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Reimbursement Recommendation

Lisocabtagene Maraleucel (Breyanzi)

Indication: For the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma, who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy, and who are candidates for autologous hematopoietic stem cell transplant (HSCT)

Sponsor: Bristol Myers Squibb Canada

Final recommendation: Reimburse with conditions

Summary

What Is the CDA-AMC Reimbursement Recommendation for Breyanzi?

CDA-AMC recommends that Breyanzi be reimbursed by public drug plans for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma, who have disease that is refractory to first-line chemoimmunotherapy or who experience relapse within 12 months of first-line chemoimmunotherapy, and who are candidates for autologous hematopoietic stem cell transplant (HSCT), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Breyanzi should only be covered to treat adults with DLBCL not otherwise specified, PMBCL, HGBCL, or DLBCL arising from follicular lymphoma who do not experience a response to first-line therapy or who experience relapse within 12 months of first-line therapy; who are eligible for autologous HSCT; and who are in relatively good health (as measured by performance status).

What Are the Conditions for Reimbursement?

Breyanzi should only be reimbursed for patients who have not yet been treated with chimeric antigen receptor (CAR) T-cell therapy, if it is prescribed and administered by clinicians with expertise in lymphomas and CAR T-cell therapy in a hospital setting with adequate resources, and if the cost of Breyanzi is not more than that of axicabtagene ciloleucel (axi-cel). It must also be feasible to administer Breyanzi.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Breyanzi improved the time until disease progression, and that it may prolong survival in patients with refractory or relapsed DLBCL compared to standard of care (SOC) treatment.
- Breyanzi is an effective alternative treatment option for second-line therapy that may prolong remission and survival for patients.
- Based on CDA-AMC's assessment of the health economic evidence, Breyanzi does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Breyanzi than axi-cel.
- Based on public list prices, Breyanzi is estimated to cost the public drug plans approximately $3.5 million over the next 3 years, provided that

Summary

axi-cel becomes publicly reimbursed. If axi-cel does not become publicly reimbursed, the cost to the drug plans will be much higher.

Additional Information

What is B-Cell Lymphoma?

B-cell lymphoma, the most common type of non-Hodgkin lymphoma (NHL), is closely related to cancers formed from B lymphocytes, a type of white blood cell. An estimated 11,700 people living in Canada will be diagnosed with NHL each year and 3,100 will die.

Unmet Needs in B-Cell Lymphoma

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

How Much Does Breyanzi Cost?

Treatment with Breyanzi is expected to cost $501,900 per patient per infusion.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that lisocabtagene maraleucel (liso-cel) be reimbursed for adults with DLBCL not otherwise specified, PMBCL, HGBCL, and DLBCL arising from follicular lymphoma, who have disease that is refractory to first-line chemoimmunotherapy or who experience relapse within 12 months of first-line chemoimmunotherapy, and who are candidates for autologous HSCT, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT) — the TRANSFORM trial — demonstrated that treatment with liso-cel resulted in added benefit in event-free survival (EFS) for adults with relapsed or refractory (r/r) DLBCL within 12 months of first-line therapy, compared to SOC with salvage immunochemotherapy followed — depending on response — by high-dose chemotherapy (HDCT) and autologous HSCT. At the time of the second interim analysis (data cut-off date: March 8, 2021), the median EFS (i.e., time to death from any cause, progressive disease, not experiencing complete response [CR] or partial response [PR] by 9 weeks following randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first) was 10.1 months (95% confidence interval [CI], 6.1 to not estimable [NE]) in the liso-cel group versus 2.3 months (95% CI, 2.2 to 4.3) in the SOC group (1-sided P value < 0.0001), with a between-group hazard ratio (HR) of 0.35 (95% CI, 0.23 to 0.53). When compared to SOC, the Kaplan-Meier (KM)–estimated between-group differences in probability of EFS at 12 months (data cut-off date: March 8, 2021) and 36 months (data cut-off date: October 23, 2023) were 20.8% (95% CI, 2.5 to 39.1) and 26.7% (95% CI, 13.3 to 40.1) in favour of liso-cel, respectively. In addition to the TRANSFORM trial, pERC discussed the indirect evidence from the sponsor-submitted matching-adjusted indirect comparison (MAIC) comparing liso-cel to axi-cel. The results of the anchored MAIC assessing efficacy did not support a clinically meaningful difference between liso-cel and axi-cel for EFS, complete response rate (CRR), progression-free survival (PFS), and overall survival (OS); however, the estimates were subject to uncertainty due to imprecision. Based on the unanchored MAIC comparing liso-cel to axi-cel for harms outcomes, the results for reduced cytokine release syndrome (CRS), investigator-identified neurologic toxicity (iiNT), pyrexia, and encephalopathy favoured liso-cel. However, these estimates were subject to uncertainty due to imprecision and imbalances in potential effect modifiers and prognostic factors; therefore, pERC could not draw definitive conclusions about the safety of liso-cel compared to axi-cel.

Patients identified a need for accessible and effective treatment options that control disease, prolong life, improve quality of life, and have fewer side effects. pERC concluded that liso-cel met some important needs identified by patients (such as prolonged EFS and PFS), that it may improve OS, and that it represents an additional treatment option for second-line therapy.

At the sponsor-submitted price for liso-cel and publicly listed price for comparators, liso-cel was more costly than axi-cel and SOC. As liso-cel is considered similarly effective to axi-cel and definitive conclusions could not be made about comparative safety, the drug program cost of liso-cel should not exceed that of axi-cel.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Liso-cel should be reimbursed in adults aged 18 years or older with DLBCL not otherwise specified, PMBCL, HGBCL, or DLBCL arising from follicular lymphoma who meet all the following criteria: 1.1. refractory to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy 1.2. eligible for autologous HSCT 1.3. good performance status.	The TRANSFORM trial enrolled patients who had either primary refractory disease or relapse within 12 months of completing first-line therapy, were eligible for autologous HSCT, and had an ECOG performance status of 0 or 1.	Patients with grade 3B follicular lymphoma were included in the TRANSFORM trial. pERC noted that patients with grade 3B follicular lymphoma are treated in the same manner as DLBCL and should be eligible for treatment with liso-cel.
2. Liso-cel 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 liso-cel because these patients were excluded from the TRANSFORM trial.	—
Renewal		
3. Treatment with liso-cel is a 1-time therapy.	There was no evidence available for pERC to review on repeating treatment with liso-cel.	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. Liso-cel should be prescribed by clinicians with expertise in the management of lymphomas and CAR T-cell toxicities. Liso-cel should be administered in a hospital setting with adequate infrastructure, resources, and expertise to perform the procedure and manage side effects.	This is to ensure liso-cel is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
5. Liso-cel should be negotiated so that it does not exceed the drug program cost of treatment with axi-cel reimbursed for the treatment of large B-cell lymphoma in patients who are refractory or have relapsed within 12 months of first-line therapy and are candidates for autologous HSCT.	There is insufficient evidence to justify a cost premium for liso-cel over axi-cel for use in the indicated population.	—
Feasibility of adoption		
6. The feasibility of adoption of liso-cel must be addressed.	The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given	—

Reimbursement condition	Reason	Implementation guidance
	the difference between the sponsor's estimate and CDA-AMC's estimate(s).	
7. The organizational feasibility must be addressed. The administration of CAR T-cell therapy such as liso-cel requires expertise, infrastructure, and human resources to ensure that the treatment and adverse events are managed in an optimized and timely manner for patients. Prioritization considerations may include patient prognosis, prior therapy, and/or geographic location if the need for CAR T-cell therapy exceeds manufacturing or delivery capacity.	Due to the resource-intensive nature of CAR T-cell therapy and currently limited human resources and logistical constraints, a standardized process to prioritize utilization should be developed to promote treatment for the optimal clinical benefit in an ethical and equitable manner.	—

CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HGBCL = high-grade B-cell lymphoma, HSCT = hematopoietic stem cell transplant; PMBCL = primary mediastinal large B-cell lymphoma.

Discussion Points

- **Patients eligible for autologous HSCT:** pERC noted that the TRANSFORM trial enrolled patients with r/r disease after first-line therapy who were eligible for autologous HSCT. pERC recognized that there is also a need in patients with r/r disease after first-line therapy who are not eligible for HSCT; however, the approved indication is limited to patients who are candidates for autologous HSCT. pERC noted that there are no standard criteria to determine HSCT eligibility; criteria vary widely across treatment centres depending on local clinical practices and resources. Given clinical challenges in determining eligibility criteria for HSCT, 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.
- **OS:** Although the OS data were immature, the results were considered promising by pERC. At the time of the final analysis (data cut-off date: October 23, 2023), with a median duration of follow-up of 33.9 months in all patients, 34 patients (37.0%) had died in the liso-cel group and 42 patients (45.7%) had died in the SOC group. The median OS had not been reached in either treatment group, with a between-group HR of 0.76 (95% CI, 0.481 to 1.19). The KM-estimated between-group difference in probabilities of being alive at 12 months and 36 months were 11.4% (95% CI, −0.7 to 23.5; primary analysis data cut-off date: May 13, 2022) and 11.0% (95% CI, −3.7 to 25.7; final analysis data cut-off date: October 23, 2023), respectively, in favour of liso-cel.
- **Side effects:** pERC acknowledged that patients expressed a need for treatments that have fewer side effects. Although a higher proportion of notable harms were reported in patients taking liso-cel than in those taking SOC — with CRS, prolonged cytopenia and iiNT being the most common — pERC considered the side effects of liso-cel to be manageable, albeit more burdensome than SOC, given that treatment is expected to be prescribed and overseen by clinicians who are experienced in

treating patients with r/r DLBCL. pERC could not draw definitive conclusions about the safety of liso-cel compared to axi-cel based on the sponsor-submitted unanchored MAIC due to the methodological limitations.

- **Health-related quality of life (HRQoL):** pERC noted that patients and clinicians highlighted improvement in quality of life as an important outcome and treatment goal for patients with r/r DLBCL. However, pERC was unable to draw definitive conclusions regarding the effects of liso-cel compared to SOC on HRQoL due to concerns about imprecision and missing outcome data in the TRANSFORM trial. HRQoL was not assessed in the MAIC; therefore, pERC could not determine if there would be a benefit in HRQoL with liso-cel compared to axi-cel.
- **Ethical and equity considerations related to evidence and use:** pERC discussed uncertainties in the evidence for liso-cel, especially in earlier lines of therapy, and resulting implications for addressing unmet patient needs, consent conversations, the stewardship of limited hematological oncological and broader health care budgets. The committee also discussed the need for collection of long-term data on safety, efficacy, and comparative effectiveness to better support clinical and health systems decision-making. pERC acknowledged preliminary evidence indicating that CAR T-cell therapies may pose a class-level risk of other hematologic malignancies. Although these were not observed in the TRANSFORM trial, the committee recognized the importance of robust consent conversations to inform patients about these risks and the need for lifelong monitoring.
- **Ethical and equity considerations related to priority setting and access:** pERC identified the need for engaging national perspectives of patients, clinicians, and drug programs to develop a fair and equitable patient selection process and criteria for allocation of treatment slots for CAR T-cell therapy across treatment sites, if demand for liso-cel exceeds manufacturing or delivery capacity. The committee noted that clinicians may experience moral distress in the face of capacity constraints and the need for difficult prioritization decisions, as well as the recognition of the potential opportunity costs within and beyond the hematological oncological space. pERC acknowledged that offering liso-cel earlier in the disease course may expand access to therapeutic options, including for patients who must travel to receive treatment or for whom a more favourable toxicity profile would enable treatment with CAR T-cell 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.
- **Implementation considerations:** 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 liso-cel to patients in Canada. Patients also identified the need for improved access to CAR T-cell therapies. Implementation considerations should take into account equitable access to liso-cel, especially for equity-deserving groups who may face disparities in diagnosis and in their experiences with DLBCL. This may be supported through accessible information about DLBCL and liso-cel, 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 liso-cel 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.

- **Budget impact:** pERC noted that the estimated budget impact of reimbursing liso-cel depends on whether axi-cel becomes publicly funded. If axi-cel does not become publicly reimbursed, the budgetary impact of reimbursing liso-cel will be much higher than estimated in CDA-AMC's budget impact reanalysis. pERC further discussed that CDA-AMC's estimated budget impact of reimbursing liso-cel assumes that reimbursement of liso-cel will not affect overall demand for CAR T-cell therapy. However, because liso-cel may be administered in the outpatient setting for some patients, access to CAR T-cell therapy may be increased. If patients who would have otherwise received SOC are considered candidates for liso-cel, the overall demand for CAR T-cell therapy is likely to be higher than anticipated and may have important budget and capacity implications.

Background

NHL is the most common type of blood cancer that originates from lymphocytes (a type of white blood cell crucial to the immune system) and represents 90% of all lymphomas. The Canadian Cancer Society estimated that, in 2024, 11,700 Canadians would be diagnosed with NHL and 3,100 Canadians would die from it.[2] The 2023 Canadian Cancer Statistics reported an age-standardized incidence rate of 24.0 per 100,000 Canadians for NHL. Large B-cell lymphoma (LBCL), a diverse and aggressive NHL type, prominently features large lymphoid cells expressing B-cell antigens such as CD19 and CD20. The most common subtype of LBCL is DLBCL, accounting for 30% to 40% of NHL cases. The median diagnosis age for DLBCL is in the mid-60s, with males more commonly affected. Patients with DLBCL typically present with enlarged lymph nodes and systemic issues like fever, weight loss, and night sweats. Most individuals with DLBCL have a type that remains biologically and clinically heterogeneous, for which there are no clear and accepted criteria for subclassification. It is known as *not otherwise specified*, which constitutes 80% to 85% of all DLBCL cases. Other subtypes of DLBCL include PMBCL, a rare subtype of DLBCL that occurs in the thymus or in lymph nodes in the mediastinum (centre of the chest) and represents approximately 10% of all DLBCLs.

Liso-cel is a genetically modified autologous cell immunotherapy targeting CD19. It specifically binds to CD19, a protein expressed on the surface of B-cell precursors and malignant B cells in DLBCL and other lymphomas. By binding to CD19, liso-cel activates and proliferates the chimeric antigen receptor (CAR) T-cell therapies, resulting in the release of pro-inflammatory cytokines and cytotoxic agents that destroy the targeted cancer cells.

Liso-cel has been approved by Health Canada for the treatment of adult patients with DLBCL not otherwise specified, PMBCL, HGBCL, and DLBCL arising from follicular lymphoma, who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy, and who are candidates for autologous HSCT. The sponsor reimbursement request is as per the indication.

CDA-AMC has reviewed liso-cel previously for the treatment of adult patients with r/r LBCL after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, HGBCL, and DLBCL arising from follicular lymphoma, PMBCL, and grade 3B follicular lymphoma after at least 2 prior therapies. pERC recommended the medication to be reimbursed with condition (June 29, 2022).

Sources of Information Used by the Committee

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

- a review of 1 phase III, open-label, RCT in patients with r/r DLBCL
- patient perspectives gathered by 1 patient group, Lymphoma Canada (LC)
- input from public drug plans and cancer agencies that participate in the CDA-AMC review process
- 2 clinical specialists with expertise diagnosing and treating patients with r/r DLBCL
- input from 3 clinician groups, including LC, the Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee, and the Leukemia and Lymphoma Society of Canada (LLSC) Nurses Network
- a review of the indirect evidence from 1 MAIC submitted by the sponsor
- a review of relevant ethical issues related to liso-cel.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One patient group, LC, responded to CDA-AMC's call for patient input on the current review of liso-cel. LC conducted an anonymous online survey from March 18, 2024, to May 13, 2024. The survey included responses from 90 patients with LBCL, primarily in Canada. Of these, 23 patients had experience with liso-cel in the third line or later, and 5 had experience with this therapy in the second line (2 males and 3 females, aged 25 to 44 years).

The majority of LC survey respondents lived in Canada (66%) and were aged 25 to 44 years (30%) or 35 to 44 years (21%), and many (38%) were diagnosed with DLBCL not otherwise specified. They reported significant physical impacts, including fatigue, enlarged lymph nodes, body aches, swelling, and night sweats. Psychosocial effects included stress, difficulty sleeping, fear of disease progression, trouble with daily activities, concentration problems, and depression. LC survey respondents indicated that these challenges severely impacted their daily life, with many struggling to travel and manage work or family obligations.

LC survey respondents reported receiving 1 or 2 lines of treatment for LBCL, with satisfaction decreasing from first-line to third-line treatments. Common treatments included rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP); dose-adjusted etoposide,

prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R); radiation; and various salvage therapies. Patients reported that difficult side effects like fatigue, hair loss, and nausea significantly impacted their quality of life. Many patients reported that access to treatment was challenging, with barriers such as local availability and financial burdens from drug costs and travel expenses.

Most LBCL patients in the LC survey stressed the need for more treatment options. They prioritized longer remission, survival, improved quality of life, and normalizing blood counts. Additionally, they indicated that they were willing to tolerate short-term, nonsevere side effects for new treatments, emphasizing the desire for options with fewer side effects and effective disease control. Based on the input, 5 patients, including 1 residing in Canada, reported that they were receiving liso-cel as second-line treatment and that they were currently in remission. The main side effects observed were decreased appetite, nausea or vomiting, and fever. All patients were experiencing positive outcomes and unanimously recommended it for r/r LBCL.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts indicated that the treatment goal for fit patients with r/r LBCL is cure and long-term survival. The experts noted that fit patients typically receive salvage platinum-containing chemotherapy as second-line treatment, followed by an autologous stem cell transplant in eligible patients who respond to salvage chemotherapy. The experts also noted that many patients are not eligible for stem cell transplant due to age (e.g., those older than 70 to 75 years), comorbidities (e.g., those related to liver, pulmonary, and cardiac function), chemorefractory disease, or inability to mobilize stem cells, and that these criteria vary across treatment centres. The experts noted that patients who experience relapse soon after first-line therapy or who do not experience a response to first-line therapy typically have disease that is chemotherapy refractory, and they are unlikely to benefit from autologous stem cell transplant (ASCT). As such, the experts indicated that the unmet needs of patients would be new treatments that would prevent progression, prolong OS, and improve quality of life, while exposing patients to reduced toxicity. The clinical experts agreed that liso-cel would be used in the second-line setting for patients with DLBCL who are refractory to first-line therapy or relapse within 12 months of the end of first-line therapy. Because axi-cel is approved for the same indication, liso-cel would be in direct competition with axi-cel. The experts noted that they believe it is important for more than 1 CAR T-cell product to be available for this indication, given differences in product availability, manufacturing technique, and safety profile. The clinical experts noted that the patients most likely to benefit from second-line liso-cel would be those with similar characteristics to those in the TRANSFORM trial (e.g., patients who are refractory to or relapse within 12 months of first-line therapy, with adequate performance status and organ function), and that patients would not be suitable for treatment with second-line liso-cel if they have later relapses. The clinical experts indicated that there should be some leeway with age, ECOG performance status, and organ function parameters. The clinical experts indicated that, in clinical practice, response rates on imaging beyond 30 to 90 days and clinical symptoms are used to determine whether a patient is responding or progressing on treatment. The clinical experts indicated that patients receiving liso-cel should be under the care of a clinician (e.g., hematologist or medical oncologist) who can manage toxicity associated with the therapy, within centres that have cellular therapy experience.

The experts also noted that patients should have access to an intensive care unit in case of rare high-grade toxicities, and consultative support from an infectious disease specialist or neurologist if needed.

Clinician Group Input

Three clinician groups, LC (3 clinicians contributed to the input), the OH-CCO Hematology Cancer Drug Advisory Committee (7 clinicians contributed to the input), and the LLSC Nurses Network (5 clinicians contributed to the input), responded to CDA-AMC's call for clinician group input. Overall, the input was aligned with the clinical experts consulted by CDA-AMC.

Clinician groups stated that the primary treatment goals are prolonging life, slowing disease progression, and enhancing quality of life for DLBCL patients, aiming to minimize the need for additional treatments and toxic chemotherapy. As per the clinician groups, available treatments for DLBCL are effective for some patients, but there are unmet needs, particularly for high-risk patients, such as those with primary refractory disease or early relapse. Second-line chemoimmunotherapy and ASCT are successful in a subset of patients, but only about 20% experience durable remission with this approach. CAR T-cell therapy in the second line could address this gap by offering more effective treatment earlier in the disease course, potentially leading to more cures and reducing the need for other salvage strategies.

According to the clinician groups, liso-cel is best suited over salvage chemotherapy and ASCT for those with high-risk disease. Patients with low tumour burden or other DLBCL subtypes may also benefit. Fitness for treatment will be determined by primary hematologists or oncologists based on institutional guidelines, considering factors like performance status and organ function. Clinical practice and trials use various outcomes, including overall response rates and CRRs, PFS, and OS, employing the Lugano criteria for remission confirmation. Response assessment involves restaging CT or PET-CT scans at 1, 3, and 6 months after infusion, with patients sustaining responses beyond 6 to 12 months typically experiencing long-lasting remissions.

The clinician groups agreed that liso-cel is administered as a single infusion; the concept of discontinuation does not typically apply in the context of CAR T-cell treatment. Liso-cel should only be administered in established CAR T-cell therapy programs approved to deliver this therapy.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC Reimbursement Review process. The clinical experts consulted by CDA-AMC provided advice on the potential implementation issues raised by the drug programs (refer to Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The TRANSFORM trial comparator was salvage chemo-immunotherapy (R-DHAP, R-ICE, R-GDP), depending on response, followed by HDCT and HSCT. This is aligned with	Comment from the drug plans to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
standard of care. Yescarta (axi-Cel) received a positive CDA-AMC review for the same indication.	
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)?	The clinical experts indicated that a biopsy-proven DLBCL is sufficient to qualify for liso-cel (if the patient received R-CHOP or similar treatment for FL and then transformed to DLBCL within 12 months). pERC agreed with the clinical experts. pERC also noted 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.
Patients in the TRANSFORM trial were aged 18 to 75 years; had ECOG performance status scores of 1 or lower; had PET-positive disease per Lugano (2014) criteria; and had DLBCL (transformed from indolent NHL, B-cell lymphoma with MYC, and either BCL2, BCL6 or both with DLBCL histology; primary mediastinal B-cell lymphoma, T-cell LBCL, or follicular lymphoma grade 3B). Patients with secondary CNS lymphoma were allowed. Can pERC clarify what is meant by relapsed or refractory disease? Should patients with the following be considered for liso-cel, who were excluded from the trial? • ECOG performance status score > 1 • Primary cutaneous LBCL • Epstein-Barr virus positive diffuse LBCL • Burkitt lymphoma • Richter transformation (transformation from CLL or SLL) • Treatment with any prior gene therapy • Previous CD19 targeted therapy.	The clinical experts noted that there is variability among definitions across trials, but generally, refractory disease refers to patients who do not experience a complete response by the end of first-line therapy, and relapsed disease refers to patients who have an initial response but then experience disease progression within 1 year of completing therapy. pERC agreed with the clinical experts. The clinical experts noted that eligibility for CAR T-cell therapy is based on provincial or program guidelines. The experts indicated that patients with an ECOG performance status of 0 to 2 and rare subtypes of DLBCL, including Richter transformation, should be considered for liso-cel. Burkitt lymphoma is a separate entity which is managed differently, and pERC agreed these patients should not be eligible for liso-cel. The experts also noted that there are limited data if patients with prior gene or CD19-targeted therapy should be considered for liso-cel treatment. pERC noted that there is no evidence to support using liso-cel in patients who received prior CD19-targeted therapy. pERC also 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 generally agreed with the clinical experts but determined that patients with Richter transformation should not be eligible for liso-cel. pERC also noted that patients with CNS involvement were enrolled in the TRANSFORM trial, and thus should be eligible for liso-cel.
The TRANSFORM trial allowed immunochemotherapy as bridging while awaiting liso-cel with R-DHAP, R-ICE, or R-GDP. Could patients be bridged with corticosteroid or other treatments?	The clinical experts noted that patients could receive bridging therapy, if needed to control symptoms or disease burden, with corticosteroids or other treatments (radiation, combination chemotherapy) before receiving liso-cel treatment. pERC agreed with the clinical experts.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
Liso-cel is a single-dose, 1-time treatment, infused at a target dose of 60 × 10^6 to 120 × 10^6 CAR-positive viable T cells.	Comment from the drug plans to inform pERC deliberations.
In the trial, one-fifth of the patients in the liso-cel arm received liso-cel in the outpatient setting. Is it safe to administer liso-cel in the outpatient setting and what criteria can be used to determine outpatient eligibility?	The clinical experts noted that most provinces have outpatient CAR T-cell treatment standards, and in general it would be safe to administer liso-cel in the outpatient setting, if patients are able to reside close to the treatment centre, have an available caregiver, and do not have significant comorbidities or uncontrolled disease burden. pERC agreed with the clinical experts.
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 remains necessary in many parts of Canada. Due to geographical site limitations, patients may need to travel for treatment requiring interprovincial agreements to ensure equitable access.	Comment from the drug plans to inform pERC deliberations.
Consider alignment with prescribing criteria for axi-cel.	Comment from the drug plans to inform pERC deliberations.
Generalizability	
Can patients who recently started second-line chemotherapy (SOC) be allowed to switch to CAR T-cell therapy, provided all criteria are met?	The clinical experts noted that patients who recently started second-line chemotherapy could be allowed to switch to CAR T-cell therapy, at the discretion of the physician and patient and provided they meet the eligibility requirements for second-line CAR T-cell therapy. pERC 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 plans to inform pERC deliberations.
Care provision issues	
Patients will require hospitalization for adverse events and possible intensive care unit admission. CRS may be managed by tocilizumab or siltuximab and steroids.	Comment from the drug plans to inform pERC deliberations.
System and economic issues	
The 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 plans to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
Liso-cel will require a specialized facility eligible for CAR T-cell therapy and patients may require interprovincial travel. This therapy requires facilities that are not available in all provinces. Drug plans (or the sponsor) may need to cover travel expenses for eligible patients.	Comment from the drug plans to inform pERC deliberations.
At the time of PAG input, axi-cel is undergoing pCPA negotiations for the same indication as liso-cel.	Comment from the drug plans to inform pERC deliberations.
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 plans to inform pERC deliberations.

axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HDCT = high-dose chemotherapy; HSCT = hematopoietic stem cell transplant; LBCL = large B-cell lymphoma; NHL = non-Hodgkin lymphoma; PAG = Provincial Advisory Group; pCPA = pan-Canadian Pharmaceutical Alliance; R-DHAP = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; R-GDP = rituximab plus dexamethasone plus gemcitabine plus cisplatin; R-ICE = rituximab plus ifosfamide plus etoposide plus carboplatin; SLL = small lymphocytic lymphoma; SOC = standard of care.

Clinical Evidence

Systematic Review

Description of Studies

One trial, the TRANSFORM trial (N = 184), met the inclusion criteria for the systematic review conducted by the sponsor. The objective of the TRANSFORM trial was to assess the efficacy and safety of liso-cel 100 × 10^6 CAR T cells, 1-time IV infusion, compared with SOC (defined as 3 cycles with 1 of 3 prespecified salvage immunochemotherapy regimens followed, depending on response, by 1 cycle of high-dose chemotherapy and autologous HSCT) in adult patients with r/r LBCL. Patients in the liso-cel group could receive bridging therapy with 1 of the 3 defined salvage immunochemotherapy regimens allowed in the SOC group during liso-cel manufacturing, if needed. The trial enrolled patients who had LBCL that was refractory to first-line therapy or relapsed within 12 months after initial response to first-line therapy (including an anthracycline and an anti-CD20 monoclonal antibody), who were considered candidates for autologous HSCT, with ECOG scores of 1 or lower. The approved Health Canada indication and reimbursement request aligned with the trial population. The outcomes most relevant to the CDA-AMC review included the primary outcome of EFS per independent review committee (IRC), and secondary outcomes of CRR, PFS, OS, HRQoL, and safety. The HRQoL outcomes included the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status score and Functional Assessment of Cancer Therapy Lymphoma Subscale (FACT-LymS) total score. The trial population was predominately white (approximately 59%), male (57%), and had a median age of 59 years (range, 20 to 75 years). Most patients had an ECOG performance status of 0 (52.0%) or 1 (47%), indicating good overall performance, a second-line Age-Adjusted International Prognostic Index (sAAIPI) of 0 or 1 (60%), had disease that was refractory to or relapsed with their last therapy (74%; 26% respectively), and

had the LBCL subtype of DLBCL not otherwise specified (56%), followed by HGBCL (23%), PMBCL (9%), and DLBCL from transformed indolent lymphoma (8%). The liso-cel group had a lower proportion of male patients (47.8% versus 66.3%), and a higher proportion of patients who were chemorefractory (28.3% versus 19.6%) than the SOC group.

Efficacy Results

Only those efficacy outcomes and analyses of subgroups identified as important to this review are reported. Efficacy and safety data were evaluated at the second interim analysis (data cut-off date: March 8, 2021), primary analysis (data cut-off date: May 13, 2022) and final analysis (data cut-off date: October 23, 2023). The primary efficacy outcome of EFS was met at second interim analysis and was presented descriptively (i.e., not included in the hierarchical testing strategy) in the primary analysis. Therefore, hypothesis testing on the key secondary outcomes of CRR, PFS, and OS was performed hierarchically in the primary analysis.

Event-Free Survival

At the time of the second interim analysis, the median duration of follow-up in all patients was 6.2 months (interquartile range [IQR], 4.4 to 11.5), and EFS events had been reported for 35 patients (38.0%) in the liso-cel group and 63 patients (68.5%) in the SOC group. The median EFS was 10.1 months (95% CI, 6.1 to NE) in the liso-cel group versus 2.3 months (95% CI, 2.2 to 4.3) in the SOC group (1-sided P value < 0.0001), with a between-group HR of 0.35 (95% CI, 0.23 to 0.53). The results of sensitivity analyses were consistent with the primary analysis. The KM-estimated probability of EFS at 12 months was 44.5% (95% CI, 29.4% to 59.6%) for the liso-cel group versus 23.7% (95% CI, 13.4% to 34.1%) for the SOC group, with a between-group difference of 20.8% (95% CI, 2.5% to 39.1%).

At the time of the primary efficacy analysis, the median duration of follow-up in all patients was 17.5 months (IQR, 0.9 to 37), and EFS events had been reported in 44 patients (47.8%) in the liso-cel group and 71 patients (77.2%) in the SOC group. The median EFS was not reached (NE; 95% CI, 9.5 to NE) in the liso-cel group versus 2.4 months (95% CI, 2.2 to 4.9) in the SOC group (HR = 0.36; 95% CI, 0.24 to 0.52). The KM-estimated probability of EFS at 12 months was consistent with the second interim analysis, with a between-group difference of 34.6% (95% CI, 21.2 to 48.0).

At the final analysis, the median duration of follow-up of 33.9 months (IQR, 11.6 to 39.2), and EFS events had been reported in [redacted] patients in the liso-cel group and [redacted] patients in the SOC group. The median EFS was 29.5 months (95% CI, 9.5 to NE) in the liso-cel group and 2.4 months (95% CI, 2.2 to 4.9) in the SOC group, with a between-group HR of 0.38 (95% CI, 0.259 to 0.542). The KM-estimated probability of EFS at 12 months was consistent with the interim and primary analysis, and at 36 months was 45.8% (95% CI, 35.2% to 56.5%) for the liso-cel group versus 19.1% (95% CI, 11.0% to 27.3%) for the SOC group, with a between-group difference of 26.7% (95% CI, 13.3% to 40.1%).

At the second interim analysis, the efficacy results for EFS were consistent across the subgroup analyses by histological subtypes, use of bridging therapy (data not shown) and prior response status, in favour of liso-cel. In general, the results of the subgroup analyses were consistent across all data cut-offs.

Complete Response Rate

At the time of the primary analysis, the CRR in the liso-cel group was 73.9% (95% CI, 63.7% to 82.5%) versus 43.5% (95% CI, 33.2% to 54.2%; stratified 1-sided P < 0.0001), with a between-group difference of 29.3% (95% CI, 16.4% to 42.2%). The CRR remained consistent at the final analysis. The results of sensitivity analyses were consistent with the primary analysis.

Progression-Free Survival

At the time of the primary analysis, PFS events had been reported for 37 patients (40.2%) in the liso-cel group and 52 patients (56.5%) in the SOC group. The median PFS was not reached (95% CI, 12.6 to NE) in the liso-cel group versus 6.2 months (95% CI, 4.3 to 8.6) in the SOC group (1-sided P < 0.0001), with a between-group HR of 0.40 (95% CI, 0.26 to 0.62). The results of sensitivity analyses were consistent with the primary analysis. The KM-estimated probability of PFS at 12 months was 63.1% (95% CI, 53.0% to 73.3%) in the liso-cel group versus 31.2% (20.2% to 42.3%) in the SOC group, with a between-group difference of 31.9% (95% CI, 16.9% to 46.9%).

At the time of the final analysis, PFS events had been reported in [redacted] patients in the liso-cel group and [redacted] patients in the SOC group. The median PFS was not reached (95% CI, 12.6 to NE) in the liso-cel group and 6.2 months (95% CI, 4.3 to 8.6) in the SOC group. The KM-estimated probability of PFS at 12 months was consistent with the primary analysis, and at 36 months was 50.9% (95% CI, 39.9% to 62.0%) for the liso-cel group versus 26.5% (95% CI, 15.9% to 37.1%) in the SOC group, with a between-group difference of 24.4% (95% CI, 9.1% to 39.7%).

Overall Survival

By the primary analysis, there were 28 [redacted] deaths in the liso-cel group and 38 [redacted] deaths in the SOC group. The median OS was not reached (95% CI, 29.5 to NE) in the liso-cel group versus 29.9 months (95% CI, 17.9 to NE) months in the SOC group (1-sided P = 0.0987), with a between-group HR of 0.72 (95% CI, 0.44 to 1.18). The KM-estimated probability of being alive at 12 months was 83.4% (95% CI, 75.7% to 91.1%) in the liso-cel group versus 72.0% (95% CI, 62.7% to 81.3%) in the SOC group, with a between-group difference of 11.4% (95% CI, −0.7% to 23.5%).

At the time of final analysis, there were 34 [redacted] deaths in the liso-cel group and 42 [redacted] deaths in the SOC group. The median OS was not reached for both treatment groups (liso-cel: 95% CI, 42.8 to NE; SOC: 95% CI, 18.2 to NE), with a between-group HR of 0.76 (95% CI, 0.481 to 1.19). The KM-estimated probability of OS at 12 months was consistent with the primary analysis, and at 36 months was 62.8% (95% CI, 52.7% to 72.9%) in the liso-cel group versus 51.8% (95% CI, 41.2% to 62.4%) in the SOC group, with a between-group difference of 11.0% (95% CI, −3.7% to 25.7%)

Health-Related Quality of Life

At baseline, EORTC QLQ-C30 global health status scores were similar between treatment groups, and there were clinically meaningful changes observed (defined by the sponsor as change in the score from baseline of ≥ 5 points) in both groups at 6 months. The between-group least squares (LS) mean difference in change from baseline was [redacted]. At baseline, total FACT-LymS scores were

similar between groups. At 6 months, there was no clinically meaningful change (defined by the sponsor as change in the score from baseline of ≥ 3 points) observed in the liso-cel group, and a clinically meaningful change observed in the SOC group. The between-group LS mean difference in change from baseline was [redacted]

Harms Results

Harms data reported in this section are from the primary analysis (data cut-off date: May 13, 2022). There were no significant changes in the incidence of treatment-emergent adverse events (TEAEs) from the time of the interim analysis to the time of the primary analysis. Almost all patients in the trial reported at least 1 TEAE (liso-cel: 100%; SOC: 98.9%). The most frequently reported TEAEs of any grade in both treatment groups were neutropenia (liso-cel: 82.6%; SOC: 54.9%), anemia (liso-cel: 67.4%; SOC: 68.1%), thrombocytopenia (liso-cel: 59.8%; SOC: 72.5%), and nausea (liso-cel: 53.3%; SOC: 58.2%). Of these TEAEs, a numerically higher proportion of neutropenia was reported in patients taking liso-cel and a higher proportion of thrombocytopenia was reported in patients taking SOC. Most patients in both groups reported at least 1 grade 3 or 4 TEAE (liso-cel: 92.4%; SOC: 89.0%). The incidence of grade 3 or 4 neutropenia (liso-cel: 81.5%; SOC: 51.6%) and lymphopenia (liso-cel: 26.1%; SOC: 9.9%) was numerically higher in the liso-cel group versus the SOC group. The incidence of serious TEAEs was similar between groups (liso-cel: 47.8%; SOC: 48.4%). The most frequently reported serious TEAEs were CRS (liso-cel: 13%; SOC: 0%), febrile neutropenia (liso-cel: 7.6%; SOC: 9.9%), pyrexia (liso-cel: 6.5%; SOC: 7.7%), and neutropenia (liso-cel: 7.6%; SOC: 4.4%). The frequency of these TEAEs was similar between groups, although a higher proportion of CRS was reported in patients taking liso-cel. Four patients (4.4%) in the SOC group experienced TEAEs leading to treatment withdrawal. No patients in the liso-cel group had a TEAE that led to withdrawal of the study drug (including bridging therapy and lymphodepleting chemotherapy). Deaths were reported in 14.1% of patients in the liso-cel group and 8.8% of patients in the SOC group. The majority of deaths in both groups were attributed to disease progression (liso-cel: 7.6%; SOC: 4.4%), followed by TEAEs (liso-cel: 2.2%; SOC: 4.4%). A numerically higher proportion of notable TEAEs were reported in patients taking liso-cel (90.2%) than SOC (75.8%). The most frequently reported notable harms of any grade were neurologic toxicity (liso-cel: 64.1%; SOC: 62.6%), CRS (liso-cel: 48.9%; SOC: 0.0%), prolonged cytopenia (liso-cel: 43.5%; SOC: 3.3%), and iiNT (liso-cel: 10.9%; SOC: not applicable). These events occurred more frequently in patients taking liso-cel, except for neurologic toxicity, which was similar in both groups.

Critical Appraisal

The TRANSFORM trial randomization procedures, including stratification by response to first-line therapy (relapsed versus refractory) and sAAIPI (0 to 1 versus 2 to 3) were appropriate and conducted by interactive response technology. The liso-cel group had a lower proportion of male patients (47.8% versus 66.3%) and a higher proportion of patients who were chemorefractory (28.3% versus 19.6%) than the SOC group. According to the clinical experts consulted by CDA-AMC, it was unlikely that these imbalances confounded the effect between treatment and outcomes. Treatment period discontinuation was numerically higher in the SOC group (59.8%) versus the liso-cel group (12.0%), with lack of efficacy being the most common reason (SOC: 30%; liso-cel: 0%). The open-label design introduced a potential bias in the assessment of efficacy for EFS, CRR, and PFS, and a potential reporting bias for the subjective outcomes of HRQoL

and safety. However, this bias was mitigated by the use of IRC for EFS, CRR, and PFS. To minimize the risk of differential measurement error, the trial performed tumour assessments using Lugano criteria, and radiographic scans were assessed by IRC. For the HRQoL and safety outcomes, the source of bias could overestimate the efficacy of liso-cel. Sample size and power calculations were based on EFS, and the trial was powered to detect significant differences between groups for EFS. Prespecified analyses of EFS, CRR, PFS, and OS were appropriately controlled for multiple comparisons. All other analyses were descriptive. This included the HRQoL outcomes of EORTC QLQ-C30 and FACT-LymS scores, which were deemed clinically important outcomes for the disease. The sample size for most subgroup analyses of interest appeared large enough to detect subgroup differences for EFS, except for DLBCL transformed from indolent NHL, which may not have been powered to detect subgroup differences. The findings of the sensitivity analyses for the primary outcome of EFS were consistent with the primary analysis. The proportional hazards assumption was assessed via inspection of Schoenfeld residuals, and the trial authors stated that there was no evidence of a violation of this assumption. The median OS was not reached in either treatment group at the primary and final analysis, due to the small number of OS events. As such, longer follow-up is needed to inform the true effect of liso-cel compared with SOC on survival. In addition, patients were permitted to receive posttreatment anticancer medications after study treatment had been discontinued (liso-cel: 34.8%; SOC: 70.7% [65 patients, of which 61 patients were approved to cross over to liso-cel]), which were not balanced between groups and may influence the assessment of OS due to crossover bias. The certainty of evidence for the HRQoL outcomes was limited due to risk of bias resulting from missing outcomes data, both at baseline and at the selected follow-up times, and imprecision due to the 95% CI for the between-group difference, including the possibility of both benefit and little to no difference. However, the direction and extent of bias is unclear, and as such, the potential differences in patients' HRQoL remains very uncertain.

The population requested for reimbursement aligns with the approved Health Canada indication. The dosing and administration of liso-cel was consistent with the approved product monograph. According to the clinical experts consulted by CDA-AMC, the eligibility criteria and baseline characteristics of the TRANSFORM trial were generalizable to adults with r/r LBCL in the Canadian setting, although the trial did not include patients with a poor ECOG performance status. The clinical experts noted that only enrolling patients with ECOG scores of 0 or 1 is not entirely representative of patients with r/r LBCL in Canada, as they expect to see patients with higher ECOG scores in their practice. The clinical experts also noted that ASCT eligibility is highly variable in clinical practice across Canada as there is no standardized criteria to identify patients. The trial included outcomes that were important to patients and clinicians. The patient group indicated that stopping disease progression, prolonging life, improving HRQoL, and reducing treatment side effects are important to them.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (referring to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance was unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for EFS, CRR, PFS, OS, and EORTC QLQ-C30 global health status score were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review, and ranges identified in the literature for EORTC QLQ-C30. The reference point for the certainty of the evidence assessment for FACT-LymS total score was set according to the presence or absence of an important effect based on a threshold suggested by the sponsor that was informed by the literature.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- survival outcomes (EFS, PFS, and OS)
- CR
- HRQoL outcomes (EORTC QLQ-C30 global health status and FACT-LymS scores).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for liso-cel versus SOC.

Table 3: Summary of Findings for Liso-Cel Versus SOC for Patients With Relapsed or Refractory Large B-cell Lymphoma – TRANSFORM Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			SOC	Liso-cel	Difference		
EFS (ITT set, second interim analysis data cut-off date of March 8, 2021)							
Probability of EFS at 12 months Median follow-up for all patients: 6.2 months	184 (1 RCT)	NA	237 per 1,000	445 per 1,000 (294 to 596)	208 per 1,000 (25 more to 391 more)	High[a]	Liso-cel results in a clinically important increase in the probability of EFS at 12 months when compared with SOC.
EFS (ITT set, final analysis data cut-off date of October 23, 2023)							
Probability of EFS at 36 months Median follow-up for all patients: 33.9 months	184 (1 RCT)	NA	191 per 1,000	458 per 1,000 (352 to 565)	267 per 1,000 (133 more to 401 more)	High[a]	Liso-cel results in a clinically important increase in the probability of EFS at 36 months when compared with SOC.
CRR (ITT set, primary analysis data cut-off date of May 13, 2022)							
Complete response rate Median follow-up for all patients: 17.5 months	184 (1 RCT)	NR	435 per 1,000	739 per 1,000 (637 to 825)	293 more per 1,000 (164 more to 422 more)	High[b]	Liso-cel results in a clinically important increase in the proportion of patients who experience a complete response when compared with SOC.
PFS (ITT set, primary analysis data cut-off date of May 13, 2022)							
Probability of PFS at 12 months Median follow-up for all patients: 17.5 months	184 (1 RCT)	NA	312 per 1,000	631 per 1,000 (530 to 733)	319 per 1,000 (169 more to 469 more)	High[a]	Liso-cel results in a clinically important increase in the probability of PFS at 12 months when compared with SOC.
PFS (ITT set, final analysis data cut-off date of October 23, 2023)							
Probability of PFS at 36 months Median follow-up for all patients: 33.9 months	184 (1 RCT)	NA	265 per 1,000	509 per 1,000 (399 to 620)	244 per 1,000 (91 more to 397 more)	Moderate[c]	Liso-cel likely results in a clinically important increase in the probability of PFS at 36 months when compared with SOC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			SOC	Liso-cel	Difference		
OS (ITT set, primary analysis data cut-off date of May 13, 2022)							
Probability of survival at 12 months Median follow-up for all patients: 17.5 months	184 (1 RCT)	NA	720 per 1,000	834 per 1,000 (757 to 911)	114 per 1,000 (7 fewer to 235 more)	Moderate[d]	Liso-cel likely results in a clinically important increase in the probability of survival at 12 months when compared with SOC.
OS (ITT set, final analysis data cut-off date of October 23, 2023)							
Probability of survival at 36 months Median follow-up for all patients: 33.9 months	184 (1 RCT)	NA	518 per 1,000	628 per 1,000 (527 to 729)	110 per 1,000 (37 fewer to 257 more)	Moderate[d]	Liso-cel likely results in a clinically important increase in the probability of survival at 36 months when compared with SOC.
EORTC QLQ-C30 global health status score (HRQoL set, primary analysis data cut-off date of May 13, 2022)							
LS mean change from baseline in global health status; scores range from 0 to 100, with higher scores indicating better health status Time point: 6 months	36 (1 RCT)	NA				Very low[e]	The evidence is very uncertain about the effect of liso-cel on global health status at 6 months when compared with SOC.
FACT-LymS total score (HRQoL set, primary analysis data cut-off date of May 13, 2022)							
LS mean change from baseline in symptoms score; scores range from 0 to 60, with higher scores indicating lower levels of symptoms Time point: 6 months	37 (1 RCT)	NA				Very low[f]	The evidence is very uncertain about the effect of liso-cel on symptoms at 6 months when compared with SOC.

CI = confidence interval; CRR = complete response rate; EFS = event-free survival; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-LymS = Functional Assessment of Cancer Therapy Lymphoma Subscale; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HRQoL = health-related quality of life; ITT = intention-to-treat; liso-cel = lisocabtagene maraleucel; LS = least squares; NA = not applicable; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SOC = standard of care.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. The between-group absolute effects for EFS, CRR, PFS, and OS at the time points included in the table were requested by CDA-AMC from the sponsor to facilitate the GRADE assessment.

[a]A between-group absolute risk difference of 15% and 10% (150 and 100 fewer or more events per 1,000 patients) at 12 and 36 months, respectively, was clinically important according to the clinical experts. The point estimate and entire confidence exceeded the threshold.

[b]A between-group absolute risk difference of 15% (150 fewer or more events per 1,000 patients) was clinically important according to the clinical experts. The point estimate and entire confidence interval exceeded the threshold.

[c]Rated down 1 level for serious imprecision due to the 95% CI for the between-group absolute risk difference including the possibility of an important benefit and a trivial effect when compared with SOC; a between-group absolute risk difference of 10% (100 fewer or more events per 1,000 patients) at 36 months was clinically important according to the clinical experts.

[d]Rated down 1 level for serious imprecision due to the 95% CI for the between-group absolute risk difference including the possibility of an important benefit and little to no difference when compared with SOC; a between-group absolute risk difference of 10% and 5% (100 and 50 fewer or more events per 1,000 patients) at 12 and 36 months, respectively, was clinically important according to the clinical experts.

[e]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both benefit and little to no difference when compared with SOC; based on the ranges identified in the literature and suggested by the clinical experts, a 10-point change from baseline in EORTC QLQ-C30 scale score was considered clinically important. Rated down 2 levels for risk of bias due to missing outcome data.

[f]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both harm and little to no difference when compared with SOC; based on the sponsor's suggestion that was informed by ranges identified in the literature, a 3-point change from baseline in FACT-LymS total score was considered clinically important. Rated down 2 levels for risk of bias due to missing outcome data.

Source: TRANSFORM Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence and the sponsor's response to requested additional information.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

The sponsor submitted 1 matching-adjusted indirect comparison (MAIC)[17] to fill gaps in the comparative evidence for other treatments of interest for r/r LBCL, and 1 indirect treatment comparison (ITC) using the Bucher approach was conducted to inform the pharmacoeconomic model. The MAIC is the focus of this report. The authors did not report a systematic literature search or describe the methods for study selection, data extraction, and quality assessment for both ITCs.

Description of Studies

A feasibility assessment using study design, eligibility criteria, baseline characteristics, and outcomes was performed and determined the TRANSFORM and ZUMA-7 trials to be comparable enough to allow for the indirect comparison between liso-cel and axi-cel on key efficacy and safety outcomes through unadjusted (Bucher) or population-adjusted ITC methods. MAIC and simulated treatment comparison approaches were considered feasible to minimize potential sources of bias while comparing these therapies, and the MAIC approach was preferred by the investigators over simulated treatment comparison. The MAIC assessed the comparative efficacy and safety of liso-cel and axi-cel using individual patient data (IPD) from the TRANSFORM trial (for liso-cel) and summary-level data from the ZUMA-7 trial in patients with r/r LBCL who were intended for transplant. Outcomes of interest included EFS, CRR, PFS, OS, and TEAEs. IPD from the TRANSFORM trial were adjusted to match the marginal distribution (e.g., mean, variance) of clinical factors among patients from the ZUMA-7 trial. For EFS, PFS, and OS, an anchored MAIC was performed using a Cox proportional hazards model to estimate HRs of liso-cel versus axi-cel. Generalized linear models for CRR were used to estimate ORs. For the unanchored analysis of safety outcomes, weighted log odds for liso-cel were estimated in the TRANSFORM trial by fitting an intercept-only logistic regression model with MAIC adjustment weights. Point estimates (HRs or odds ratios [ORs]) and 95% CIs were reported for all analyses. The Bucher ITC used a mixture cure modelling framework to derive relative efficacy estimates for EFS and OS, and these were reported as ORs and 95% CIs.

Efficacy Results

Based on the anchored MAIC, the results did not support a clinically meaningful difference between liso-cel and axi-cel for EFS, CRR, PFS, and OS. The Bucher ITC results for EFS and OS were consistent with the MAIC findings.

Harms Results

Based on the unanchored MAIC, the results showed no difference between liso-cel and axi-cel for grade 3 or greater TEAE events, prolonged cytopenia, severe infections, and hypogammaglobulinemia. The results for CRS, neurologic toxicity, pyrexia, and encephalopathy favoured liso-cel.

Critical Appraisal

For the MAIC and Bucher ITC, the authors did not report a systematic literature search, describe their methods for data extraction, or conduct quality assessment of the TRANSFORM and ZUMA-7 trials. The

MAIC included relevant outcomes identified by the CDA-AMC team (EFS, CRR, PFS, OS, and safety). However, because data for several safety outcomes (e.g., CRS) were very limited or not available for the SOC arm in both the TRANSFORM and ZUMA-7 trials, an anchored MAIC was not feasible. Therefore, an unanchored MAIC was conducted for the safety outcomes. The Bucher ITC only assessed EFS and OS. For the MAIC, to account for between-study differences in patient baseline characteristics, several potentially relevant clinical factors (i.e., treatment effect modifiers) were matched in the weighting process. The methods used to identify and rank the clinical factors were considered appropriate. The process involved a systematic literature review and a panel of 3 clinical experts to validate the selection and ranking of the treatment effect modifiers based on their strength to influence the specific outcomes under study for patients with r/r LBCL. For the anchored MAIC efficacy analysis, 10 clinical factors were adjusted for, and sensitivity scenarios — which included all relevant clinical factors available (total = 14) — were conducted to test robustness of the findings. After matching and adjusting for the 11 factors in the primary efficacy analyses, imbalances remained for ECOG performance status and cell of origin, although the clinical experts consulted by CDA-AMC did not think these imbalances could bias the results. The authors noted that although the definition of EFS was similar between trials, some EFS events between randomization and treatment were treated differently. Among randomized patients who did not receive treatment in ZUMA-7, the majority were assigned an event immediately (i.e., at time 0, or day 1, of the KM curves) for the ITT analysis, given commencement of new lymphoma therapy and lack of evaluable disease assessment. This was considered as a potential source of bias favouring axi-cel. In contrast, the date of imaging that served as the basis of starting new antineoplastic therapy was used in the TRANSFORM trial (rather than day 1, which was used in the ZUMA-7 trial). Overall, the magnitude and direction of potential bias due to imbalances in the efficacy estimates cannot be predicted. Among the 17 identified clinical factors for the unanchored MAIC safety analyses, 2 factors (prior HSCT and number of prior lines of therapy) were excluded because they were not relevant to the second-line proposed indication; 6 factors (bulky disease, metabolic tumour volume, serum albumin, interleukin-6, fibrinogen level, and C-reactive protein) were not considered due to lack of reporting in the ZUMA-7 trial; and lactate dehydrogenase at baseline and bridging therapy were excluded due to differences in definitions between the TRANSFORM trial and ZUMA-7 trial. ECOG performance status was also not included in the MAIC, which was considered by the clinical experts consulted by CDA-AMC to be an important potential effect modifier. In addition, the TEAE reporting window differed between trials. Events from bridging therapy were included only for the TRANSFORM trial, potentially biasing the safety comparison against liso-cel. Following the weighting process, the effective sample size (ESS) for all efficacy outcomes declined by more than 50% of the original sample size in the comparison with axi-cel. This declined further for the adjusted safety analyses and sensitivity analyses, which included all relevant clinical factors available. These reductions in the ESS meant the final matched patient population was highly selective when compared to the original patient population and may lead to uncertainty in estimated treatment effects. Because there were no major generalizability issues in the axi-cel population compared to the liso-cel population, the concern for bias due to influential subgroups is less of a concern. Overall, the relative efficacy and safety estimates were subject to uncertainty due to imprecision, and the unanchored safety analysis was also subject to imbalances in potential effect modifiers and prognostic factors.

The Bucher ITC, which was used to inform the economic model, showed similar results to the MAIC for EFS and OS. The main limitation of this approach was that the ITC estimates did not adjust for between-study differences in patient baseline characteristics. Because there were notable baseline differences between the TRANSFORM and ZUMA-7 trials, as described in the MAIC approach, definitive conclusions based on the Bucher results are not recommended.

Studies Addressing Gaps in the Evidence From the Systematic Review

One study that was submitted by the sponsor was excluded because it did not match the patient population of the proposed Health Canada indication.

Conclusions

Evidence from 1 phase III, open-label RCT (the TRANSFORM trial) reported on outcomes that were important to both patients and clinicians. The trial showed high certainty of evidence that treatment with liso-cel results in a clinically meaningful increase in EFS at 12 and 36 months and in CRR, compared to SOC in adults with r/r LBCL. The trial also showed high and moderate certainty of evidence that liso-cel results in a clinically meaningful increase in PFS at 12 months and 36 months, respectively. At the time of the final analysis, median OS had not been reached in either group, and no definitive conclusions can be drawn on HRQoL due to concerns of imprecision and missing outcome data. There were no new safety signals identified and the safety of liso-cel was consistent with the known safety profile of the drug. The results of the ITC did not support a clinically meaningful difference between liso-cel and axi-cel for EFS, CRR, PFS, and OS, but were suggestive of a more favourable safety profile for liso-cel; however, these estimates were subject to uncertainty due to imprecision and imbalances in potential effect modifiers and prognostic factors.

Ethical Considerations

Patient and clinician group and drug program input, as well as consultation with clinical experts and clinical and economic reviewers, was reviewed to identify ethical considerations specific to the use of liso-cel for the treatment of adults with the indication of DLBCL not otherwise specified, PMBCL, HGBCL, and DLBCL arising from follicular lymphoma, who have disease that is refractory to first-line chemoimmunotherapy or who experience relapse within 12 months of first-line chemoimmunotherapy, and who are candidates for autologous HSCT.

- **Treatment options for LBCL and patient experiences:** LBCL is a heterogeneous and aggressive subtype of NHL, which is the most common type of blood cancer. These burdens are further exacerbated by geographic barriers to accessing treatment and variability in reimbursement and financial supports across jurisdictions. Overall, 30% to 50% of patients with LBCL become refractory or experience relapse following first-line treatment with SOC chemotherapy. Approximately 50% of those with r/r LBCL are eligible for autologous HSCT in the second line. Patients who are refractory or experience relapse after 2 or more lines of therapy may be eligible for 3 CAR T-cell therapies currently approved for use in the third line, which include liso-cel, axi-cel, and tisagenlecleucel (tisa-

cel). Additionally, axi-cel is under negotiation with pCPA for a similar indication in the same line of therapy currently under review. LBCL and existing treatments options are physically, psychosocially, and financially burdensome for patients and their caregivers. Patient and clinician group input received for this review identified that patients' goals include the desire for more treatment options, including in earlier lines of therapy, which offer advantages such as longer remission and survival (including cure) as well as improved quality of life and fewer side effects.

- **Evidentiary uncertainties related to liso-cel for r/r LBCL:** The safety and efficacy of liso-cel compared to SOC (defined as 3 cycles with 1 of 3 prespecified salvage immunochemotherapy regimens followed, depending on response, by 1 cycle of high-dose chemotherapy and autologous HSCT) in adult patients with r/r LBCL was evaluated in the pivotal phase III, open-label, randomized TRANSFORM trial. Patients in the liso-cel group could receive bridging therapy with 1 of the 3 defined salvage immunochemotherapy regimens allowed in the SOC group during liso-cel manufacturing, if needed. The conclusions from the Clinical Review of the TRANSFORM trial were that treatment with liso-cel resulted in a clinically meaningful increase in the primary end point of EFS at 12 and 36 months and CRR compared with SOC, with a high certainty of evidence. At the time of the final analysis, median OS had not been reached in either group, and no definitive conclusions can be drawn on HRQoL due to concerns of imprecision and missing outcome data. No new safety signals were reported. The sponsor also submitted comparative evidence in the form of a MAIC and an ITC used to inform the pharmacoeconomic model, with the Clinical Review focusing on the MAIC. The MAIC assessed the comparative efficacy and safety of liso-cel (from the TRANSFORM trial) with that of axi-cel (from the ZUMA-7 trial). The Clinical Review concluded that results of the MAIC did not demonstrate a clinically meaningful difference between liso-cel and axi-cel for efficacy end points including EFS, CRR, PFS, and OS. However, the results of the MAIC were suggestive of a more favourable safety profile for liso-cel, including lower rates of serious adverse events such as CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). However, the Clinical Review reported that there is uncertainty in these estimates due to imprecision and imbalances in potential effect modifiers and prognostic factors. The TRANSFORM trial did not yield long-term safety and efficacy data. Clinical experts stated that they were comfortable recommending liso-cel in the second line based on currently available evidence, but they noted a desire for long-term data on safety, efficacy, and comparative effectiveness (especially with axi-cel) to further inform clinical decision-making. Together, the uncertainties in comparative effectiveness and long-term effectiveness and safety have ethical implications for informed consent. As described in the Pharmacoeconomic Review report, uncertainty about long-term safety, efficacy, and comparative effectiveness also presents challenges for pharmacoeconomic assessments. This presents challenges for understanding the opportunity costs of implementing liso-cel and associated resource allocation decisions at the health system level.
- **Risk of secondary T-cell lymphomas:** CAR T-cell therapies, including liso-cel, may pose a rare, class-level risk of secondary malignancy of developing CAR-positive T-cell lymphoma. Although the development of CAR-positive T-cell lymphoma was not observed in the TRANSFORM trial, clinical experts acknowledged the possibility of this risk with liso-cel. However, the clinical experts suggested

that, based on currently available evidence, this risk would not alter their decision-making regarding liso-cel, given the rarity of the risk, survival advantage offered by liso-cel over SOC in the second line, and lack of available alternatives in the third line. They also noted that currently available second-line treatments, including HSCT, also pose the risk of secondary malignancies. Additionally, clinical experts noted the importance of informing patients of this risk, which requires lifelong monitoring as described in the product monograph, during consent conversations.

- **Increasing therapeutic options and access:** Clinical experts and clinician group input noted that offering liso-cel in the second line could increase access to more effective therapy over SOC for patients with LBCL earlier in the disease course. Notably, they discussed how patients who experienced treatment failure with second-line therapy may no longer be sufficiently fit to be eligible to receive and withstand the intensity of CAR T-cell therapy in the third line. They noted that offering liso-cel in earlier lines of therapy could potentially help to address some geographic barriers to accessing CAR T-cell therapy for patients residing far from treatment centres, given that patients have to be sufficiently well to endure more significant travel, including potential interjurisdictional travel. Clinical experts and clinician group input noted that CAR T-cell therapy in the second line is advantageous over auto-HSCT, as it tends to be less burdensome for patients and eliminates the need for salvage chemotherapy and stem cell collection. They also noted the benefit of having liso-cel in the second line for patients who were ineligible for transplant but were otherwise fit for CAR T-cell therapy. Clinical experts noted that having access to multiple CAR T-cell therapies for r/r LBCL in the second line would be preferable, as liso-cel and axi-cel have different toxicity profiles and would thus allow choice of therapy to be tailored to a patient's needs, would increase access with additional options, and/or would reduce the need for resources (e.g., ICU care, hospitalizations) to address severe toxicities. They noted that liso-cel may be a preferable option for patients who are older or may have comorbidities that would make them less likely to tolerate axi-cel.
- **Outpatient delivery of liso-cel**: Clinical experts noted that they would offer liso-cel in the outpatient setting (if available) because of what they perceived to be a relatively favourable safety profile (characterized by lower rates of CRS and ICANS as compared to axi-cel). However, a more favourable safety profile for liso-cel was not supported by the Clinical Review assessment of the MAIC, given uncertainty due to methodological limitations. The clinical experts suggested that outpatient delivery could improve quality of life for patients and help expand capacity to deliver CAR T-cell therapy by requiring fewer institutional resources. They described that the choice of outpatient treatment should be determined on a case-by-case basis (most likely for patients who lived close to treatment centres, had a reliable caregiver, and those who did not have significant comorbidities or uncontrolled tumour burden). The clinical experts emphasized the importance of having a reliable caregiver to facilitate safe outpatient delivery and recovery. However, they also highlighted the importance of continuing to offer inpatient treatment with CAR T-cell therapy, given that exclusive outpatient delivery would disadvantage patients without reliable caregiver support or those otherwise ineligible for outpatient treatment. They noted that, in the future, outpatient delivery might also permit the expansion of CAR T-cell therapy delivery to some additional centres that are currently unable to offer CAR T-cell therapy due to capacity constraints (e.g., bed shortages).

- **Health system considerations associated with the use of liso-cel in earlier lines of therapy for LBCL:** Clinical experts reiterated that Canada still lacks sufficient health systems capacity to deliver CAR T-cell therapy to all eligible patients, given the resource-intensive, personnel-intensive, and infrastructure-intensive nature of CAR T-cell therapy. There are ethical, equity, and access challenges arising from existing limitations in manufacturing and delivery capacity for CAR T-cell therapy, which raise questions related to the fair and equitable prioritization of access to limited therapy. However, clinical experts noted that the use of liso-cel for the treatment of LBCL in the second line may reduce demand for CAR T-cell therapy in the third line. They also noted that, as the use of liso-cel in the second line was meant to replace auto-HSCT, health systems resource (e.g., infrastructure and personnel) utilization may be attenuated by resources saved by not conducting transplants. Nonetheless, they cautioned that the high cost of liso-cel and CAR T-cell therapies raised ethical considerations about fair and equitable resource allocation and opportunity costs within and beyond the health care system. Clinical experts also reiterated the importance of offering support for patients and caregivers who reside in rural or remote communities to reduce geographic and financial barriers to equitable access to liso-cel, which is currently expected to be offered at [redacted] specialized treatment centres in [redacted] jurisdictions. The sponsor's implementation plan indicates a plan to offer a travel assistance program to cover travel and accommodation expenses for patients and caregivers for a period before and following administration of liso-cel.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with LBCL refractory to first-line treatment or who have relapsed within 12 months, and are eligible for transplant
Treatment	Liso-cel
Dose regimen	Single infusion containing 60 × 10^6 to 120 × 10^6 CAR-positive viable T cells
Submitted price	$501,900.00 per patient per infusion
Submitted treatment cost	$508,934[a] per patient per infusion
Comparators	• Axi-cel • SOC, aligned with the TRANSFORM trial, includes salvage chemotherapy with platinum-based chemoimmunotherapy regimens which may be followed by high-dose chemotherapy and autologous HSCT
Perspective	Canadian publicly funded health care payer

Component	Description
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data sources	Efficacy (EFS, OS) of liso-cel and SOC informed by the TRANSFORM trial; efficacy of axi-cel informed by Bucher ITCs[b]
Key limitations	• The comparative efficacy of liso-cel relative to axi-cel is uncertain due to limitations identified in the sponsor's ITCs. The results of the sponsor-submitted ITCs ([redacted], MAIC[c]) suggest that there may be no differences in EFS and OS between liso-cel and axi-cel. • The impact of adverse events on the cost-effectiveness of liso-cel was based on naive comparison, and it is not possible to determine if any differences between the therapies are due to the treatment or due to bias or confounding factors. Although the sponsor-conducted MAIC suggests that liso-cel may have a more favourable safety profile compared to axi-cel, these adjusted data were not used in the economic model, and the CDA-AMC review noted important differences in trial populations for liso-cel and axi-cel. • The long-term effectiveness of liso-cel is uncertain due to a lack of long-term clinical data. Efficacy data for liso-cel in the economic model was based on median follow-up of 33.9 months, and 83% of QALYs estimated by the sponsor's model were predicted on the basis of extrapolation. • The sponsor used a PSM to estimate costs and outcomes associated with the use of liso-cel in the second-line setting, with the assumption that patients who remain event-free after 2 years are cured. The structure of the sponsor's model does not account for patients who remain event-free after receiving CAR T-cell therapy in a later line of therapy (e.g., in the third line after second-line failure of SOC). Clinical experts noted that the assumption of cure at 2 years is not consistent with clinical practice. • The utility estimates used by the sponsor lacked face validity, in that the utilities for patients in the event-free health state (i.e., initiating second-line treatment) were assumed to be equal to those for patients event-free in the third line (i.e., initiating a later line of therapy, when patients have been impacted longer by their disease).
CDA-AMC reanalysis results	• CDA-AMC was unable to address uncertainty in the comparative clinical evidence or the identified limitations in the submitted economic evaluation. A CDA-AMC base case could therefore not be specified. • There is insufficient economic evidence to justify a price premium for liso-cel over axi-cel in the second-line setting. If negotiations with the pCPA for the use of axi-cel in the second line conclude without a letter of intent, a price reduction of at least 35% would be required for liso-cel to be considered cost-effective relative to SOC at a willingness-to-pay threshold of $50,000 per QALY gained.

EFS = event-free survival; ICER = incremental cost-effectiveness ratio; LBCL = Large B-cell lymphoma; HSCT = hematopoietic stem cell transplant; LY = life-year; PSM = partitioned survival model; MAIC = matched-adjusted indirect comparison; OS = overall survival; QALY = quality-adjusted life-year; SOC = standard of care.

[a]Costs included by the sponsor: liso-cel acquisition, leukapheresis, bridging therapy, lymphodepleting chemotherapy.[1]
[b]In their ITC, the sponsor utilized reconstructed patient data from the ZUMA-7 trial. The sponsor additionally submitted a MAIC as part of their clinical evidence package. Data from the MAIC were not used in the sponsor's economic evaluation.

Budget Impact

CDA-AMC identified the following limitations in the sponsor's budget impact analysis: uncertainties with the expected savings arising from the management of adverse events and subsequent therapy, underestimation of the projected market share of axi-cel, and underestimation of the projected market share of liso-cel. The sponsor's submitted model was also not user-friendly and was programmed in an unnecessarily complicated way.

The CDA-AMC reanalysis removed the subsequent therapy and AE management costs, as well as markups, dispensing fees, and co-payment discounts. The price of axi-cel was based on the public list price, which is currently being negotiated at pCPA. In the CDA-AMC base case, the 3-year budget impact of reimbursing liso-cel is expected to be $3,488,830 (year 1: $540,904; year 2: $1,323,470; year 3: $1,624,457), if liso-cel is reimbursed as per Health Canada's indication. The estimated budget impact is highly sensitive to the cost of subsequent therapy and market share of CAR T-cell therapies.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: October 9, 2024

Regrets: None.

Conflicts of interest: None.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.