care. The system of follow-up appointments has been the same since the beginning, but the administrators now regularly confuse timing of scans and blood work, they didn't before.
>
> "My life is sort of in limbo, unfortunately, knowing that my lymphoma is not curable and will come back even though I've already had 2 lines of treatment. Because I look good and take care of my health, the mental impact is hard because I don't know how long I have nor when it will strike again. It's hard to plan anything in life."

Summary of the Disease Experience

- The most common physical symptoms FL patients found challenging at the time of diagnosis and on their current quality of life fatigue, bodily aches and pain, enlarged lymph nodes, indigestion, and bodily swelling. Top-rated psychosocial factors included stress of diagnosis, anxiety/worry, fear of progression, and difficulty sleeping.
- There was a wide range of experiences in which FL symptoms impacted the daily lives of survey respondents. The ability to travel, spend time with family/friends, exercise, concentrate, and to work/complete school/volunteer were reported as significant impact by patients.

Experiences With Currently Available Treatments

Based on survey responses, 49% of patients underwent a period of watchful waiting before starting treatment. Patients were also asked about the number of lines of therapy received to date to treat their follicular lymphoma, majority had 1 line of treatment (43%). Table 6 outlines the most common treatments received by follicular lymphoma patients in this survey. Most patients in first or second line received chemotherapy, chemoimmunotherapy, rituximab with or without bendamustine, or radiation.

Table 5: Number of Lines of Therapy Survey Respondents Received

Respondents	Have not received therapy	1	2	3 +	Skipped	Total
Patients with follicular lymphoma	20	42	19	16	46	97
	21%	43%	20%	16%	—	100%

Table 6: Most Common Treatments Received by Respondents From Lymphoma Canada Survey

Line of Therapy	Treatment	Number of respondents
1st	Chemotherapy or Chemoimunotherapy (R-CHOP, CVP)	31
1st	Bendamustine + Rituximab	17
1st	Rituximab	8
1st	Radiation	7
2nd	Chemotherapy or Chemoimmunotherapy	10
2nd	Rituximab	9
2nd	Bendamustine + Rituximab	7
2nd	Radiation	5

In the "follicular lymphoma treatment experience" section of LC's survey, patients were asked to rate their satisfaction with the number of treatment options available in the frontline or relapsed/refractory setting. 57% of patients indicated they were satisfied or very satisfied with treatment options available to them in the frontline setting, whereas 22% of patients were satisfied or very satisfied with their relapsed/refractory options. This suggests more treatment options are needed for those in the second or higher line of treatment.

Survey respondents were asked to rate the statement: "My current therapy (or most recent therapy) was able to manage my follicular lymphoma symptoms" on a scale of 1 (strongly disagree) to 5 (strongly agree). Most patients either strongly agreed with this statement (40%) or strongly disagreed (20%). Top factors rated by patients as having a significant negative impact (5 out of 5) included treatment-related fatigue (28%), immediate side effects of treatment (26%), and low activity level (23%). Most common side effects reported from treatment include fatigue (69%), hair loss (41%), and constipation (38%). These results highlight follicular lymphoma treatments need to be improved to manage patient symptoms.

A few patient quotes below can be used to highlight the difficult side effects patients experience and other challenges they go through during treatment:

> "When experiencing heart palpitations, fear of late or long-term side effects to heart, live with worries of fear of reoccurrence. Living with a compromised immune system. Infertility."
>
> "Doctors need to involve patients more in their treatment discussions and plans."
>
> "Seems to be a lack of knowledge here in Alberta about treatment options and emerging therapies- our oncologist wasn't even aware car- t was approved by the FDA for follicular… worries us immensely

about the treatment options being presented to us."

Summary of Currently Available Treatments

The majority of survey respondents received one line of treatment for their FL, with chemotherapy or chemoimmunotherapy as the most common treatment regimen. 40% of patients were very satisfied with their treatment options, 20% were very unsatisfied. More treatment options are needed for FL patients in the relapsed and refractory setting.

Improved Outcomes

FL patients who completed LC's survey rated the following factors as very important (5 out of 5) - allow me to live longer (84%), longer disease remission (82%), improve quality of life and perform daily activities (69%), control disease symptoms (63%), and normalize blood counts (58%). 68% of respondents indicated they would be willing to tolerate non-serve side effects over a short-term period when considering a novel therapy, and 42% of respondents indicated it is extremely important (10 out of 10) to have a choice in deciding which drug to take based on known side effects and expected outcomes. 79% of patients felt there is a need for more therapeutic options for FL, in terms of options to choose from and drugs proven to be effective that are accessible.

Several patients left comments when asked about expectations of novel treatments to manage their lymphoma:

> "With the continual investment and donations going to cancer research, I would expect treatments to be on a continuous, positive trajectory. Adding new drugs to limit or reduce symptoms and eventually cure or prolong life should and are a occurring."
>
> "Would hopefully like to see new therapies and treatment options that are less toxic and have little to no side effects either late or long term. Hopefully the research is on-going to find a cure."
>
> "Car-T should be an available first line choice if it will lengthen the time of remission for follicular lymphoma."
>
> "Number one expectation is that it will extend life and have minimal short term and long-term side effects. With Covid out there (forever) it is important to minimize risk of future or ongoing infections."
>
> "There is a lot of studies in the US with great results than we as Canadians don't have access to. I would love to try some of those!"
>
> "Everyone reacts differently to treatment, if there are options for those that have a bad reaction to one treatment then it would make life much easier for them. Options are good."
>
> "CAR-T needs to be funded."

Summary of Currently Available Treatments

- Factors important to FL patients when considering novel therapies include longer disease remission, controlled disease symptoms, longer survival, normalized blood counts and improved quality of life to include daily activities.

- Majority of patients indicated it is extremely important to them to have access and choice to a variety of treatment options. A few patients specifically commented CAR T- cell therapy should be funded and available in earlier lines of treatment.

Experience With Drug Under Review

Two FL patients completed all the Yescarta treatment questions in LC's survey. 1 patient confirmed Yescarta treatment but skipped all other treatment questions. Of the 2 responses, both patients accessed this therapy via clinical trial, one in their second line of treatment, the other as fifth line. Side effects reported include cytokine release syndrome, neutropenia, febrile neutropenia, thrombocytopenia, constipation, and swelling.

These patients rated factors such as monitoring side-effects post-inf/sion, inability to perform daily activities, and being away from family and friends as significant (4 out of 5) or very significant (5 out of 5) impact on their physical and mental health. One person was away from home for 1-3 months, the other was away from home receiving treatment for longer than 3 months. These CAR-T patients also indicated they experienced financial challenges due to absence from work, and travel or accommodation expenses during the clinical trial. Overall, both FL patients rated their experience as good and very good, and would recommend it to other patients with R/R FL.

At Lymphoma Canada, we hear from lymphoma patients consistently, that CAR T-cell therapy should be available in earlier lines of treatment. Canadian lymphoma patients should be able to receive this treatment locally and not be expected to travel far distances to receive care. Local access will significantly improve the patient experience by reducing the fear and risk of getting sick while traveling and improving quality of life by keeping patients close to their caregivers and support systems.

Companion Diagnostic Test

Not applicable.

Anything Else?

Not applicable.

Conflict of Interest Declaration — Lymphoma Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 7: Financial Disclosures for Lymphoma Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Gilead	–	–	–	X
Novartis	–	–	X	–
Bristol Myers Squibb	–	–	X	–

Clinician Input

Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

About Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering
Information was gathered via video conferencing and email.

Current Treatments and Treatment Goals
Current standard of care involves chemotherapy, chemo-immunotherapy, autologous stem cell transplant, and in selected patients allogeneic stem cell transplant. Radiation may also be used for symptom control and in very palliative scenarios. The disease course can be quite variable with some patients having very long remissions between therapies and others behaving in a more refractory manner.

Treatment goal is mostly palliative with some curative intent with alloSCT. There are some reports of very long-term remissions following autologous stem cell transplantation. Most important goals are delaying disease progression, improve health-related quality of life, and alleviate symptoms.

Kymriah is currently under review by CADTH, for the same indication. Toxicity profiles may differ for Yescarta and Kymriah.

Treatment Gaps (Unmet Needs)
Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Patients eventually becomes chemotherapy refractory and there are no treatment options afterwards. Also repeated courses of cytotoxic therapy can be associated with marrow damage (i.e., MDS) which then limits the ability to treat further and adversely affects quality of life. CART therapy would not be expected to

have long-term marrow damage issues. Although data is early, we wonder whether CART therapy might be potentially curative for some patients, compared with the currently available therapies.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

3L therapy would be an appropriate time to consider CAR T-cell therapy given the benefit of available treatment is lower **for these patients**. It is uncertain at this time whether **this CAR-T therapy** may replace autologous stem cell transplant. We suspect that CART may be tried in advance of autologous stem cell transplant in those patients who have a more chemotherapy-refractory history for their follicular lymphoma.

There will be a prevalent FL population that would be eligible for this CAR-T therapy at the time of implementation.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Most suitable patients would be as per the clinical trial population. Exclusion may include severe organ dysfunction and poor performance status, uncontrolled infections.

Despite being excluded in the pivotal study, we would like to consider CAR-T in selected patients who had received prior CD19- directed therapy or allogeneic stem cell transplant. CART therapy might be preferred to be used prior to autologous stem cell transplantation in some patients.

There should be some flexibility around ECOG or KPS status.

There is an existing CAR-T therapy network in Ontario that can handle patient referrals.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

As per standard lymphoma response criteria.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Not applicable as this is a single infusion. Some patients may become ineligible for therapy during CAR-T cell manufacturing.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Centers that have expertise in CAR T-cell therapy.

Additional Information

Not applicable.

Conflict of Interest Declarations — Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided secretariat function to the group.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1

Name: Dr. Tom Kouroukis

Position: Lead, OH-CCO Hematology Cancer Drug Advisory Committee

Date: 23-02-2023

Table 8: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 1

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 2

Name: Dr. Pierre Villeneuve

Position: Member, OH-CCO Hematology Cancer Drug Advisory Committee

Date: 29-03-2022

Table 9: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 2

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	—	—	—	—

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