



CADTH Reimbursement Recommendation

Axicabtagene ciloleucel (Yescarta)

Indication: For the treatment of adult patients with relapsed or refractory grade 1, 2, or 3a follicular lymphoma after 2 or more lines of systemic therapy.

Sponsor: Gilead Sciences Canada, Inc.

Final recommendation: Reimburse with conditions



Summary

What Is the CADTH Reimbursement Recommendation for Yescarta?

CADTH recommends that Yescarta be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Yescarta should only be covered to treat adult patients who have grade 1, 2, or 3a FL and whose disease has returned following second-line treatment or later lines of treatments.

What Are the Conditions for Reimbursement?

Yescarta should only be reimbursed for patients who have not already received a chimeric antigen receptor (CAR) T-cell therapy and are in relatively good health, and if the cost of Yescarta is reduced. Yescarta should be prescribed and administered by clinicians with expertise in blood cancers in a hospital setting with adequate resources to treat patients and manage side effects.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial suggested that treatment with Yescarta results in maintained tumour shrinkage and may improve the average length of time patients are alive after starting treatment. In addition, treatment with Yescarta may improve the length of time until the cancer grows or spreads, or until death.
- Yescarta may be an effective treatment option for patients who have received multiple unsuccessful therapies and are seeking new treatments that may prolong survival.
- Based on CADTH's assessment of the health economic evidence, Yescarta does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Yescarta is estimated to cost the public drug plans approximately \$210,586,531 over the next 3 years.

Additional Information

What Is FL?

FL is a common type of non-Hodgkin lymphoma that develops when the body makes abnormal white blood cells (WBCs). In FL, the abnormal WBCs cluster together to form lumps in lymph nodes or other tissues. FL tends to progress slowly over many years; however, patients whose FL does not



Summary

respond to treatment or whose FL returns after responding to previous treatments have a shortened life expectancy. It is estimated that 1 in 3,000 people have FL.

Unmet Needs in FL

Patients with FL whose cancer does not respond to treatment or whose cancer returns after treatment have a poor prognosis and limited treatment options. Further, not all patients benefit from the limited treatments that are available. Therefore, there is a need for additional treatments that can prolong survival, cure the disease, and improve quality of life.

How Much Does Yescarta Cost?

Treatment with Yescarta is expected to cost approximately \$485,000 per infusion.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that axicabtagene ciloleucel be reimbursed 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 only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One phase II, multicentre, single-arm, open-label trial (ZUMA-5; N = 127) demonstrated that treatment with axicabtagene ciloleucel resulted in benefits in the primary end point of response rates for adult patients with r/r FL after 2 or more lines of systemic therapy. The objective response rate (ORR) was 94% (95% confidence interval [CI], ■■■) and the complete response rate (CRR) was 79% (95% CI, ■■■). The observed response rates in the ZUMA-5 trial were deemed clinically meaningful by clinical experts compared with expected outcomes in adult patients with r/r grade 1, 2, or 3a FL. Axicabtagene ciloleucel was associated with potential benefits in survival outcomes; at the 36-month follow-up analysis, median overall survival (OS) was not reached, while the median progression-free survival (PFS) was 40.2 months (95% CI, 28.9 to not evaluable [NE]). The Kaplan-Meier (KM) survival probability at 36 months was 75.5% (95% CI, 66.9 to 82.2).

Patients identified a need for more effective treatments that extend survival and disease remission and improve quality of life. Furthermore, patients indicated that there is a need for easier access to new therapies such as chimeric antigen receptor (CAR) T-cell therapy. pERC considered that axicabtagene ciloleucel offers a subsequent therapy option for a heavily pretreated population in the form of a single treatment. Given the totality of the evidence, pERC concluded that axicabtagene ciloleucel may meet some of the needs identified by patients, since it appears to have durable responses, may prolong survival, and has a manageable toxicity profile.

The committee considered analyses conducted by CADTH, which evaluated the cost-effectiveness of axicabtagene ciloleucel relative to the current standard of care for the treatment of adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy. Given the magnitude of uncertainty surrounding OS for axicabtagene ciloleucel, its comparative efficacy against standard of care, and the durability of such a benefit, CADTH could not estimate a robust single base-case estimate of cost-effectiveness for axicabtagene ciloleucel. Using the sponsor's submitted price for axicabtagene ciloleucel and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) ranged from \$243,879 to \$544,875 per quality-adjusted life-year (QALY) gained, based on CADTH reanalyses exploring possible ranges of the extrapolated OS benefits for axicabtagene ciloleucel. In all reanalyses, a price reduction would be required for axicabtagene ciloleucel to achieve an ICER of \$50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Axicabtagene ciloleucel should be reimbursed in adult patients with relapsed or refractory grade 1, 2, or 3a FL defined as: relapsed or refractory disease after 2 or more lines of prior therapy (which must have included an anti-CD20 monoclonal antibody combined with an alkylating drug).	In the ZUMA-5 trial, treatment with axicabtagene ciloleucel demonstrated a clinical benefit in adult patients with relapsed or refractory grade 1, 2, or 3a FL with the characteristics listed in this condition.	—
2. Patients must: 2.1. have good performance status 2.2. be 18 years of age or older.	The ZUMA-5 trial enrolled patients who had an ECOG performance status of 0 or 1 and who were aged 18 years or older.	—
3. Patient must not have had any of the following: 3.1. grade 3b FL 3.2. transformed FL 3.3. prior CAR T-cell therapy 3.4. active CNS involvement 3.5. received auto-SCT within 6 weeks of planned axicabtagene ciloleucel infusion.	No evidence was identified to support a beneficial effect of axicabtagene ciloleucel when used in patients with grade 3b FL, transformed FL, prior CAR T-cell therapies, prior auto-SCT within 6 weeks of planned axicabtagene ciloleucel infusion, or active CNS involvement, as these patients were excluded from the ZUMA-5 trial.	—
Prescribing		
4. Treatment with axicabtagene ciloleucel is a 1-time therapy.	At this time, CAR T-cell therapy re-treatment has not been established as an efficacious strategy and is not considered standard of care. In the ZUMA-5 trial, re-treatment was permitted; however, there is insufficient evidence to support re-treatment.	Patients should receive a 1-time infusion with appropriate conditioning chemotherapy before axicabtagene ciloleucel infusion. In the ZUMA-5 trial, all patients were required to receive conditioning chemotherapy before axicabtagene ciloleucel infusion.
5. Axicabtagene ciloleucel should only be prescribed by clinicians with expertise in the treatment of hematological malignancies. Axicabtagene ciloleucel should be administered in specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with CAR T-cell therapy.	To ensure that axicabtagene ciloleucel is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC acknowledges that the availability of specialized centres with adequate infrastructure and resources to administer CAR T-cell therapy in Canada is a barrier that needs to be addressed.
Pricing		
6. A reduction in price.	Based on CADTH reanalyses, a price reduction of 82% to 95% would be required for axicabtagene ciloleucel to be cost-	—

Reimbursement condition	Reason	Implementation guidance
	effective at a WTP threshold of \$50,000 per QALY gained, relative to current standards of care. This range reflects uncertainty around the extrapolation of survival in the absence of long-term data. The magnitude of survival benefit is uncertain given the limitations with comparative evidence for axicabtagene ciloleucel and current standards of care. Given the degree of remaining uncertainty, it was noted that greater price reductions may be required.	
Feasibility of adoption		
7. The feasibility of adoption of axicabtagene ciloleucel must be addressed.	At the submitted price, the incremental budget impact of axicabtagene ciloleucel is expected to be greater than \$40 million in years 2 and 3.	—

CAR = chimeric antigen receptor; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HSCT = hematopoietic stem cell transplant; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; WTP = willingness-to-pay.

Discussion Points

- Since there was uncertainty associated with the single-arm study design of the ZUMA-5 trial, pERC deliberated on axicabtagene ciloleucel considering the criteria for significant unmet need described in section 9.3.1 of the [Procedures for CADTH Reimbursement Reviews](#). Considering the severity of r/r grade 1, 2, or 3a FL in adult patients, and the unmet need for effective third-line and later treatments, the committee concluded that the available evidence reasonably suggests that axicabtagene ciloleucel could substantially reduce morbidity and mortality associated with the disease.
- Due to the noncomparative study design of the ZUMA-5 trial, pERC considered a comparison of axicabtagene ciloleucel versus a retrospective standard of care cohort estimated using propensity scores with standardized mortality ratio (SMR) weights. pERC noted that while the analysis showed improvements in OS and progression-free survival (PFS) were associated with axicabtagene ciloleucel, the interpretation of the comparative efficacy estimates is limited by the potential for selection bias of patients into the ZUMA-5 clinical trial, and residual imbalances in important prognostic and effect modifying patient characteristics, despite propensity score weighting.
- pERC acknowledged that 1 of the requirements of the conditional market authorization for axicabtagene ciloleucel is to conduct a confirmatory randomized controlled trial (RCT) comparing axicabtagene ciloleucel with standard of care therapy in patients with r/r FL. The primary end point will be PFS, and secondary end points will include OS and ORR. This confirmatory RCT is currently recruiting patients, with an estimated study completion date in 2029.
- pERC agreed with the clinical experts that the response rates observed in the trial appeared compelling and clinically relevant in this heavily pretreated patient population, in a setting that

currently has no standard of care treatment options. pERC noted the durability of response, as the median duration of response was 38.6 months in the ZUMA-5 trial.

- pERC agreed with the clinical experts that the safety profile of axicabtagene ciloleucel appeared consistent with other CAR T-cell therapies, and no unexpected safety signals were observed in the ZUMA-5 trial. pERC noted that it appears that there are different rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) between different CAR T products. pERC agreed with the clinical experts that this might influence the choice of product depending on patient characteristics such as performance status and comorbidities that might predict their ability to tolerate an episode of CRS or ICANS. However, given the lack of head-to-head evidence or an indirect treatment comparison, the comparative safety profiles are unknown.
- pERC noted that uncertainties remain regarding the implementation of CAR T-cell therapy and the systems needed to optimize timely access and deliverability of axicabtagene ciloleucel in the real-world setting. Furthermore, patients identified the need for improved access to CAR T-cell therapies. Axicabtagene ciloleucel must be administered at specialized treatment centres with the infrastructure and resources required to administer the treatment and manage adverse events (AEs). However, a limited number of centres in Canada have the expertise and resources to deliver CAR T-cell therapy, and it is unlikely that qualified centres will be available in all jurisdictions. pERC considered that some patients may be unable to travel outside the province or country to receive therapy. The need for adequate financial support to facilitate equitable access and mitigate cost-related barriers to access that are exacerbated by geography was also discussed.
- Regarding ethical considerations in the treatment of FL with axicabtagene ciloleucel, pERC discussed whether there are any subpopulations of patients with FL who should be prioritized for treatment, and that consideration should be given to addressing socioeconomic and structural barriers to equitable access, including if delivery shifts to outpatient settings and places greater responsibility for care on patients and caregivers. pERC also discussed how uncertainties in the evidence for axicabtagene ciloleucel in the treatment of FL have implications for considering the stewardship of limited health budgets, as well as how postmarket surveillance and the ongoing collection of RCT data and real-world evidence could contribute to a more robust understanding of long-term safety and efficacy, and the balance of risks and benefits in diverse practice settings and communities. Finally, regarding health system considerations, pERC discussed the need for fair and equitable pan-Canadian priority-setting criteria if the demand for therapy exceeds manufacturing or delivery capacity, and the overall need for considering the sustainability of the health care system, fair resource allocation, and the potential opportunity costs within and beyond the hematological-oncological space.

Background

Non-Hodgkin lymphoma (NHL) encompasses a heterogeneous group of more than 80 closely related cancers. 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. FL, a subtype of NHL, is an indolent B-cell lymphoma

originating from the germinal centre of lymphoid tissues; characterized by slow growth and spread, it accounts for 20% to 30% of all NHL cases. The sponsor-calculated overall incidence rate of FL in Canada (based on NHL age-standardized incidence rates [25.7 per 100,000] and the proportion of FL among NHL cases [25%]) was 7.21 per 100,000. Although responsive to initial first-line 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 treatment declines upon repeated therapy. The clinical experts consulted by the sponsor reported that approximately 31% of patients with incident FL would progress to third-line therapy, of which 60% would proceed to receive active therapy. 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. Grades 1, 2, and 3a diseases are generally considered low-grade or slow-growing compared to grade 3b, which grows quickly and is considered high-grade lymphoma. Statistics reported by the Canadian Cancer Care Society highlight that patients considered “low-risk” at diagnosis, according to the Follicular Lymphoma Internal Prognostic Index (FLIPI) score, have a 91% 5-year survival rate and 71% 10-year survival rate; intermediate-risk patients have a 78% 5-year survival rate and 51% 10-year survival rate; and high-risk patients have a 53% 5-year survival rate and 36% 10-year survival rate.

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 T cells per kg of body weight with a maximum of 2×10^8 CAR-positive viable T cells, IV infusion, in the treatment of adult patients with r/r FL after 2 or more prior lines of systemic therapy.

Axicabtagene ciloleucel has been approved by Health Canada 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 is a CAR T-cell therapy, available as an IV drug. The dosage recommended in the product monograph is a target of 2×10^6 CAR-positive T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of a phase II, open-label, single-arm study in patients with r/r FL after 2 or more prior lines of systemic therapy
- patients' perspectives gathered by 1 patient group, Lymphoma Canada (LC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with FL
- input from 1 clinician group, the Ontario Health – Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to axicabtagene ciloleucel from published literature.

Stakeholder Perspectives

Patient Input

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. 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.

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. 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 expressed that FL symptoms impacted their daily lives by presenting challenges to their ability to travel (46%), affecting time spent with family or friends (41%), impacting their ability to exercise (37%), impacting their ability to concentrate (36%), and impacting their ability to 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 therapy included chemotherapy, chemoimmunotherapy, rituximab with or without bendamustine, or radiation. The most significant symptoms that negatively impacted patients following treatment 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, ability to perform daily activities (69%), control of disease symptoms (63%), and the ability to normalize blood counts (58%). More than half of the respondents indicated that they were willing to tolerate nonsevere side effects in the short term as a trade-off for a novel treatment. Two respondents that had experience with axicabtagene ciloleucel reported having access to the drug via a clinical trial. Side effects reported were CRS, neutropenia, febrile neutropenia, thrombocytopenia, constipation, and swelling. Some of the challenges the patients highlighted 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 expressed that they had a good or very good experience with axicabtagene ciloleucel and would recommend 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 need, place in therapy, patient populations most likely 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 need exists in patients with cancer that progresses within 2 years after their initial therapy, patients who have already received autogenic 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 a third or later line of treatment for patients with r/r FL. These patients usually have a treatment response lasts less than 6 months from their last treatment (medication or stem cell transplant).

The clinical panel indicated that, in practice, CAR T-cell therapy is used in a broader patient population than in clinical trials, where a more selective population would be recruited. The panel indicated that, in clinical practice, patients are evaluated and followed in a similar manner to that described in the clinical trials of FL. Remission and survival are measured, and 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, in addition to durability of treatment response and long-term PFS and OS. The panel indicated that after infusion with axicabtagene ciloleucel, patients may participate in a clinical trial. In the absence of a clinical trial, they may try a different chemoimmunotherapy that they have not been exposed to, or undergo auto-SCT if they have not already. The panel emphasized the importance of an accredited multidisciplinary team involving hematologists, infectious disease specialists, neurologists, ICU team and all other specialists to diagnose, treat, and monitor the patients who would receive axicabtagene ciloleucel, and to ensure the safe and effective delivery of this treatment.

Clinician Group Input

Input from 1 clinician group, the 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 (HRQoL), 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 group mentioned that patients who become refractory to chemotherapy have no other treatment options to delay the disease. In addition, the group 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 clinician members, is not anticipated to cause long-term marrow damage issues. The clinicians expressed that a third-line therapy with CAR T-cell therapy would be appropriate, given that current therapy provides lower benefit to patients with relapse or refractory FL disease. Patients eligible to receive axicabtagene ciloleucel in clinical practice would reflect patients included in the clinical trial, according to the experts. However, patients with severe organ dysfunction, poor performance status, and uncontrolled infections would be excluded from receiving therapy. 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 Eastern Cooperative Oncology (ECOG) performance status or Karnofsky Performance Status of patients. The group noted that some patients might become ineligible to receive CAR T-cell therapy during manufacturing, which might lead to discontinuation.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
<p>Should the following patients be considered for axicabtagene ciloleucel?</p> <ul style="list-style-type: none"> • ECOG PS > 1 • Prior CD19-targeted therapy (e.g., blinatumomab, tafasitamab) • Prior allogeneic transplant • Prior CAR T-cell therapy • Active CNS involvement • Other types of low-grade lymphoma (e.g., marginal zone lymphoma, Waldenström macroglobulinemia, MALT lymphoma) • Follicular grade 3B lymphoma 	<p>ECOG PS > 1: The clinical experts and pERC agreed that despite the ZUMA-5 trial being limited to patients with ECOG PS 0 and 1, physicians would likely use axicabtagene ciloleucel in patients with ECOG PS 2. Patients with an ECOG PS of 3 or higher would not be suitable for treatment with axicabtagene ciloleucel.</p> <p>Prior CD19-targeted therapy: The clinical experts had differing opinions. Some suggested that any prior CD19-targeted therapy would preclude the use of axicabtagene ciloleucel. Others suggested that only patients that are refractory to CD-19 targeted therapy (those who did not respond or relapsed within 6 months) would not be suitable for treatment with axicabtagene ciloleucel. pERC noted that there is no evidence to support using axicabtagene ciloleucel in patients who received prior CD-19-targeted therapy.</p> <p>Prior allogeneic transplant: The clinical experts had differing 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 GVHD. pERC agreed that prior allogeneic transplant should not preclude the use of axicabtagene ciloleucel provided there is no active GVHD.</p> <p>Prior CAR T-cell therapy: The clinical experts and pERC agreed that patients that have received prior CAR T-cell therapy should not be given axicabtagene ciloleucel.</p> <p>Active CNS involvement: The clinical experts suggested that patients with active CNS involvement should not be given axicabtagene ciloleucel. pERC noted that the prescribing decision should be at the discretion of the treating physician. As long as the CNS disease is being treated and the patient is neurologically stable, a patient should not be excluded from consideration for axicabtagene ciloleucel.</p> <p>Other types of low-grade lymphoma: The clinical experts noted that a small number of patients with marginal zone lymphoma 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. pERC noted that the other low-grade lymphomas are</p>

Implementation issues	Response
	<p>outside the scope of the reimbursement request.</p> <p>Follicular grade 3B lymphoma: The clinical experts and pERC agreed that patients with follicular grade 3B lymphoma should not be eligible for treatment with axicabtagene ciloleucel. The clinical experts noted that these patients would fall under the category of diffuse large B-cell lymphoma and treatment decisions should be made from that perspective.</p>
In the trial, single-drug rituximab is not counted as a line of therapy. In some jurisdictions, single-drug rituximab is a funded option. What is the place in therapy for axicabtagene ciloleucel in these patients?	The clinical experts and pERC agreed with the design of the ZUMA-5 trial and did not believe that single-drug rituximab should be considered as a line of therapy. Single-drug 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 move the eligibility for axicabtagene ciloleucel earlier in the disease course than is appropriate.
Is there sufficient evidence to support re-treatment?	The clinical experts and pERC 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	
<p>Delivery must take place at specialized treatment centres that are accredited and certified by the sponsor. There continues to be limited access to CAR T-cell services in Canada. While access is expanding, interprovincial travel or out-of-country funding remain necessary in many parts of Canada.</p> <p>Due to geographical site limitations, patients may need to travel for treatment requiring interprovincial agreements to ensure equitable access.</p>	Comment from the drug plans to inform pERC deliberations.
PAG noted that tisagenlecleucel is also under review for relapsed or refractory FL. Should the criteria for axicabtagene ciloleucel be aligned with that of tisagenlecleucel?	The clinical experts and pERC agreed that given the similarities between axicabtagene ciloleucel and tisagenlecleucel, the prescribing criteria should be aligned.
Generalizability	
Should patients who recently started a third-line (or later-line) systemic therapy be switched to CAR T-cell therapy, provided all other criteria are met?	The clinical experts and pERC agreed that if a patient is responding to and tolerating a third-line or later 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 there is an expectation that axicabtagene ciloleucel and tisagenlecleucel differ in regard to safety profile. Specifically with neurologic toxicity and CRS, where a patient that may not be able to tolerate axicabtagene ciloleucel would be given tisagenlecleucel instead. It is noted that no comparative evidence is available to inform this decision. pERC agreed that decisions will be at the discretion of the treating physician.
Care provision issues	
Is postprogression biopsy needed to confirm that the disease has not transformed to DLBCL or other	The clinical experts and pERC agreed that while a postprogression biopsy is preferred, it is not always feasible. As such, a postprogression

Implementation issues	Response
excluded histology before starting axicabtagene ciloleucel?	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, PAG 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 and pERC noted that, given the slow-growing nature of relapsed or refractory FL, manufacturing delays are not expected to significantly impact clinical effectiveness (as might be the case 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 = European Cooperative Oncology Group performance status; FL = follicular lymphoma; GVHD = graft versus host disease; MALT = mucosa associated lymphoid tissue; PAG = provincial advisory group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

The ZUMA-5 trial was 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 after 2 or more prior lines of systemic therapy. Between [REDACTED], 127 patients with FL were enrolled at 15 sites in the US and 2 sites in France. No study sites were 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 days 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 per kg of body weight. Analyses were conducted at 18 months, 24 months, and 36 months. The statistical analysis plan prespecified tests to be conducted on the inferential analysis set at 18 months, defined as 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 date for the 18-month analysis set was September 14, 2020, while the data cut-off date for the 36-month analysis set was March 31, 2022.

The primary end point of the ZUMA-5 trial was ORR, defined as the incidence of a complete response (CR) or a partial response (PR), as determined by central read. These end points were defined by the Lugano classification criteria. Key secondary end points determined by central read included CR rate, defined as the incidence of CR as the best response to treatment, and the ORR and CR rate in patients who had 3 or more lines of prior therapy. Other secondary end points included best overall response (BOR), defined using CR,

PR, stable disease, progressive disease, or “nonevaluable” as the best responses to treatment adjudicated by central read. Duration of response (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 axicabtagene ciloleucel infusion date for the inferential or safety analysis sets (or date of leukapheresis for the full analysis set [FAS]) to the date of disease progression or death, while OS was defined as the time from axicabtagene ciloleucel infusion date for the inferential or safety analysis set (or date of leukapheresis for the FAS) to the date of death. Time to next treatment (TTNT) was defined as the time from axicabtagene ciloleucel infusion date to the start of new lymphoma therapy or death. Patient-reported outcomes were not reported in the ZUMA-5 trial.

At the 36-month time point for analysis, the median age (range) was [REDACTED] and [REDACTED] I. Of the enrolled patients, [REDACTED] had refractory disease, 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] had received 3 prior therapies, [REDACTED] had received 4 prior therapies, and [REDACTED] had received 5 or more prior therapies). The proportion of patients that had received prior auto-SCT was [REDACTED], while the proportion of patients with high-bulk tumour was [REDACTED]. 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 [REDACTED].

Efficacy Results

Overall Survival

The proportion of patients that 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 they acknowledged that, due to the extended survival periods seen in r/r FL, immature OS results are common. The KM survival probability was 92.0% (95% confidence interval [CI], 85.7 to 95.6) at 18 months, 88.0% (95% CI, 81.0 to 92.6) at 24 months, and [REDACTED] at 36 months.

Progression-Free Survival

The proportion of patients who had experienced a progression event was [REDACTED] after 36 months of follow-up. The median PFS was 40.2 months (95% CI, 28.9 to NE). The Kaplan-Meier PFS probability (95% CI) at 18 months was [REDACTED], at [REDACTED], and at 36 months was 54.4% (95% CI, 44.2 to 63.5).

Objective Response Rate

At the 36-month time point for analysis, the estimated ORR as per investigator assessment was a clinically meaningful 94% (95% CI, [REDACTED]) in the FAS, while the CRR was 79% (95% CI, [REDACTED]). According to clinical experts, and within the context of the extended survival periods in r/r FL, ORR and CRR are considered acceptable and 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 review in the 18-month inferential analysis set was [REDACTED]; the CRR was [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, ■ of patients with a response had experienced a loss of response event. The estimated median DOR was 38.6 months (95% CI, 29.0 to NE), which was considered clinically meaningful by the clinical experts consulted by CADTH. The KM event-free estimated probability (95% CI) at 18 months was ■ (■■■■), at 24 months was ■■■■■, and at 36 months was ■■■■■).

Time to Next Treatment

At the 36-month time point for analysis, ■ of patients had experienced a TTNT event; the median TTNT was NE (95% CI, 37.8 months to NE). The KM-estimated event-free probability (95% CI) at 18 months was ■■■■■ at 24 months was ■■■■■, and at 36 months was ■■■■■).

Harms Results

At the 36-month time point for analysis, a total of ■ of patients in the safety analysis set experienced a treatment-emergent adverse event (TEAE), with pyrexia (■%), hypotension (■■), headache (■■), and fatigue (■■) being the most commonly reported TEAEs. A total of 49% of patients in the safety analysis set experienced a serious adverse event (SAE), with pyrexia (■■) and pneumonia (I%) being the most commonly reported SAEs. At the 36-month time point, ■ of patients in the safety analysis set had died. The most common reason was progressive disease (■■), followed by AEs due to reasons other than progressive disease or subsequent therapy (■■) and secondary malignancy (■■).

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

Critical Appraisal

The ZUMA-5 trial, which was 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 the 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, DOR, and PFS) and subjective harms are at risk of measurement or reporting bias, although the direction of this bias is unclear. It was noted that these limitations were partly addressed through the use of a prespecified threshold for ORR and CRR end points and the use of central review.

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. Additionally, 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 study population generally represents the patients in Canada with r/r FL 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 performance status of 0 or 1, whereas clinical experts suggest that those with an ECOG performance status of 2 may be treated in the clinical setting), and patients who have more comorbidities. The clinical experts had differing opinions regarding patients who had received prior CD19-targeted therapy; 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 (who did not respond or relapsed within 6 months) would not be suitable 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 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.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor aimed to provide an estimate of relative efficacy against standard-of-care therapies in patients with r/r FL who have received 2 or more prior lines of therapy.¹⁹

Description of Studies

The relative efficacy of axicabtagene ciloleucel versus standard of care was estimated in the treated population in the ZUMA-5 trial using propensity scores with SMR weights. The SCHOLAR-5 study, which included the standard of care cohort, is a retrospective, observational, multicentre database study in 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 studies 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. Variable selection for the propensity score model was determined in a hierarchical manner and based on the advice of investigators and 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, with an odds ratio (OR) of 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, with an OR of 6.90 (95% CI, 3.62 to 13.18). The median (95% CI) DOR in the ZUMA-5 population was [REDACTED] compared to [REDACTED] in the propensity score-weighted SCHOLAR-5 population, with a hazard ratio (HR) (95% CI) of [REDACTED].

The median PFS in the ZUMA-5 population was 40.21 months (95% CI, 28.94 to NE) compared to 12.97 months (95% CI, 7.75 to 15.47) in the propensity score-weighted SCHOLAR-5 population, with an HR of 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

(95% CI, 38.40 to NE) in the propensity score–weighted SCHOLAR-5 population, with an HR of 0.56 (95% CI, 0.33 to 0.95). The median TTNT in the ZUMA-5 population was NE (95% CI, 37.85 to NE) compared to 26.61 months (95% CI, 12.65 to NE) in the propensity score–weighted SCHOLAR-5 population, with an 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 in treatment allocation between the ZUMA-5 and SCHOLAR-5 cohorts, there is the possibility 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 FLIP score, could not be adjusted for due to missing data. Characteristics such as ECOG performance status, FL grade, and whether patients were double refractory were significantly different between populations after propensity score weighting. The clinical experts consulted by CADTH suggested that differences in ECOG performance status and the proportion of patients that are double refractory could have an impact on how patients would be expected to 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 performance status) 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 study. The removal of the subset of patients from the SCHOLAR-5 cohort necessary to conduct the PFS analysis resulted in a statistically significant change in the mean (standard deviation [SD]) number of prior lines of therapy, [REDACTED] in the SCHOLAR-5 study compared to [REDACTED] in the ZUMA-5 trial. Differences in the number of prior lines of therapy between populations are particularly impactful in determining how patients would be expected to respond to treatment. The proportion of patients that were POD24 and the proportion of patients whose disease was refractory to their most recent treatment were also reduced with the exclusion of a subset of patients required to conduct the PFS analysis, indicating that the removal of these patients from the analysis resulted in a population with a lower-risk prognosis.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with r/r grade 1, 2, or 3a FL after 2 or more lines of systemic therapy
Treatment	Axi-cel
Dose regimen	One-time infusion of axi-cel, cell suspension of 2×10^6 CAR T cells per kg body weight, with a maximum of 2×10^8 CAR T cells
Submitted price	Axi-cel : \$485,021 per 1-time infusion
Treatment cost	One-time cost of \$485,021
Comparator	SOC is composed of chemotherapy (50%), SCT (12%), idelalisib (5%), and clinical trials (33%). Chemotherapy includes 6 different regimens: <ul style="list-style-type: none"> • BR • CHOP • CVP • GB • GDP • R-CVP
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (50 years)
Key data source	<ul style="list-style-type: none"> • 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 in or after July 2014) • Comparative efficacy data were informed from the ITC of the SCHOLAR-5 and ZUMA-5 studies through propensity score weighting on prespecified prognostic factors using SMR
Key limitations	<ul style="list-style-type: none"> • The sponsor implemented a cure model that assumed 40% of patients receiving axi-cel who remain progression-free for 5 years would be considered clinically cured. CADTH notes that it is premature to determine the fraction and time point upon which patients would achieve long-term remission, given that follow-up in the ZUMA-5 trial is limited; long relapses are common in FL; and 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 for the OS of axi-cel to converge with that of SOC within the model's lifetime horizon (that is, for axi-cel's treatment effect to wane within the patient's lifetime). • 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, as well as 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. Additionally, the pretreatment cost of leukapheresis considered by the sponsor for patients

Component	Description
	<p>receiving CAR T-cell therapy was underestimated.</p> <ul style="list-style-type: none"> The sponsor assigned different utility estimates to be accrued by patients with progressed disease according to subsequent treatment status. Clinical experts indicated that quality of life is not expected to differ between those who are on and off subsequent treatment. The sponsor omitted the R2 regimen (lenalidomide + rituximab) from the analysis despite evidence that the therapy is used off-label in current Canadian clinical practice.
CADTH reanalysis results	<ul style="list-style-type: none"> 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 surrounding OS for axi-cel, its comparative efficacy against SOC, and the durability of such a benefit, CADTH 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.

BR = rituximab plus bendamustine; CHOP = cyclophosphamide plus doxorubicin plus vincristine plus prednisone; CVP = cyclophosphamide plus vincristine plus prednisone; GB = obinutuzumab plus bendamustine; GDP = gemcitabine plus cisplatin plus prednisone; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; KM = Kaplan-Meier; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; R-CVP = rituximab plus cyclophosphamide plus vincristine plus prednisone; r/r = relapsed or refractory; SCT = stem cell transplant; SMR = standardized mortality ratio; SOC = standard of care; WTP = willingness-to-pay.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the projected market share of axicabtagene ciloleucel is underestimated, the proportion of patients who receive second-line therapy is underestimated, the proportion of patients who receive active therapy in the third line is underestimated, and CAR T-cell therapy pretreatment costs are underestimated. CADTH conducted reanalyses of the budget impact analysis by adjusting the projected share of axicabtagene ciloleucel and increasing the proportion of patients with FL who would relapse and continue with treatment in the second line. Based on the CADTH base case, the estimated budget impact associated with the reimbursement of axicabtagene ciloleucel 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, from 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 the third line resulted in an increase of axicabtagene ciloleucel'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.

Ethical Considerations

Normative and empirical literature on CAR T-cell therapies, as well as past CADTH ethics reports, were reviewed to summarize ethical considerations relevant across CAR T-cell therapies in the treatment of hematological cancers described in the summary report *Ethical Considerations in the Use of CAR-T Therapies for Hematological Cancers*. Ethical considerations specific to the use of axicabtagene ciloleucel for the treatment of adult patients with r/r grade 1, 2, or 3a 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, and have a need for therapies with fewer toxicities and more durable response. Patients who become chemoimmunotherapy refractory have no remaining standard of care 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 a consideration of 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 in patients 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 refractory to chemotherapy. Shared decision-making may be part of this process, given the range of therapies available and individualized risk-benefit calculus.
- **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 the ZUMA-5 trial 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 trial 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 to 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 highly costly, resource intensive, and administratively burdensome, and thus presented significant opportunity costs for publicly funded oncology and non-oncology drug budgets and health care systems. Moreover, 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 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. Additionally, and as discussed in the CADTH Economic Report for this review, clinical experts also noted that there is presently insufficient long-term evidence to support the sponsor's assumed 40% cure rate at 5 years following treatment with axicabtagene ciloleucel, and thus it would be premature to determine whether axicabtagene ciloleucel was curative for FL, including consideration of the indolent and heterogenous nature of the disease.

- **Implications of capacity constraints and outpatient delivery for the use of CAR T-cell therapy for FL:** Clinical experts emphasized that offering CAR T-cell therapy for FL would require increasing CAR T-cell delivery capacity in Canada, given the resource-intensive, personnel-intensive, and infrastructure-intensive nature of CAR T-cell therapy. 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. 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 over patients with FL. Moreover, clinical experts noted that some centres were shifting to outpatient delivery of CAR T-cell therapy to expand treatment capacity, unless patients were deemed to be at high risk of SAEs (e.g., CRS or ICANS). However, they discussed how capacity constraints and the resulting shift to outpatient delivery could have implications for choice of CAR T-cell 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, if it were reimbursed in a piecemeal manner for patients in Canada. The Summary Report discusses additional inequities and barriers to accessing CAR T-cell therapy that patients may face due to geography, socioeconomic status, race, or referral patterns, even when

a therapy is reimbursed, since CAR T-cell therapies are administered through a limited number of tertiary treatment centres in Canada.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: September 13, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None

ISSN: 2563-6596

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