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CADTH Reimbursement Recommendation

Axicabtagene Ciloleucel (Yescarta)

Indication: For the treatment of adult patients with diffuse large B-cell lymphoma or high-grade B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy

Sponsor: Gilead Sciences Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Yescarta?

CADTH recommends that Yescarta should be reimbursed by public drug plans for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy, who are eligible for autologous stem cell transplant (ASCT) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Yescarta should only be covered to treat adults with DLBCL or HGBL that did not respond to or relapsed within 12 months of first-line therapy and are eligible for ASCT.

What Are the Conditions for Reimbursement?

Yescarta should only be reimbursed for patients who have not yet been treated with chimeric antigen receptor (CAR) T-cell therapy, are in relatively good health, and if the cost of Yescarta is reduced. It should be prescribed and administered by clinicians with expertise in lymphomas and CAR T-cell therapy in a hospital setting with adequate resources.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Yescarta increased the time until disease progression, a new treatment for lymphoma, or death in patients with refractory or relapsed LBCL compared with standard-of-care treatment.
- Yescarta is an effective alternative treatment that may prolong remission and/or survival for patients.
- 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 $348 million over the next 3 years. However, the actual budget impact is uncertain as the analysis is sensitive to the expected market uptake rates.

Additional Information

What Is B-Cell Lymphoma?

BCLs, the most common types of non-Hodgkin lymphomas (NHLs), are closely related cancers formed from B lymphocytes, a type of white blood cell. An estimated 11,400 people living in Canada will be diagnosed with NHL each year and 3,000 will die.

Unmet Needs in B-Cell Lymphoma

Not all patients with BCL benefit from available treatments. Patients need additional treatment options that can prolong survival and remission and improve quality of life.

How Much Does Yescarta Cost?

Treatment with Yescarta is expected to have a 1-time cost of $485,021 per patient. Additional costs associated with pre- and postinfusion management (i.e., leukapheresis, bridging therapy, conditioning chemotherapy) and administration will also apply.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that axicabtagene ciloleucel be reimbursed for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy and who are eligible for autologous stem cell transplant (ASCT) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, randomized, open-label trial (ZUMA-7) demonstrated that treatment with axicabtagene ciloleucel resulted in added clinical benefit compared with standard of care (SOC) (salvage chemoimmunotherapy followed by high-dose therapy [HDT] and ASCT) as second-line treatment in ASCT-eligible patients with refractory or relapsed large B-cell lymphoma (LBCL) within 12 months of first-line therapy. The ZUMA-7 trial demonstrated that treatment with axicabtagene ciloleucel was associated with statistically significant and clinically meaningful improvements in event-free survival (EFS) compared with SOC. Median EFS based on blinded central assessment was 8.3 months (95% confidence interval [CI], 4.5 to 15.8) in the axicabtagene ciloleucel arm and 2.0 months (95% CI, 1.6 to 2.8) in the SOC arm; the stratified hazard ratio (HR) for event or death was 0.398 (95% CI, 0.308 to 0.514; $P < 0.0001$).

Patients indicated that there is a need for treatments that prolong survival and remission, improve quality of life, and have fewer side effects. Furthermore, patients indicated that treatment choice is important to them, and there is a need for more treatment options and improved access to chimeric antigen receptor (CAR) T-cell therapy. Given all the evidence, pERC concluded that axicabtagene ciloleucel met some of the needs identified by patients, such as prolonged EFS and an additional treatment option.

Using the sponsor-submitted price for axicabtagene ciloleucel and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for axicabtagene ciloleucel was $404,418 per quality-adjusted life-year (QALY) gained compared with SOC. At this ICER, axicabtagene ciloleucel is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY for adult patients with refractory or relapsed LBCL who are candidates for ASCT. A price reduction is required for axicabtagene ciloleucel to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Axicabtagene ciloleucel should be reimbursed in adult patients with DLBCL or HGBL only if all of the following criteria are met:	The ZUMA-7 trial enrolled patients who had either primary refractory disease or relapse within 12 months of completing first-line therapy, were eligible for ASCT,	—

Reimbursement condition	Reason	Implementation guidance
1.1. refractory to first-line chemoimmunotherapy or relapsed within 12 months of first-line chemoimmunotherapy 1.2. eligible for ASCT 1.3. have a good performance status.	and had an ECOG performance status of 0 or 1.	
2. Axicabtagene ciloleucel should not be reimbursed for patients who have had previous CAR T-cell therapy.	There is no evidence that patients previously treated with CAR T-cell therapy can benefit from axicabtagene ciloleucel because these patients were excluded from the ZUMA-7 study.	—
Renewal		
3. Treatment with axicabtagene ciloleucel is a 1-time therapy.	There was no evidence available for review by pERC for repeating treatment with axicabtagene ciloleucel.	At this time, CAR T-cell re-treatment has not been established as an efficacious strategy and is not considered standard of care.
Prescribing		
4. Axicabtagene ciloleucel should be prescribed by clinicians with expertise in the management of lymphomas and CAR T-cell toxicities. Axicabtagene ciloleucel should be administered in a hospital setting with adequate infrastructure, resources, and expertise to perform the procedure and manage side effects.	To ensure axicabtagene ciloleucel is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
5. A reduction in price.	The ICER for axicabtagene ciloleucel is $404,418 per QALY gained compared with SOC, assuming 50% of patients who fail SOC would be treated with CAR T-cell therapies in the third-line setting. A price reduction of 45% would be required for axicabtagene ciloleucel to achieve an ICER of $50,000 per QALY gained compared with SOC in the ASCT-eligible population.	—
Feasibility of adoption		
6. 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 all 3 years. • The magnitude of uncertainty in the budget impact must be addressed to	—

Reimbursement condition	Reason	Implementation guidance
	ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	

ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HGBL = high-grade B-cell lymphoma; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Discussion Points

- pERC discussed that the ZUMA-7 trial enrolled patients with relapsed or refractory disease after first-line therapy who were eligible for ASCT. pERC recognized that there is also a need in patients with relapsed or refractory disease after first-line therapy who are not eligible for ASCT; however, there is currently no evidence supporting the use of axicabtagene ciloleucel as second-line therapy in patients who are not eligible for ASCT. pERC noted that there are no standard criteria to determine ASCT eligibility; criteria vary widely across treatment centres depending on local clinical practices and resources. Given clinical challenges in determining eligibility criteria for ASCT, or for CAR T-cell therapies more generally, there is a need to develop standardized criteria for eligibility and for these criteria to be applied fairly across populations.
- Patients indicated that there is a need for treatments that prolong survival, and overall survival (OS) was a key secondary outcome in the ZUMA-7 study. The OS data were immature at the time of review by pERC. As of the interim OS analysis (data cut-off date of March 18, 2021), 72 patients (40%) had died in the axicabtagene ciloleucel arm and 81 patients (45%) had died in the SOC arm. The HR for death was 0.730 (95% CI, 0.530 to 1.007). pERC noted that the interim analysis of OS did not reach statistical significance.
- Patients expressed a need for treatments that improve quality of life. In the ZUMA-7 study, health-related quality of life (HRQoL) was assessed as a secondary outcome. There were clinically meaningful differences in mean change of scores from baseline to study day 100 for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status and physical functioning scale and EQ-5D-5L visual analogue scale (VAS) for axicabtagene ciloleucel compared with SOC. However, the findings were uncertain due to large amounts of missing data that was also imbalanced between the groups. Therefore, based on these data, it is unclear if axicabtagene ciloleucel provides better HRQoL compared with SOC in patients with relapsed or refractory LBCL.
- pERC noted that uncertainties remain regarding the implementation of CAR T-cell therapy and the support system needed to optimize timely access and deliverability of axicabtagene ciloleucel in a real-world setting. Patients also identified the need for improved access to CAR T-cell therapies. Implementation considerations should take into account equitable access to axicabtagene ciloleucel, especially for marginalized groups who may face disparities in diagnosis and in their experiences with LBCL. Implementation should aim to prevent further disadvantaging or the entrenchment of disparities in health outcomes. This may be supported through accessible information about LBCL and axicabtagene ciloleucel, additional assistance and navigation of treatment, collaborative care, reductions in travel burden, and diminishing barriers to access programs. Access to CAR T-cell therapy centres that can deliver axicabtagene ciloleucel is currently limited by geographical availability, and increased access needs to be balanced with safety and

quality of treatment centres and consideration of the development and application of criteria that promote equity of access.

- pERC identified the need for national stakeholder engagement to develop a fair patient selection process and criteria for allocation of treatment slots for CAR T-cell therapy across treatment sites.
- pERC noted that axicabtagene ciloleucel is a costly treatment, and the estimated budget impact of reimbursing axicabtagene ciloleucel may have implications for the feasibility of adoption, particularly if uptake of axicabtagene ciloleucel is as high as expected. Market uptake is a key driver to the expected budget impact of axicabtagene ciloleucel. Although the sponsor assumed lower market uptake rates within their analysis, the CADTH base-case reanalysis adjusted projected market share of axicabtagene ciloleucel to 77.4%, 87.6%, and 93.8% in years 1, 2, and 3, respectively, based on feedback sought from CADTH clinical experts. This reanalysis demonstrates that, with higher rates of uptake, the 3-year budget impact could be more than $347 million.

Background

Non-Hodgkin lymphoma comprises a diverse group of closely related cancers of the lymphocytes. It is the most prevalent hematological malignancy and the fifth most common cancer diagnosed in Canada. LBCL is the most common subtype of non-Hodgkin lymphoma in Canada, constituting 30% to 40% of all cases. LBCL is an aggressive but potentially curable non-Hodgkin lymphoma that is typically diagnosed at an advanced stage (stage III or IV).

The SOC first-line treatment for patients with newly diagnosed LBCL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), often in combination with rituximab (R-CHOP). However, 30% to 50% of patients are refractory to or relapse after first-line therapy. OS in patients with primary refractory disease is very poor. Patients with partial response (PR) or complete response (CR) to first-line treatment also have poor survival at relapse. For patients who relapse or whose disease is refractory to first-line chemoimmunotherapy, second-line treatment comprises salvage chemotherapy; if responsive to salvage therapy, this is followed by HDT and ASCT. However, only about half of the patients with relapsed or refractory LBCL are fit enough for transplant (i.e., have adequate organ function with no major comorbidities), and only half of transplant-eligible patients respond to salvage chemotherapy and can proceed to ASCT. Treatment options for patients with relapsed or refractory LBCL who are ineligible for ASCT, do not respond to salvage chemotherapy, or relapse post-ASCT include palliative chemotherapy, radiotherapy, clinical trials, or third-line CAR T-cell therapy if the patient meets the eligibility criteria.

Axicabtagene ciloleucel is a CD19-directed, genetically modified autologous T-cell immunotherapy (i.e., CAR T-cell therapy). Axicabtagene ciloleucel has been approved by Health Canada for the treatment of adult patients with LBCL that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. It is available as an IV infusion (target of 2 × 106 anti-CD19 CAR T cells per kg body weight).

Submission History

In 2019, CADTH published an Optimal Use Report evaluating the beneficial and harmful effects of axicabtagene ciloleucel as third-line therapy for eligible types of relapsed or refractory B-cell lymphomas in adult patients. The original CADTH review of axicabtagene ciloleucel included the ZUMA-1 trial, which was a phase I/phase II, single-arm, multicentre, open-label clinical trial in patients with relapsed or refractory LBCL who had received at least 2 previous systemic therapies.

Sources of Information Used by the Committee

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

- a review of a phase III, multicentre, randomized, open-label study in patients with relapsed or refractory LBCL after first-line therapy
- patients perspectives gathered by 1 patient group: Lymphoma Canada
- 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 LBCL
- input from 3 clinician groups, including Lymphoma Canada, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee, and Cell Therapy Transplant Canada (CTTC)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical considerations related to axicabtagene ciloleucel and LBCL.

Ethical Considerations

- Patient and clinician group, clinical expert, and drug program input as well as relevant literature were reviewed to identify ethical considerations relevant to the use of axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory LBCL.
- Ethical considerations arising in the context of LBCL highlight the effects on patients and disparities in the incidence, treatment, and outcomes of LBCL, especially as they affect racialized or marginalized groups. The diagnosis of relapsed or refractory disease, as well as determinations of ASCT eligibility, were cited as complex barriers to treatment.
- Ethical considerations arising in the evidence used to evaluate axicabtagene ciloleucel indicated some limitations in clinical trial data, including limitations on included groups and long-term data on safety and effectiveness. As well, budget forecasting may underestimate the overall budget impact of CAR T-cell therapies if implemented fairly and as needed.
- Several access considerations arise in the context of CAR T-cell therapies in Canada, including those related to geographical access, especially because they may disproportionately affect racialized or marginalized groups; as well as inequities that might emerge in the process of patient referral. Considerations also arise in the context of cell and tissue use and ownership in the course of CAR T cell manufacture and disposal, as

do considerations related to informed consent and balanced communication about CAR T-cell therapies.

- Ethical considerations for health systems related to the implementation of axicabtagene ciloleucel include challenges to implementation and scaling CAR T-cell therapy sites across Canada, and health system sustainability considerations related to high-cost therapies.

Stakeholder Perspectives

Patient Input

One patient group, Lymphoma Canada, submitted patient input for this review. This group gathered information from patients with DLBCL in Canada through 2 online surveys: 1 in 2018 and another in 2022. In both surveys, patients reported that fear of progression or relapse was the most common psychosocial impact (67%) affecting quality of life, followed by anxiety (37%), memory loss (37%), and concentration problems (36%). The majority of respondents (83%) were treated with CHOP with or without rituximab as their first-line of treatment since diagnosis. The respondents stated long-term treatment side effects (i.e., lasting longer than 2 years or that appeared at least 2 years after the end of treatment) included fatigue (52%) and "chemo brain" (42%). Patients from the 2018 survey reported their lymphoma treatment had the greatest negative impact on their work, travel, and other activities. Patients rated longer survival, longer remission, better quality of life, and fewer side effects as important outcomes expected from their treatment. More than half of the patients stated that they would choose a treatment with potentially serious side effects if their doctor recommended it to be the most effective option for DLBCL. Respondents also indicated treatment choice was an important factor, and 91% of patients felt a need for more therapy options for DLBCL patients.

Three patients reported receiving axicabtagene ciloleucel as third-line therapy. All were away from home for more than 3 months while receiving the treatment, and they highlighted the challenge of accessing CAR T-cell therapy currently. All 3 patients reported thrombocytopenia as a side effect of treatment with axicabtagene ciloleucel; fever, anemia, nausea/vomiting, neutropenia, diarrhea, joint or muscle pain, and fatigue were reported by 2 patients. Fear of progression or relapse and difficulty sleeping were reported by all 3 patients as psychosocial effects related to their CAR T-cell therapy.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Four clinical experts from across Canada contributed input to the CADTH review. The clinical experts consulted by CADTH noted that there is an unmet treatment need for patients who are refractory to or who relapsed after front-line therapy. Although HDT and ASCT has curative potential for the treatment of patients with relapsed or refractory LBCL, many patients are ineligible for ASCT or do not respond to salvage chemotherapy. The clinical experts indicated that axicabtagene ciloleucel would fit well earlier in the lines of treatment. The clinical experts suggested that axicabtagene ciloleucel could be used in second line and replace ASCT for most patients. The clinical experts noted that patient outcomes are expected to be better when they receive a potentially curative therapy earlier in the course of disease because some patients deteriorate rapidly and thus may be less likely to survive if definitive treatment is delayed.

The clinical experts noted that although the ZUMA-7 trial recruited only patients who were eligible for ASCT, in standard clinical practice there is no clinical rationale for restricting axicabtagene ciloleucel only to those who are candidates for ASCT and that any patient with adequate organ function and good performance status (Eastern Cooperative Oncology Group [ECOG] performance status ≤ 2) who, based on the clinician's judgment can tolerate the known toxicities of CAR T-cell therapy (e.g., cytokine release syndrome [CRS]) would be suitable for axicabtagene ciloleucel treatment. The clinical experts noted that axicabtagene ciloleucel treatment can be provided by oncologists or hematologists in a hospital setting with adequate infrastructure for cell therapy with access to highly specialized multidisciplinary clinical care, including critical/intensive care and specialist care (e.g., neurology, nephrology) to manage toxicities as well as laboratory support to handle and process samples. The clinical experts also pointed out that the 13-day median manufacturing time reported in the ZUMA-7 study is rapid but may not be reproducible outside the clinical trial setting and longer delays may compromise patient outcomes.

Clinician Group Input

Clinician group input was received from 3 groups: Lymphoma Canada, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee, and CTTC. The clinician groups agreed that there are unmet needs in the current second-line treatment for patients with relapsed or refractory LBCL. The clinician groups indicated that there may be limited eligibility or tolerability to further salvage chemotherapy for some patients (e.g., patients with primary refractory disease or early relapse, older patients). The clinician groups also noted that toxicities, such as febrile neutropenia, bacteremia and other infections, gastrointestinal toxicity, and mucositis, as well as the need for transfusion support and the secondary malignancies associated with ASCT treatment, have made it unsuitable for high-risk patients who are refractory to treatment or who relapse within 12 months of diagnosis.

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
Relevant comparators	
The ZUMA-7 trial comparator was platinum-chemoimmunotherapy (R-GDP, R-ICE, R-DHAP, R-ESHAP) followed by high-dose chemotherapy and then ASCT, which is aligned with the standard of care.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
For DLBCL arising from FL, do patients need to have a record of treatment for the diagnosis of DLBCL or is a biopsy-proven DLBCL sufficient (e.g., the patient only received treatment for FL and then transformed to DLBCL)?	pERC agreed with the clinical experts, who indicated that in clinical settings, the diagnosis of transformation may be clinically driven, based on patient symptoms and signs, rather than pathologically driven. In some cases, biopsy is unavailable or risky to obtain. Therefore, a high clinical suspicion of transformation is sufficient and biopsy-proven DLBCL is not necessary to confirm transformation to DLBCL.

Implementation issues	Response
	The clinical experts indicated that, generally, once the diagnosis of transformation is made, line of therapy for the transformation (i.e., disease eligible for CAR T-cell therapy) starts at that point. However, the clinical experts noted that if a patient FL has already been given therapy that is an active regimen for high-grade lymphoma including DLBCL that includes a rituximab-containing regimen with anthracycline (e.g., R-CHOP), especially when treatment is recent, the patients should be regarded as having failed first-line therapy and should be eligible for second-line CAR T-cell therapy. To be considered for second-line CAR T-cell therapy, the clinical experts noted that patients should have been exposed to a rituximab-containing regimen with an anthracycline as in the ZUMA-7 trial (or etoposide if an anthracycline was unavailable), whether for DLBCL or FL.
Can pERC clarify the definition of relapsed disease? In the ZUMA-7 trial, relapse was defined as relapse from complete remission no more than 12 months after the completion of first-line chemoimmunotherapy.	The clinical experts clarified that the definition used in the ZUMA-7 trial is reasonable and indicated this definition could be applied to eligibility criteria for axicabtagene ciloleucel (i.e., relapse, within 12 months from date of last exposure to active therapy). pERC noted that this is specified in the Health Canada indication.
Should patients with the following be considered for axicabtagene ciloleucel because they were excluded from the ZUMA-7 trial: • ECOG performance status > 1 • prior CD19-targeted therapy (e.g., blinatumomab, tafasitamab) • prior CAR T-cell therapy or other genetically modified T-cell therapy • history of a Richter's transformation of chronic lymphocyte leukemia or PMBCL • known or history of CNS metastases or CNS lymphoma?	pERC agreed with the clinical experts, who indicated patients with ECOG performance status ≤ 2 can be considered for CAR T-cell therapy. pERC noted that there is no evidence to support using of axicabtagene ciloleucel in patients who received prior CD-19-targeted therapy. pERC noted that patients with a history of a Richter's transformation of chronic lymphocyte leukemia are managed differently than patients with LBCL. The clinical experts indicated that patients with PMBCL should be eligible for CAR T-cell therapy. pERC noted that there is currently no evidence to support CAR T-cell re-treatment in patients who had received a prior CAR T-cell therapy. pERC agreed with the clinical experts, who indicated that as long as the CNS disease is treated and the patient is neurologically stable, they should be eligible for CAR T-cell therapy.
ZUMA-7 only allowed bridging with corticosteroids. Should patients who are given other bridging therapies be considered for axicabtagene ciloleucel? If yes, what other bridging therapies can be considered?	pERC agreed with the clinical experts, who indicated that bridging therapies other than corticosteroids can be used. Any standard salvage chemotherapy regimen (e.g., R-GemOx, R-GDP, R-ICE, R-DHAP, R-ESHAP, pola-BR) could be used as bridging therapy.

Implementation issues	Response
CAR T-cell therapy is funded in some jurisdictions for relapsed or refractory LBCL after 2 or more lines of systemic therapy. Is there evidence to support re-treatment with CAR T-cell therapy with either the same product, or a different product, or allogenic CAR T-cell therapy?	pERC noted that there is no evidence supporting re-treatment with a CAR T-cell therapy, and that this may cause ethical challenges around equity of access.
Considerations for prescribing of therapy	
Axicabtagene ciloleucel is a single-dose, 1-time treatment, infused at a target dose of 2 × 106 CAR T cells per kilogram of body weight.	Comment from the drug programs to inform pERC deliberations.
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 services in Canada. Although 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 programs to inform pERC deliberations.
Generalizability	
Should patients who recently started second-line platinum-chemoimmunotherapy be allowed to switch to CAR T-cell therapy provided all other criteria are met?	The clinical experts indicated that depending on where the patient is in the course of treatment (e.g., completed salvage chemotherapy and a plan is in place for transplant), they should be allowed to switch to CAR T-cell therapy. pERC agreed that the decision to have CAR T-cell therapy rather than ASCT would be at the discretion of the treating hematologist in discussion with the patient.
Funding algorithm (oncology only)	
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
Hospitalization for adverse events does occur and may include ICU admission. Cytokine release syndrome is sometimes managed with tocilizumab. In the event of a tocilizumab shortage, is there another treatment that can be used to manage CRS?	pERC agreed with the clinical experts, who reported that other treatments may be used to manage cytokine release syndrome. These include siltuximab, a next-generation IL-6 inhibitor, and steroids if an IL-6 inhibitor is unavailable.
System and economic issues	
Feasibility of adoption must be addressed. Given the anticipated patient volumes, PAG is concerned that existing capacity may not be able to meet demand.	Comment from the drug programs to inform pERC deliberations. pERC noted that the sponsor's stated capacity to manufacture axicabtagene ciloleucel exceeded the expected need in Canada.
Accessing CAR T-cell therapy may require interprovincial travel. A program to cover travel and accommodation expenses should be offered by the manufacturer until widespread access across Canada is available.	Comment from the drug programs to inform pERC deliberations. pERC noted that this is part of the sponsor's implementation plan and is discussed in the Ethics Review Report.

Implementation issues	Response
There are patient privacy and patient cell ownership concerns due to the fact that CAR T cells are manufactured by a US-based company outside of Canadian jurisdiction (this is also the case for the other CAR T-cell therapies that are publicly funded).	Comment from the drug programs to inform pERC deliberations. pERC noted that this issue and potential solutions is discussed in the Ethics Review Report. Specifically, informed consent processes have to be carefully planned.

ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; ICU = intensive care unit; IL = interleukin; LBCL = large B-cell lymphoma; PAG = provincial advisory group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PMBCL = primary mediastinal large B-cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin; R-ESHAP = rituximab, etoposide, solu-medrone, high-dose cytarabine, and cisplatin; R-GDP = rituximab, gemcitabine, dexamethasone, and cisplatin; R-GemOx = rituximab, gemcitabine, and oxaliplatin; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide; pola-BR = polatuzumab vedotin, bendamustine, and rituximab.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

A single sponsor-submitted pivotal study was included in this review. The ZUMA-7 study is a phase III, multicentre, randomized, open-label study evaluating the efficacy of axicabtagene ciloleucel compared with SOC (salvage chemoimmunotherapy followed by HDT and ASCT) as a second-line therapy in patients with relapsed or refractory LBCL after first-line rituximab-plus anthracycline-based chemotherapy. The trial was conducted in 14 countries; 20 patients from 8 centres were recruited in Canada. The first patient was enrolled (randomized) on January 25, 2018, and enrolment was completed on October 4, 2019; ZUMA-7 is currently ongoing. All patients had either primary refractory disease or relapse within 12 months of completing first-line therapy, were potentially eligible for ASCT, and had not yet received second-line treatment. The data cut-off date for the primary analysis was March 18, 2021. For patients in the axicabtagene ciloleucel arm (N = 180), treatment consisted of lymphodepleting chemotherapy followed by a single IV infusion of axicabtagene ciloleucel. Bridging therapy consisting of corticosteroids was allowed before lymphodepleting chemotherapy for patients with high disease burden at the discretion of the investigator. For patients in the SOC arm (N = 179), treatment consisted of a single protocol-defined, platinum-based salvage chemotherapy regimen for 2 to 3 cycles as selected by the treating investigator. Patients who responded to salvage chemotherapy were to proceed to HDT followed by ASCT. The mean age of patients was 57 years (standard deviation [SD] = 12 years); 30% of the patients were 65 years of age or older. Overall, 74% of the study population had primary refractory disease and 26% had early relapse. Approximately one-quarter of patients in both treatment arms had achieved a best response of CR to first-line treatment.

Efficacy Results

Overall Survival

OS was a key secondary outcome in the ZUMA-7 study. The OS data remain immature at the time of this review. At the time of the data cut-off date (March 18, 2021), 72 patients (40%) had died in the axicabtagene ciloleucel arm and 81 patients (45%) had died in the SOC arm (153 OS events were observed in the full analysis set). The primary OS analysis will occur at approximately 210 deaths or 5 years after the first patient was enrolled. At the interim

OS analysis, the HR for death was 0.730 (95% CI, 0.530 to 1.007; 1-sided stratified log-rank P = 0.0270).

An addendum to ZUMA-7 Clinical Study Report was made to provide data generated in response to a Health Authority request to obtain additional survival follow-up data, including from public records, for patients who discontinued from the ZUMA-7 trial. This was not available at the time of the interim OS analysis for completeness of the interim OS data. At the time of this analysis, there were an additional 4 deaths in the SOC arm identified for a total of 157 OS events (72 deaths in the axicabtagene ciloleucel arm and 85 deaths in the SOC arm). The stratified HR was 0.708 (95% CI, 0.515 to 0.972; P = 0.0159).

Event-Free Survival

EFS based on blinded central assessment was the primary outcome of the ZUMA-7 study. At the time of the data cut-off, 252 EFS events based on blinded central assessment had occurred in 108 patients (60%) in the axicabtagene ciloleucel arm and 144 patients (80%) in the SOC arm. The median EFS was 8.3 months (95% CI, 4.5 to 15.8 months) in the axicabtagene ciloleucel arm and 2.0 months (95% CI, 1.6 to 2.8 months) in the SOC arm. The stratified HR for event or death was 0.398 (95% CI, 0.308 to 0.514; P < 0.0001).

Health-Related Quality of Life

HRQoL assessed by changes from screening in the global health status scale and the physical functioning domain of the EORTC QLQ-C30 and the EQ-5D-5L index and VAS scores were secondary outcomes. There was a clinically meaningful (based on the trial-specified threshold of ± 10 points) and statistically significant difference in mean change of scores from baseline to study day 100 for the EORTC QLQ-C30 global health status and physical functioning scores and EQ-5D-5L VAS scores with axicabtagene ciloleucel compared with SOC. However, the high attrition rate, which was imbalanced between groups, at all follow-up time points limits interpretation of these data.

For EORTC QLQ-C30 global health status there was a clinically meaningful difference in mean change of scores from screening at study day 100 (estimated difference = 18.1; 95% CI, 12.3 to 23.9; adjusted P < 0.0001) for patients treated with axicabtagene ciloleucel compared with SOC. At study day 150, the estimated difference was 9.8 (95% CI, 2.6 to 17.0; adjusted P = 0.0124).

For EORTC QLQ-C30 physical functioning, there was a clinically meaningful difference in mean change of scores from screening to study day 100 for patients treated with axicabtagene ciloleucel compared with SOC (estimated difference = 13.1; 95% CI, 8.0 to 18.2; adjusted P < 0.0001).

For EQ-5D-5L VAS, there was a clinically meaningful difference in mean change of scores for the EQ-5D-5L VAS from screening in the axicabtagene ciloleucel arm compared with SOC at study day 100 (estimated difference = 13.7; 95% CI, 8.5 to 18.8; adjusted P < 0.0001) and study day 150 (estimated difference = 11.3; 95% CI, 5.4 to 17.1; adjusted P = 0.0004).

Progression-Free Survival

Progression-free survival (PFS) was a secondary outcome. At the data cut-off date, the median duration of PFS based on investigator disease assessments was 14.9 months (95% CI, 7.2 months to not estimable [NE]) in the axicabtagene ciloleucel arm and 5.0 months (95% CI, 3.4 to 8.5 months) in the SOC arm, with a stratified HR of 0.562 (95% CI, 0.414 to 0.762).

Objective Response Rate

Objective response rate (ORR) per blinded central assessment was a key secondary outcome in the ZUMA-7 trial. The ORR (CR or PR) per blinded central assessment was 83% in the axicabtagene ciloleucel arm and 50% in the SOC arm (difference in ORR = 33.1%; 95% CI, 23.2% to 42.1%; P < 0.0001).

The CR rates in the axicabtagene ciloleucel arm and the SOC arm were 65% (95% CI, 57.6% to 71.9%; n = 117) and 32% (95% CI, 25.6% to 39.8%; n = 58), respectively, and the PR rates were 18% (95% CI, 13.0% to 24.8%; n = 33) and 18% (95% CI, 12.6% to 24.3%; n = 32), respectively.

Duration of Response

Duration of response was a secondary outcome. For the 150 patients in the axicabtagene ciloleucel arm and the 90 patients in the SOC arm who achieved an objective response of CR or PR by blinded central assessment, the Kaplan-Meier estimated median duration of response was 26.9 months (95% CI, 13.6 months to NE) in the axicabtagene ciloleucel arm compared with 8.9 months (95% CI, 5.7 months to NE) in the SOC arm (stratified HR = 0.736; 95% CI, 0.488 to 1.1085).

The Kaplan-Meier estimates of the percentage of patients who remained in response at 12 and 24 months from first objective response were 60.9% (95% CI, 52.4% to 68.4%) and 54.0% (95% CI, 45.1% to 62.0%), respectively, in the axicabtagene ciloleucel arm compared with 47.6% (95% CI, 35.2% to 58.9%) and 45.6% (95% CI, 33.2% to 57.1%), respectively, in the SOC arm.

Time to Next Treatment

Time to next treatment was an exploratory outcome. Time to next treatment events occurred for 99 patients (55%) in the axicabtagene ciloleucel arm and 135 patients (75%) in the SOC arm. The median time to next treatment was 14.7 months (95% CI, 6.5 months to NE) and 3.4 months (95% CI, 3.1 to 4.4 months), respectively (stratified HR = 0.430; 95% CI, 0.329 to 0.560).

Health Care Resource Utilization

A total of 42 patients (25%) in the axicabtagene ciloleucel arm and 9 patients (5%) in the SOC arm were admitted to the ICU. Median duration of ICU hospitalization was 5 days (range, 1 to 12 days) and 3 days (range, 2 to 17 days) in the axicabtagene ciloleucel and SOC arms, respectively. Median duration of hospitalization for axicabtagene ciloleucel infusion was 16 days (range, 5 to 103 days); median duration of inpatient hospitalization for stem cell transplant in the SOC arm was 21 days (range, 1 to 53 days).

Harms Results

All patients in the axicabtagene ciloleucel arm (n = 170; 100%) and the SOC arm (n = 168; 100%) had at least 1 treatment-emergent adverse event (TEAE), including 155 patients (91%) in the axicabtagene ciloleucel arm and 140 patients (83%) in the SOC arm who had a grade 3 or higher TEAE. The most frequently reported TEAEs of grade 3 or higher (reported in ≥ 20% of patients in both treatment arms) were neutropenia (n = 73; 43%), anemia (n = 51; 30%), decreased neutrophil count (n = 49; 29%), decreased and white blood cell count (n = 43; 25%) in the axicabtagene ciloleucel arm and anemia (n = 65; 39%), decreased platelet count (n = 60 patients; 36%), decreased neutrophil count (47 patients; 28%), febrile neutropenia (n = 46; 27%), and thrombocytopenia (n = 37; 22%) in the SOC arm.

A total of 85 patients (50%) in the axicabtagene ciloleucel arm and 77 patients (46%) in the SOC arm had at least 1 serious adverse event. The most frequently (in ≥ 5% of patients) reported serious adverse events of any grade were pyrexia (n = 27; 16%), encephalopathy (n = 17; 10%), hypotension (n = 15; 9%), aphasia (n = 9; 5%), and pneumonia (n = 8; 5%) in the axicabtagene ciloleucel arm and febrile neutropenia (n = 22; 13%), and acute kidney injury (n = 8; 5%), and pyrexia (n = 8; 5%) in the SOC arm.

No patient discontinued treatment due to TEAEs in the axicabtagene ciloleucel arm. Two patients in the SOC arm discontinued treatment due to TEAEs of grade 4 acute kidney injury and grade 1 blood stem cell harvest failure.

Among patients in the axicabtagene ciloleucel arm, 64 patients (38%) had died by the data cut-off date for reasons including progressive disease (n = 47; 28%), TEAEs (n = 6; 4%), other reasons (n = 10; 6%), and 1 patient (1%) died from an event reported by the investigator as a "secondary malignancy" (lung adenocarcinoma). In the SOC arm, 78 patients (46%) had died at the data cut-off date due to reasons including progressive disease (n = 64; 38%), TEAEs (n = 2; 1%), or other reasons (n = 12; 7%).

A total of 102 patients (60%) in the axicabtagene ciloleucel arm and 33 patients (20%) in the SOC arm had at least 1 treatment-emergent neurologic event; 36 patients (21%) and 1 patient (1%) in the axicabtagene ciloleucel and SOC arms, respectively, had a grade 3 or higher neurologic event. Of these, 10 patients (6%) in the axicabtagene ciloleucel arm had a grade 4 neurologic event, and no patients in either treatment arm had a grade 5 neurologic event. Serious treatment-emergent neurologic events of any grade were reported for 34 patients (20%) in the axicabtagene ciloleucel arm and 1 patient (1%) in the SOC arm, including 26 patients (15%) in the axicabtagene ciloleucel arm with a serious grade 3 or higher neurologic event and 1 patient (1%) in the SOC arm with a serious grade 2 neurologic event.

CRS of any grade was reported for 157 patients (92%), including 11 patients (6%) who had a grade 3 or higher CRS; no patient had grade 5 CRS.

The most common cytopenias of any grade reported in the axicabtagene ciloleucel arm were thrombocytopenia (50 patients; 29%), neutropenia (122 patients; 72%), and anemia (73 patients; 43%). The most common cytopenias of any grade reported in the SOC arm were thrombocytopenia (101 patients; 60%), neutropenia (92 patients; 55%), and anemia (92 patients; 55%).

Seventy patients (41%) in the axicabtagene ciloleucel arm and 51 patients (30%) in the SOC arm had at least 1 treatment-emergent infection, including 24 patients (14%) and 19 patients (11%), respectively, with a grade 3 or higher infections. Three patients (2%) in the axicabtagene ciloleucel arm and 6 patients (4%) in the SOC arm had a grade 4 infections. Five patients (3%) in the axicabtagene ciloleucel arm had a grade 5 TEAE of infection (2 patients with COVID-19, 1 patient with progressive multifocal leukoencephalopathy, 1 patient with hepatitis B reactivation, and 1 patient with sepsis). No patients in the SOC arm had a grade 5 TEAE of infection.

Critical Appraisal

The ZUMA-7 trial was open label. Despite the open-label design, there is low risk of bias in the measurement of outcomes such as EFS, PFS, and ORR, which were assessed via independent blinded radiologic review of disease response, as well as OS which is an objective outcome. Although independent blinded radiologic review of disease response was

performed as the primary analysis to minimize investigator bias, patient's knowledge of their assigned treatment could affect HRQoL data and any subjective harm that is particularly susceptible to bias from a lack of blinding of patients to their treatment. The HRQoL data were also at high risk of attrition bias because there were large amounts of missing data for all follow-up time points and the amount of missing data was not balanced across treatment arms. The HRQoL tools were not validated in patients with LBCL. The primary and secondary efficacy end points of EFS, ORR, and OS are considered appropriate for the disease setting. The OS data were immature and there is a risk that the effect of axicabtagene ciloleucel compared with SOC on survival is overestimated because the results are based on an interim analysis. Although there is some evidence to suggest EFS is a robust surrogate end point for OS in hematological malignancies, it is unknown whether this could be extended to CAR T-cell therapies in the relapsed or refractory LBCL setting.

The ZUMA-7 trial included patients with relapsed or refractory LBCL with a wide range of clinical presentations, but patients with HIV and those with an ECOG PS of 2 or more were excluded. The clinical experts consulted by CADTH indicated that these patient groups should be eligible for CAR T-cell therapies including axicabtagene ciloleucel. Although the SOC treatment, including salvage chemotherapy regimens, used in the SOC arm of the ZUMA-7 trial are reflective of Canadian clinical practice, the clinical experts noted there are challenges in reproducing the same treatment processes for axicabtagene ciloleucel treatment in the real-world setting, notably because of the rapid manufacturing time (13 days in the ZUMA-7 trial). As per the clinical experts, delays in manufacturing and access times to axicabtagene ciloleucel treatment would potentially compromise patient outcomes because the probability of disease progression or other complications increase with longer axicabtagene ciloleucel manufacturing wait times. Data for all outcomes considered important to patients, clinicians, and drug plans as per the systematic review protocol were collected and reported; however, conclusions could not be drawn for effects of axicabtagene ciloleucel compared with SOC on HRQoL due to limitations in the data.

Other Relevant Evidence

The sponsor provided long-term (≥ 4 year and ≥ 5 year) data from the ZUMA-1 trial, the pivotal multicentre, single-arm, registrational phase I and II study of axicabtagene ciloleucel in patients with relapsed or refractory LBCL.

In the 2-year analysis of the ZUMA-1 trial (n = 101; median follow-up from axicabtagene ciloleucel dosing to data cut-off: 27.1 months), the ORR was 83%; 58% of patients achieved a CR. The 2-year OS rate was 50.5% (95% CI not reported).

The most recently updated survival results from the phase II ZUMA-1 study, after 5 years of follow-up, showed a 5-year OS rate of 42.6% (95% CI, 32.8% to 51.9%) among patients treated with axicabtagene ciloleucel. The 5-year OS rate among complete responders was 64.4% (95% CI, 50.8% to 75.1%). The median survival time among complete responders was not reached (95% CI, 63.4% to NE). Of 59 patients who achieved CR, 37 patients (63%) were alive at the 5-year data cut-off. Since the 4-year data cut-off, 1 death at month 63 (CR) and 1 PD at month 54 (PR) were observed.

Supportive safety data comparing populations treated with axicabtagene ciloleucel in the ZUMA-7 and ZUMA-1 trials suggested comparable TEAEs between the 2 trials.

Critical Appraisal

The ZUMA-1 trial was critically appraised in the 2019 CADTH Optimal Use Report. ZUMA-1 was a single-arm, phase I and II study of axicabtagene ciloleucel in patients with relapsed or refractory LBCL who had received at least 2 previous systemic therapies. The primary limitation of the ZUMA-1 study was the absence of a comparator group against which the treatment benefits and harms of axicabtagene ciloleucel could be compared. As such, causal effects cannot be inferred. In addition, patients in the ZUMA-1 study received axicabtagene ciloleucel as third- or later-line treatment. It is unknown whether results are generalizable to patients treated with axicabtagene ciloleucel as second-line treatment, which is the indication under review.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Reimbursement request population: Adult patients with r/r LBCL who are candidates for ASCT.
Treatment	Axicabtagene ciloleucel (Yescarta), followed by subsequent third-line therapy consisting of enrolment in clinical trials for investigational therapies (40%), salvage chemotherapy (20%), radiotherapy (20%), ASCT (10%), or no treatment (10%)
Dose regimen	Single-dose, 1-time treatment Target dose of 2×10^6 CAR T cells/kilogram body weight (range, 1×10^6 CAR T cells/kilogram to 2.4×10^6 CAR T cells/kilogram), with a maximum of 2×10^8 CAR T cells for patients weighing 100 kg or more
Submitted price	$485,021 per single infusion of axicabtagene ciloleucel
Treatment cost	$485,021
Comparator	SOC: Salvage chemotherapy (defined as a basket of chemotherapy regimens including R-GDP, R-ICE, R-DHAP, and R-DICEP) followed by HDT (HDT is defined as a basket of drug regimens including EM and BEAM) and ASCT in responders. This is followed by subsequent third-line therapy consisting of CAR T-cell therapies (50%), radiotherapy (40%), or no treatment (10%).
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (50 years)
Key data source	ZUMA-7
Key limitations	• The sponsor submitted a model based on adult patients with r/r LBCL who are candidates for ASCT. The clinical expert panel consulted by CADTH noted that the expected place in therapy for axicabtagene ciloleucel is broader than the modelled target population and would be more closely aligned with its Health Canada indication. Because there are no clinical data on patients with r/r LBCL who are not eligible for ASCT, the cost-effectiveness of axicabtagene ciloleucel in this patient population is unknown. • The OS curves were informed from the ZUMA-7 trial in which 56% of SOC patients received subsequent CAR T-cell therapy. Subsequent therapy had no impact on OS within the submitted model. Because access

Component	Description
	to CAR T-cell therapy varies across jurisdictions, this may not reflect Canadian practice. The clinical effects for alternate distributions of CAR T-cell use in third-line treatment is unknown. • The sponsor selected a mixture cure model with a predicted cure rate of 53% at 5 years for axicabtagene ciloleucel. Although an OS benefit with axicabtagene ciloleucel was deemed plausible, clinical expert feedback noted that the magnitude of such a benefit was uncertain given the immaturity in the OS data. Furthermore, because OS data were based on an interim analysis of the ZUMA-7 trial (data cut-off date: March 18, 2021), there is a risk that the effect of axicabtagene ciloleucel compared with SOC on survival is overestimated. • The utility estimates used by the sponsor had limited face validity. In the sponsor's base case, patients on treatment had similar or better quality of life than reported by the general Canadian population. Utility estimates for patients with progressed disease following axicabtagene ciloleucel treatment or SOC in second line were assumed to be equal to those derived from patients who failed CAR T-cell therapy in third line (i.e., further progressed LBCL). • The sponsor assumed that 40% of patients receiving axicabtagene ciloleucel would seek subsequent treatment by enrolling in clinical trials for investigational therapies although this assumption was extended to no patients in the SOC arm. This provided further treatment options for patients on axicabtagene ciloleucel exclusively. This lacks face validity and was modelled at no additional cost to drug plans, thereby underestimating the cost of subsequent treatment in favour of axicabtagene ciloleucel. • The sponsor applied a standardized mortality ratio of 1.09 to increase the hazard of death relative to the general population for long-term survivors. Clinical expert feedback was that this was too low to capture the excess mortality of patients who received extensive prior treatments associated with late toxicities.
CADTH reanalysis results	• CADTH conducted reanalyses by applying the following changes: selecting an alternative parametric OS curve for axicabtagene ciloleucel, revising the pre-event (for the first 149 days of treatment) and postevent utility values, adjusting the distribution of subsequent therapies to exclude investigational therapies, and applying a higher hazard of death among long-term survivors. • In the CADTH base-case reanalysis, the ICER for axicabtagene ciloleucel compared with SOC was $404,418 per QALY gained in adult patients with r/r LBCL who are candidates for ASCT, assuming 50% of patients who fail SOC would be treated with CAR T-cell therapies in the third-line setting. A price reduction of 45% would be necessary for axicabtagene ciloleucel to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. • The model was sensitive to the expected OS benefit with axicabtagene ciloleucel. The CADTH reanalysis estimated a smaller OS benefit compared with the sponsor's base case, although uncertainty remains about the expected magnitude of OS with axicabtagene ciloleucel. Results should be interpreted carefully in light of the fact that 71% of the QALY benefit was derived from the period beyond which there are observed trial data. • The cost-effectiveness of axicabtagene ciloleucel in the transplant-ineligible r/r LBCL population, which reflects a component of the proposed Health Canada indication, is unknown.

ASCT = autologous stem cell transplant; BEAM = carmustine, etoposide, cytarabine, and melphalan; EM = etoposide and melphalan; HDT = high-dose therapy; ICER = incremental cost-effectiveness ratio; LBCL = large B-cell lymphoma; LY = life-year; QALY = quality-adjusted life-year; r/r = relapsed or refractory; R-DHAP = rituximab, dexamethasone, cytarabine, , and cisplatin; R-GDP = rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide.

Budget Impact

CADTH identified the following limitations in the sponsor's budget impact analysis: axicabtagene ciloleucel use may be broader than the sponsor's reimbursement request, the projected market share of axicabtagene ciloleucel was underestimated, the projected proportion of ASCT-eligible patients who would proceed to second-line treatment was underestimated, and the mix of subsequent therapies in the axicabtagene ciloleucel arm included investigational therapies. CADTH performed reanalyses, in line with clinician

expert opinion, by revising the projected market share of axicabtagene ciloleucel, increasing the proportion of ASCT-eligible patients who would proceed to second-line treatment, and redistributing subsequent therapies in the axicabtagene ciloleucel arm. Based on the CADTH reanalyses, the budget impact from the introduction of axicabtagene ciloleucel for the treatment of r/r LBCL in adult patients who are candidates for ASCT is expected to be $103,063,855 in year 1, $117,507,525 in year 2, and $127,069,602 in year 3, with a 3-year total of $347,640,982.

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. Christopher Longo, 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: November 8, 2022

Regrets: Two expert committee members did not attend

Conflicts of interest: Two expert committee members did not participate due to considerations of conflict of interest