

CADTH Reimbursement Recommendation

Lisocabtagene Maraleucel (Breyanzi)

Indication: For the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Sponsor: Celgene Inc., a Bristol Myers Squibb Company

Final recommendation: Reimburse with conditions

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What Is the CADTH Reimbursement Recommendation for Breyanzi?

CADTH recommends that Breyanzi should be reimbursed by public drug plans for the treatment of patients with large B-cell lymphoma (LBCL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Breyanzi should only be covered to treat patients who have LBCL and have received at least 2 previous treatments that have not worked or have stopped working, as determined by a specialist.

What Are the Conditions for Reimbursement?

Breyanzi should only be reimbursed if patients have not already been treated with a chimeric antigen receptor (CAR) T-cell therapy and are in relatively good health to tolerate the treatment if it is prescribed and administered by specialists and trained personnel in dedicated centres and the cost of Breyanzi is reduced.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that Breyanzi was associated with clinically meaningful response to treatment and could potentially prolong survival.

Breyanzi would provide an effective alternative option with a potentially different side effect profile for patients with LBCL who need CAR T-cell therapy.

Based on CADTH's assessment of the health economic evidence, Breyanzi does not represent good value to the health care system at the public list price. The CADTH pCODR Expert Review Committee determined that there is not enough evidence to justify a greater cost for Breyanzi compared with other available CAR T-cell therapies (Kymriah or Yescarta).

Based on public list prices, Breyanzi is estimated to cost the public drug plans approximately \$6.8 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is LBCL?

LBCL is the most common type of non-Hodgkin lymphoma. A lymphoma, which affects types of white blood cells called lymphocytes, grows primarily in the lymph nodes but it can spread into organs or tissues such as bones, brain, or intestines. It is estimated that 11,400 people living in Canada will be diagnosed with non-Hodgkin lymphoma each year and 3,000 will die.

Unmet Needs in LBCL

Patients with LBCL can be treated with surgery, chemotherapy, radiation, immunotherapy, and stem cell transplant; however, not all patients benefit from available treatments. Some patients may also need further therapy with fewer choices of therapies available to them and have a shorter life expectancy.

How Much Does Breyanzi Cost?

Treatment with Breyanzi is expected to have a 1-time cost of \$501,900 per patient. Additional costs associated with pre- and post-infusion management (i.e., leukapheresis, bridging therapy, conditioning chemotherapy) and administration will also apply.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that lisocabtagene maraleucel (liso-cel) be reimbursed for the for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One multi-centre, open-label, phase I, single-arm clinical study (TRANSCEND) showed that liso-cel was associated with potential benefits in survival outcomes: median overall survival [OS] was 14.0 months (95% confidence interval [CI], 11.1 to 21.1; median follow-up = 18.8 months) and median progression-free survival [PFS] was 4.8 months (95% CI, 4.3 to 7.3; median follow-up of ■ months) in the intention-to-treat population. For the primary analysis set (PAS) of patients with DLBCL, response to treatment was objective response rate [ORR] of 74.4% (95% CI, 66.2% to 81.6%; $P < 0.0001$) and complete response rate [CRR] of 54.1% (95% CI, 45.3% to 62.8%; $P < 0.0001$). The ORR and CRR end points were statistically significant based on the pre-specified null hypotheses of 40% or less and 20% or less, respectively. Overall, survival and response end points were deemed meaningful by clinical experts compared with expected outcomes in patients with DLBCL who did not receive a CAR T-cell treatment in the third-line setting.

Given the poor prognosis and high symptom burden in patients with advanced DLBCL in the third line of therapy, patients and clinicians identified a need for treatment options that provide better survival and response outcomes, with better health-related quality of life, and less toxicity. Patients are also seeking improved access to CAR T-cell therapies, which is currently limited. Given the totality of the evidence, pERC concluded that liso-cel may meet some of the needs identified by patients and clinicians compared to similar CAR T-cell therapies approved for use in Canada by providing an effective alternative option with a potentially different safety profile for most R/R LBCL patients.

Although no robust evidence has been provided to suggest that liso-cel is associated with improved efficacy and safety relative to other CAR T-cell therapies used to treat LBCL, feedback from the clinical experts consulted by CADTH indicated that liso-cel is likely similarly effective to other CAR T-cell therapies. Using the sponsor-submitted price for liso-cel and publicly listed prices for all other drug costs, liso-cel was more costly compared with other available CAR T-cell therapies (axicabtagene ciloleucel [axi-cel] and tisagenlecleucel [tisa-cel]) and considered similarly effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Liso-cel should be reimbursed in	Evidence from TRANSCEND study	—

Reimbursement condition	Reason	Implementation guidance
<p>adult patients with relapsed or refractory LBCL according to the following criteria:</p> <p>1.1. DLBCL not otherwise specified, HGBCL, PMBCL, DLBCL arising from follicular lymphoma AND</p> <p>1.2. relapsed or refractory to at least 2 prior lines of systemic therapy including a CD20-targeted agent.</p>	<p>demonstrated that liso-cel is associated with benefits in outcomes deemed relevant to both patients and clinicians (OS, PFS, ORR, CRR) compared with outcomes expected in patients with R/R LBCL not using a CAR T-cell treatment.</p>	
<p>2. Patients must have a good performance status.</p>	<p>Patients enrolled in the TRANSCEND study had an ECOG performance status of 0 or 1. However, a minority had ECOG performance status of 2.</p>	<p>pERC acknowledged that liso-cel can be considered for use in patients with a higher ECOG performance status, at the discretion of the prescribing clinician.</p>
<p>3. Liso-cel should not be reimbursed for patients who have had a previous CAR T-cell therapy.</p>	<p>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 TRANSCEND study.</p>	<p>—</p>
<p>4. Liso-cel should be reimbursed in patients with secondary CNS involvement as long as they fulfill all other criteria.</p>	<p>LBCL patients with secondary CNS involvement were included in the TRANSCEND study.</p>	<p>—</p>
Renewal		
<p>5. Treatment with liso-cel is a 1-time therapy.</p>	<p>There was no evidence available for review by pERC for repeating treatment with liso-cel.</p>	<p>At this time, CAR T-cell re-treatment has not been established as an efficacious strategy and is not considered standard of care.</p>
Prescribing		
<p>6. Liso-cel should be prescribed by clinicians with expertise in the management of lymphomas and CAR T-cell toxicities. It should be administered at manufacturer-certified transplant centres with the necessary resources and human expertise to perform the procedure and manage side effects.</p>	<p>To ensure that liso-cel is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.</p>	<p>pERC acknowledges that the availability of accredited centres in Canada is a barrier that should be considered.</p>
Pricing		
<p>7. Liso-cel should be negotiated so that it does not exceed the drug program cost of treatment with the least costly CAR T-cell therapy</p>	<p>There is no robust evidence to indicate that liso-cel is more effective or safer than other available CAR T-cell therapies (axicabtagene ciloleucel or</p>	<p>—</p>

Reimbursement condition	Reason	Implementation guidance
reimbursed for the treatment of relapsed or refractory LBCL.	tisagenlecleucel) for relapsed or refractory LBCL.	
Feasibility of adoption		
8. The feasibility of adoption of liso-cel must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.	—

CAR = chimeric antigen receptor; CNS = central nervous system; CRR = complete response rate; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HGBCL = high-grade B-cell lymphoma; LBCL = large B-cell lymphoma; liso-cel = lisocabtagene maraleucel; ORR = overall response rate; OS = overall survival; pERC = CADTH pCODR Expert Review Committee; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma.

Discussion Points

- pERC discussed the natural history and poor prognosis with low cure rate of patients with DLBCL. pERC discussed that although other CAR T-cell treatments are available, liso-cel has the potential to provide an additional option with potentially fewer undesirable effects in patients with LBCL; however, evidence of comparative safety is limited.
- pERC noted that the patient population included in the trial is broader than the approved indication and included LBCL patients with follicular lymphoma (FL) grade 3B (FL3B) or LBCL transformed from indolent non-Hodgkin lymphoma (NHL). However, pERC acknowledged that these groups were excluded from the Health Canada-approved indication and are outside the scope of this review.
- pERC acknowledged the uncertainty in the survival (OS, PFS), response rates (ORR, CRR), and health-related quality of life (HRQoL) outcomes. The limitations around the effect estimates are due to the risk of bias (lack of comparative evidence, attrition bias, no blinding, lack of adjustment for multiplicity) and imprecision. Furthermore, there were concerns about the generalizability of the results due to characteristics of the populations in the TRANSCEND study that suggest a relatively stable and generally healthier population.
- pERC noted that patients treated with liso-cel experienced either improvement in their HRQoL or their quality of life remained stable, although definitive conclusions cannot be made due to the noncomparative nature of the results and lack of statistical testing.
- pERC noted that the evidence from the sponsor-submitted indirect treatment comparisons (ITCs) has considerable limitations due to the observational nature of the included studies, difficulties in estimating all relevant prognostic variables, and possible residual confounding. Acknowledging these limitations, pERC discussed results from 1 ITC suggesting improvements of liso-cel in ORR, CRR, PFS, and OS compared with tisa-cel, but not against axi-cel. Results of the ITC suggest that liso-cel has a better safety profile with fewer odds of adverse events (AEs) such as cytokine release syndrome (CRS) and neurotoxicity relative to axi-cel or tisa-cel. Similarly, evidence from a second sponsor-submitted ITC against salvage therapies suggests that liso-cel has greater improvements in efficacy and survival outcomes (OS, CRR, ORR).

- pERC noted that, upon implementation of liso-cel reimbursement, the demand for CAR T-cell therapies (including liso-cel) may exceed manufacturing and administration capacities, which may be constrained by access to highly trained personnel and facilities capable of assessing patients' eligibility for therapy, collecting, shipping, and handling cells, as well as administering the therapy. It was not clear to pERC whether availability of liso-cel would substantially increase the overall capacity of the system to provide CAR T-cell therapies. pERC recognized that jurisdictions would need to establish equitable and fair priority-setting criteria for patient access to CAR T-cell therapies with key stakeholders, including patients, that are clear, transparent, and based on rationales that are publicly defensible, and with an appeals mechanism. Opportunities to expand access, such as the delivery of liso-cel in outpatient settings or rapid manufacturing methods, will require infrastructure and accreditation, and the need to ensure safety and quality control. In that regard, a CAR T cell that is associated with less toxicity, as may be the case for liso-cel, would require fewer critical care infrastructures and may be a good candidate for broader provision in the outpatient setting, provided patient safety is adequately addressed.
- Given the limited number of centres in Canada which have the expertise and resources to deliver this treatment, and it is unlikely that qualified centres will be available in all jurisdictions, out-of-province care may be needed for administration of liso-cel. pERC considered that some patients may be unable to travel outside the province or country to receive therapy. The committee suggested that jurisdictions may need to consider developing interprovincial and international (with the US) agreements to ensure equitable access for eligible patients and their caregivers, including consideration of financial and logistic support for required travel and short-term relocation.
- pERC discussed ethical considerations regarding liso-cel in the context of LBCL, including disparities in incidence, treatment, and outcomes of LBCL, and considerations of how to support access for people who are racialized or of lower socioeconomic status. pERC also discussed barriers to access based on cost considerations (for hospitals and direct costs for patients), limited capacity for hospitals and manufacturers to provide opportunities for CAR T-cell therapy, geographical barriers to access, and patients' access to other resources, such as caregivers. It was noted that patients from areas distant from specialized centres would need to have a prolonged stay at or near these specialized centres. Travel costs for patients and their caregivers, and the requirement for time spent away from work, may disproportionately affect certain populations. For implementation purposes, pERC agreed that there is a need to advocate for equitable patient access not based on ability to pay and patient support programs or reimbursement for lodging, travel, and other expenses so that all patients in need have timely access to therapy. Given challenges to patients' understanding of their disease states and the potential for inflation of positive outcomes over potential harms for this therapy, there is a need for informed consent, balanced communication between clinicians and patients, expanded availability and accessibility of education materials, and consensus on what constitutes an ethically justifiable balance of risks and benefits related to liso-cel.
- pERC also discussed ethical considerations at the health systems level, where the high costs of CAR T-cell therapies can impact the sustainability of health systems. The committee discussed that CAR T-cell therapies, and liso-cel in particular, would require a fair and just allocation of funds and appropriate distribution of the risks and benefits. Health systems will also need to weigh the clinical uncertainty, unmet patient need, whether there are alternative care options, and the high cost of these therapies (recognizing their high cost may decline over time).

Background

Lymphomas comprise a complex group of hematological malignancies with varying molecular hallmarks and prognoses. Overall, they are divided into NHL and Hodgkin lymphoma. In Canada, the incidence of NHL is reported at 24.4 per 100,000, with age-standardized incidence rates of 29.3 per 100,000 and 20.2 per 100,000 among males and females, respectively. DLBCL is the most common type, comprising 30% to 40% of all NHL cases. Most people are diagnosed with DLBCL when they are in their mid-60s. The most common type of DLBCL is the “not otherwise specified” (NOS) form, which represents 80% to 85% of all cases. Other subtypes of DLBCL include PMBCL, a rare subtype of DLBCL. Patients with treatment failure after initial treatment often have a poor outcome – in particular, those with disease that is refractory to frontline or subsequent therapies – although some patients can have a durable remission and be cured after secondary therapies. Outcomes are worse in patients with chemotherapy-refractory disease, with only 7% achieving a complete response to standard treatment and OS of 6 months. People of older age (> 65 years), those with central nervous system (CNS) involvement, and those with comorbidities have a higher possibility of AEs. No more than 50% of patients with R/R LBCL achieve a response to subsequent treatment after a standard second-line salvage regimen, and few are cured.

Liso-cel (JCAR017) is a patient-specific cell suspension containing a target of 60×10^6 to 120×10^6 CAR-positive viable T cells for IV infusion. It has a Health Canada indication for the treatment of adult patients with R/R LBCL after 2 or more lines of systemic therapy, including DLBCL NOS, PMBCL, HGBCL, and DLBCL arising from FL. Liso-cel targets CD19, a marker expressed on B-cell precursors and malignant B cells present in DLBCL and other lymphomas. Liso-cel consists of purified CD8-positive and CD4-positive T cells in a defined composition that have been separately activated and transduced with a replication-incompetent lentiviral vector encoding an anti-CD19 CAR. Liso-cel must be administered in a qualified treatment centre under the supervision of health care professionals experienced in the treatment of hematological malignancies and familiarity with CAR T-cell toxicities and must be kept frozen at -130°C or less until it is ready to use. Some reported toxicities of Liso-cel include CRS, hypogammaglobulinemia, neurologic toxicities, cytopenia, and tumour lysis syndrome.

Sources of Information Used by the Committee

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

- a review of 1 phase I (seamless design), single-arm, open-label clinical study in patients with R/R LBCL on the third line or more of treatment: the TRANSCEND NHL 001 study
- information from 2 sponsor-submitted reports of ITCs: the first report compares liso-cel (individual patient data) versus 2 CAR T-cell therapies, axi-cel (aggregated data from ZUMA-1 study) and tisa-cel (aggregated data from JULIET study); the second report compares liso-cel (TRANSCEND study individual patient data) versus salvage chemotherapy (aggregated data from the SCHOLAR 1 study). All reports used matched-adjusted indirect comparisons (MAICs)
- patients’ perspectives gathered by 1 patient group: Lymphoma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process

- input from 2 clinical specialists with expertise diagnosing and treating patients with lymphoma
- input from 2 clinician groups, including the Ontario Health (Cancer Ontario) Hematology Cancer Drug Advisory Committee, and Lymphoma Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to Liso-cel or other CAR T-cell therapies from published literature

Note that the CADTH Reimbursement Review was conducted before issuance of Health Canada Notice of Compliance.

Stakeholder Perspectives

Patient Input

Input was obtained from 1 patient group. Lymphoma Canada, a Toronto-based, national Canadian registered charity that empowers the lymphoma community through education, support, advocacy, and research, provided an anonymous survey of patients with LBCL conducted online from June 21 to August 25, 2021. The survey participants (total = 331, DLBCL = 126, FL = 191, other LBCLs = 14) were from Canada, the US, Europe, and other countries. Past survey data for the subgroup of patients with DLBCL (2018 and 2020 surveys), FL (2017 and 2018), and those with CAR T-cell therapy experiences (April 18 to June 15, 2018) were also provided to supplement the current survey.

Respondents (n = 63) highlighted night sweats (57%), fatigue and lack of energy (54%), and aches and pains (54%) as the top symptoms of lymphoma that impact their quality of lives. In addition, anxiety/worry (75%), stress related to the diagnosis (73%), and fear of progression (64%) were cited as the key psychosocial impacts. Diagnosis combined with symptoms and mental health effects significantly impact patients' daily activities (43%), ability to sleep (41%), concentration (40%), and ability to attend work/school (40%). Of 230 respondents, 7% had not yet received therapy ("watch and wait"), 50% received 1 line of therapy, and 43% received 2 or more lines of therapies at the time of survey. For those patients with DLBCL on treatments, the most common side effects (n = 103) were hair loss (87%), fatigue (84%), and cognitive issues (68%); the most intolerable side effects (n = 85) were fatigue (41%), nausea/vomiting (19%), and "chemo-brain" (15%). For patients with FL on treatments, the most common side effects (n = 61) were fatigue (85%), nausea/vomiting (51%), and hair loss (39%); the most intolerable side effects (n = 49) were fatigue (37%), nausea/vomiting (10%) and pain (10%). Specific psychosocial impacts (n = 49) caused by treatments included fear of progression/relapse (67%), anxiety/worry (65%), and depression (47%). The most significant negative impacts on quality of life or daily living caused by treatments were treatment-related fatigue (57%, n = 273), late-onset/long-term side effects (41%, n = 49), and low activity level (39%, n = 176). In terms accessing treatment options, 13% of patients (n = 44) found these very difficult to access. Living in a community without a cancer centre (35%, n = 49) was the most common reason for difficulty accessing treatments. Absence from work (62%), travelling costs (28%), and supplementary drug costs (26%) were the top financial impacts associated with accessing necessary treatments (n = 39). The most desired outcomes from treatments included improved quality of life and performance of daily activities (93%, n = 176), longer survival (88%, n = 223), and longer disease remission (85%, n = 223). 47% of patients

responded that they would be willing to tolerate the short-term side effects of a new effective treatment and 47% said they would take the treatment recommended by their physicians even if it has potentially serious side effects. According to the past survey data (2018), none of the patients had direct experience with liso-cel therapy. Of the 7 patients who had experiences with other CAR T-cell therapies through clinical trials, 5 responded to a questionnaire asking about the effect of CAR T-cell therapy on their quality of life. Patients rated all aspects of CAR T-cell therapy less than 3 (on a scale of 1 = no negative impact on my life to 5 = significant negative impact on my life): number of clinic visits (2.8), travel to treatment centre (2.8), CAR T-cell infusion (2.6), short-term side effects (2.5), activity level (2.5), treatment-related fatigue (2.5), lasting side effects (2.0), and leukapheresis (1.8). When asked about recommending CAR T-cell therapy to other eligible patients, 5 of 7 patients said they would recommend, 1 said they would not recommend, and 1 remained unsure.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Clinical experts consulted by CADTH agreed that there is an unmet need for drugs that are better tolerated and with better safety profiles that can be used more frequently in the outpatient setting and in a broader population of patients with lymphoma. The suboptimal availability of commercially available CAR T-cell products in some provinces generates the need to refer patients outside the province or country for commercial CAR T-cell therapies. Other innovative therapies (e.g., polatuzumab vedotin) may not be widely available or can be more costly.

Although liso-cel is not the first CAR T-cell therapy on the market for R/R DLBCL in Canada, some clinical experts mentioned that it may have a better safety profile in terms of fewer toxicities as suggested by the evidence from the TRANSCEND study, although others mentioned newer therapies may benefit from prior clinical experience with similar therapies. Liso-cel would still be used as third line of therapy (in patients who have already tried 2 lines of chemotherapy) but will have the advantage of being able to be used in a broader population.

The clinical experts suggested that the patients most likely to benefit from liso-cel have similar characteristics to those included in the TRANSCEND study (e.g., ECOG PS of 0 or 1, low lactate dehydrogenase), although the experts mentioned that more data on specific subgroups (e.g., ECOG PS of 2) are needed. Patients who have had an autologous stem cell transplant and then relapsed or those who are not eligible for a transplant are likely to be favoured by the liso-cel administration. The clinical experts mentioned that patients not suitable for treatment with liso-cel would be those who do not meet established criteria (i.e., eligibility criteria from TRANSCEND) for CAR T-cell therapy. However, as with other CAR T-cell therapies, it remains difficult to predict at the start of treatment which patients would likely benefit from treatment with liso-cel.

Improved survival, reduction in the frequency and severity of symptoms, and cure were considered adequate measurements of response in clinical practice. Imaging may also be used as an objective means of assessing response to treatment.

The clinical experts recommended assessments of patients every 1 to 3 months. Criteria for discontinuing treatment with CAR T-cell therapies was not discussed because it is a treatment administered as a single dose (although re-treatment may be possible in the future). Some patients may become clinically unstable during the liso-cel manufacturing process and

require discontinuation (e.g., patients with ECOG PS of 4, sudden clinical deterioration, opportunistic infections).

CAR T-cell treatment is primarily done at transplant centres in Canada. Currently, most provinces in Canada have (or will have) the necessary expertise and resources to perform the administration of liso-cel. In some areas, however, access to these centres may be challenging (e.g., in rural areas). Therefore, access to Health Canada and Foundation for the Accreditation of Cellular Therapy (FACT)–accredited SCT centres in Canada is a limitation. The clinical experts expressed that outpatient therapy is feasible provided such programs have the appropriate infrastructure and accreditation.

Clinician Group Input

The collection of clinician group response was coordinated by Lymphoma Canada. The clinician group stated that the addition of liso-cel to the current third-line therapies or beyond is important for the following reasons: As a curative therapy, liso-cel is expected to improve remission (e.g., complete and partial responses) and prolong survival (e.g., OS and PFS) of the eligible patients; the availability of liso-cel would prevent unnecessary delay in treatment caused by short supply of the existing CAR T-cell therapies; liso-cel was demonstrated to have less frequent AEs (i.e., CRS and neurotoxicity compared with axi-cel without compromising efficacy (however, no head-to-head trial is available); and liso-cel can be safely administered in an outpatient setting similarly to tisa-cel.

Another input was provided by Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO Hem DAC). The OH-CCO’s committee indicated that liso-cel would fulfill the unmet needs of indications that are not covered by the other CAR T-cell therapies (e.g., FL3B and secondary CNS lymphoma). Moreover, the committee identified that the limited number of CAR T-cell therapy centres available across Canada could cause access issues for patients.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. 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	
<p>The TRANSCEND NHL-001 was a single-arm trial. Relevant comparators include axicabtagene ciloleucel, tisagenlecleucel, salvage chemotherapy (GDP, DHAP, ICE, gemcitabine monotherapy, oral cyclophosphamide-etoposide) and polatuzumab-BR.</p>	<p>pERC agreed with clinical experts that the comparators stated in the protocol for this review include other CAR T-cell therapies such as axi-cel and tisa-cel, and drug regimens.</p>
<p>Two other CAR T-cell products for the treatment of DLBCL (tisa-cel, axi-cel) have been assessed by CADTH and are funded in Canada. Based on the pivotal trial data and approved indication, does</p>	<p>pERC noted that although the trial included a broader population, the approved indication of liso-cel aligns with that of axi-cel. As a result, liso-cel does not expand to a population that is not currently eligible for CAR T-cell therapy. One exception would be secondary</p>

Implementation issues	Response
liso-cel expand the eligible patient population beyond that which is currently eligible for CAR T-cell therapy?	CNS disease, which was permitted in the TRANSCEND study and is not contraindicated.
Considerations for initiation of therapy	
Can it be clarified if patients should receive reconfirmation of PET-positive disease before lymphodepleting therapy? (This is not required for the 2 currently funded CAR T-cell products in Canada.)	pERC noted that PET results are not required before lymphodepleting therapy or cell infusion because PET results are expected to be positive in most patients whether or not bridging therapy is used.
For transformed DLBCL, do patients need to have received or failed treatment for the diagnosis of DLBCL or is biopsy-proven DLBCL sufficient (e.g., the patient only received treatment for SLL/CLL then transformed to DLBCL)?	pERC noted that patients would need at least 2 lines of systemic therapy from the time of diagnosis of the transformed DLBCL. Potential exceptions may include individuals with follicular lymphoma for which they already have received induction chemotherapy followed by ASCT, but then transformed to DLBCL/HGBCL. For these cases, clinicians may want to move directly to offer CAR T-cell therapies because other options are limited. Clinical experts suggest criteria could stipulate the minimum types of therapy required in these situations.
Do patient eligibility criteria overlap with existing commercial CAR T-cell therapy eligibility criteria (tisa-cel and axi-cel)? Liso-cel was also evaluated in DLBCL from indolent lymphomas and in follicular lymphoma grade 3B.	Eligibility criteria for liso-cel would overlap with axi-cel and tisa-cel. The approved indication aligns with the axi-cel indication and does not include DLBCL from indolent lymphomas and follicular lymphoma grade 3B; therefore, pERC cannot provide guidance on these populations.
Is liso-cel recommended (i.e., is there outcome data specifically for) in the following groups: <ul style="list-style-type: none"> • patients aged > 75 years (10% of patients in clinical trial) • ECOG of 2 (1%) • prior allo-SCT (3%) • secondary CNS lymphoma (3%)? 	pERC and clinical experts indicated that liso-cel would be considered for use in patients who are > 75 years old, have ECOG PS > 2, or have CNS involvement. pERC and clinical experts emphasized the need for more data, especially comparative data. TRANSCEND is the first study to include the patients with CNS involvement and prior allo-SCT. pERC and clinical experts noted that both of these subgroups of patients represent a small proportion of the population in practice, making it difficult for studies to be conducted with these subgroups specifically.
Can we confirm that patients with comorbidities are eligible (e.g., reduced cardiac and renal function)?	Yes, but patients require sufficient cardiac function to survive CRS or sepsis, and renal function to tolerate fludarabine. Currently, there is variability on the approach to patients with comorbidities by Canadian centres.
Should patients who have received other CAR T-cell therapies for DLBCL be eligible for liso-cel?	There are currently no data to support that patients who have received previous CAR T-cell therapies for DLBCL should receive liso-cel. Response to a second (different) CAR T-cell product is unknown and should be studied independently.
Please confirm that this is a single-dose treatment, and that re-treatment is not recommended.	A small proportion of patients in TRANSCEND were re-challenged with liso-cel. According to the clinical experts and pERC, there remains insufficient data on the outcome of such a scenario to support re-treatment.
Would patients with secondary CNS involvement be eligible?	pERC and the experts agreed that this patient population can be eligible as per the clinical trial eligibility criteria. This population is in great need of better therapies.

Implementation issues	Response
<p>Is liso-cel sufficiently distinct from axi-cel and tisa-cel to warrant separate eligibility criteria?</p> <p>PAG requests pERC to consider alignment with reimbursement criteria for CAR T-cell therapy: tisa-cel and axi-cel.</p>	<p>Experts would treat the same patients as with axi-cel but may add secondary CNS disease if not currently funded because these patients were included in the TRANSCEND study.</p>
Considerations for prescribing of therapy	
<p>The manufacturer's BIA assumes a single infusion, but the pivotal trial allowed for second infusions in refractory patients.</p>	<p>pERC confirmed that patients would receive only 1 infusion of liso-cel.</p>
<p>Delivery must take place at specialized treatment centres that are FACT-accredited and certified by the manufacturer.</p> <p>PAG notes that the timelines for the manufacturer's assumptions regarding delivery locations may be unrealistic, as the roll-out of CAR T-cell therapy is dependent on provincial funding and site capacity to deliver. This may affect BIA assumptions.</p>	<p>pERC noted that administration would be done preferably in Health Canada and FACT-accredited SCT centres. Outpatient therapy is feasible provided such programs have built the infrastructure to do so. FACT accreditation is not uniform in Canada.</p> <p>Sponsor companies will work with any transplant centre that has standards deemed to be at the level of FACT accreditation.</p> <p>All SCT centres are Health Canada-approved, and most centres are already FACT-accredited. Those that are not FACT-accredited may try to justify to the manufacturer that they can administer CAR T-cell therapies, so implementation in these centres is still possible.</p> <p>One clinical expert noted that in 1 centre, all companies have reached out to the clinicians to state that they no longer require FACT accreditation. However, they do require a program at the FACT standards, which effectively implies that it is a centre that does routine apheresis for stem cells or donor lymphocyte infusion.</p>
<p>There is 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.</p> <p>Due to geographical site limitations, patients may need to travel for treatment requiring interprovincial agreements to ensure equitable access as is needed for 2 prior CAR T-cell therapies that have been approved for DLBCL.</p>	<p>pERC acknowledges the access issues with CAR T-cell therapies, which should be considered by jurisdictions when implementing liso-cel.</p>
<p>Delivery sites may have capacity and feasibility issues with being certified by more than 1 CAR T-cell manufacturer (training, ongoing auditing, slightly different protocols).</p>	<p>pERC acknowledges issues of capacity, training, and process.</p>
Funding algorithm (oncology only)	
<p>Drug may change place in therapy of comparator drugs.</p> <p>When would liso-cel be preferred over currently funded CAR T-cell therapies?</p> <p>Is there sufficient clinical evidence to favour 1 CAR T-cell therapy over another, either generally or in any subpopulation?</p> <p>If this drug is the same price as tisa-cel or axi-cel, will it replace them?</p>	<p>According to experts and pERC, it is not expected that liso-cel would be better than other CAR T-cell therapies, but it may be offered to a broader population of patients with CNS disease.</p> <p>Although there is a perception of a better safety profile, experts agreed that it may be a result of clinicians having a better understanding on how to better manage CRS and ICANS, which would lead to more favourable outcomes, although the evidence is still uncertain to support any assumption.</p> <p>Another expert mentioned that there is no clear clinical evidence</p>

Implementation issues	Response
	to favour 1 CAR T-cell therapy over another for the overlapping indications. However, in practice, some centres may choose to align with a limited number of manufacturers to minimize contractual and manufacturer-specific requirements (i.e., it is possible 1 will be favoured for logistical reasons).
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products. Competing products include tisa-cel and axi-cel.	pERC acknowledges the complexity of the therapeutic space.
Other aspects: Concerns around delivery sites processing 3 different manufacturers' CAR T cells. Additional costs incurred by non-delivering sites when sending patients out-of-province for treatment.	pERC acknowledges issues of capacity and potential additional costs.
Care provision issues	
Like other CAR T-cell therapies, hospitalization for adverse events is not uncommon, which may include ICU admission. Does the adverse effect profile differ significantly from currently funded CAR T-cell therapies? CRS is sometimes managed with tocilizumab. Tocilizumab is on the Canada Drug Shortages website list due to its use in COVID-19 treatment, with an anticipated resolution date of December 31, 2021. Is there another treatment that can be used to manage CRS if tocilizumab is not available? Should treating centres ensure that tocilizumab is available before starting liso-cel (would also be an issue for other CAR T-cell therapies)?	pERC and clinical experts agree that liso-cel may have a better safety profile, but there is still uncertainty around this issue. For now, it would be important to focus on the proportion treated as outpatients in the TRANSCEND study. The use of tocilizumab and possible drug shortages is a concern because the companies require 2 doses on hand for each patient. The use of siltuximab has been considered by some clinicians if there is a severe shortage. A biosimilar tocilizumab would be helpful in the future.
System and economic issues	
CAR T-cell therapy is an expensive therapy that requires considerable resources to deliver. Because DLBCL patients are already potentially eligible for CAR T-cell therapy in Canada, PAG is interested to know the extent to which the eligible patient population will expand (assuming no delivery constraints) if liso-cel is funded.	pERC acknowledges the funding issues for the implementation of CAR T-cell therapies.
Accessing CAR T-cell therapy may require interprovincial travel. A program to cover travel expenses should be offered by the manufacturer until widespread access across Canada is available. Due to geographical site limitations, patients may need to travel for treatment requiring interprovincial agreements to ensure equitable access as is needed for 2 prior CAR T-cell therapies that have been approved for DLBCL.	pERC acknowledges issues around travelling and equitable access across provinces.
Tisa-cel and axi-cel are already funded in Canada for the treatment of relapsed/refractory DLBCL after 2 or more lines of therapy. Both tisa-cel and axi-cel have gone through price negotiations for the same indication.	pERC acknowledges the existing implementation of other CAR T-cell therapies.

Implementation issues	Response
<p>Cost-effectiveness of therapy based on long-term data is not available.</p> <p>Unknown burden and cost to staff to process cells for third product and to maintain level of training.</p> <p>Patient privacy and patient cell ownership concerns due to the fact that CAR T cells are manufactured by US-based companies outside of Canadian jurisdiction (this is also the case for the other CAR T-cell therapies that are publicly funded).</p>	<p>pERC acknowledges issues around long-term cost-effectiveness, human resource requirements, and patient privacy.</p>

ASTC = autologous stem cell transplant; axi-cel = axicabtagene ciloleucel; BIA = budget impact analysis; BR = bendamustine-rituximab; CAR = chimeric antigen receptor; CNS = central nervous system; CLL = chronic lymphocytic leukemia; CRR = complete response rate; CRS = cytokine release syndrome; DHAP = dexamethasone, high-dose cytarabine, cisplatin; GDP = gemcitabine, dexamethasone, cisplatin; DLBCL = diffuse large B-cell lymphoma; FACT = Foundation for the Accreditation of Cellular Therapy; HGBCL = high-grade B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = ifosfamide, carboplatin, etoposide; NHL = non-Hodgkin lymphoma; PAG = provincial advisory group; pERC = CADTH pCODR Expert Review Committee; SCT = stem cell transplant; tisa-cel = tisagenlecleucel.

Clinical Evidence

Description of Studies

One clinical study is included in this report evaluating the safety and efficacy of liso-cel in patients on the third line or more of treatment for R/R LDBCL. The TRANSCEND NHL 001 study ("TRANSCEND study" from hereon) is a single-arm, open-label, phase I (seamless design) multi-centre study conducted in the US. The population included in the study consisted of patients with DLBCL NOS (de novo, transformed FL, and transformed indolent NHL), HGBCL with myelocytomatosis oncogene (*MYC*) and B-cell lymphoma gene 2 (*BCL2*) and/or B-cell lymphoma gene 6 (*BCL6*) rearrangements, PMBCL, and FL3B; patients were eligible if they were R/R to at least 2 prior lines of therapy, and had ECOG PS of 0 to 2, PET-positive disease, secondary CNS involvement, prior autologous stem cell transplant or prior allogeneic stem cell transplant. Patients with primary CNS involvement and allo-HSCT within 90 days of leukapheresis were excluded. The seamless design allowed the study to go from dose-finding phases (groups of patients) to dose-expansion and then dose-confirmation groups. The study evaluated 3 levels of dose regimens, Dose level 1 at 50×10^6 CAR+ T cells, dose level 2 at 100×10^6 CAR+ T cells, and dose level 3 at 150×10^6 CAR+ T cells; of these, the dose level 2 regimen was selected for the current indication assessed in this review, for clinical use, and regulatory approval. Patients in the TRANSCEND study had a mean age of 60 years (median = 63 years) and were overall in relatively good health status.

After enrolment, patients went through leukapheresis to allow for the product (JCAR017/ liso-cel) to be manufactured (bridging therapy consisting of systemic anticancer therapy was allowed) and were required to have PET-positive disease. After product generation, patients went through lymphodepleting chemotherapy with fludarabine plus cyclophosphamide followed by 1 or 2 doses of JCAR017/liso-cel administered intravenously on day 1. After day 29, patients were followed on this study for 2 years after the last dose of liso-cel for safety, disease progression, and survival. Of 427 screened patients (341 in the DLBCL cohort), 344 went through leukapheresis (the intention-to-treat set), of which 50 could not be treated with any product, 25 received a nonconforming product, and 269 patients were treated with liso-cel (the DLBCL-treated set) and analyzed as of the cut-off date of August 12, 2019. The

main analysis was conducted on the PAS population consisting of those patients on the dose level 2 regimen.

Primary end points included AEs and ORR as assessed by an independent review committee (IRC). Secondary end points included CRR (as assessed by IRC), DOR, PFS, and OS. The ORR was defined as the proportion of patients with a best overall response of either complete response or partial response based on the Lugano 2014 criteria. A sequential testing procedure started with the first hypothesis test of ORR of 40% or less. The procedure proceeded to the second hypothesis test only after rejecting the null hypothesis in the first hypothesis test, and so on. Other efficacy end points were summarized. The Kaplan-Meier method was used to estimate the DOR, PFS, and OS rates at months 6, 12, 18, and 24. The manufacturing success rate using the proposed commercial manufacturing process was 90.0%, and the median time from leukapheresis to JCAR017/liso-cel product availability was 24.0 days (range = 17 to 51 days).

Efficacy Results

In this specific population of patients on the third line or more of treatment for DLBCL (i.e., those with DLBCL NOS, HGL, or transformed from FL) assigned to the recommended regimen of dose level 2 (100×10^6 CAR+ T cells), the ORR in the PAS (primary end point) was 74.4% (95% CI, 66.2% to 81.6%) against a null hypothesis of ORR of 40% or less. The CRR (key secondary end point) in the PAS was 54.1% (95% CI, 45.3% to 62.8%; 1-sided $P < 0.0001$). Sensitivity analyses using the per-protocol set showed similar results. The leukapheresed set (intention-to-treat population) included patients treated with a nonconforming product ($N = 25$) as well as those who received no treatment ($N = 50$). The primary reason for not receiving treatment was death ($N = 33$); most of those patients died from progressed disease ($N = 27$). The leukapheresed set had an ORR per IRC of [REDACTED], and a CRR of [REDACTED]. The lower limit of each CI was equal to or higher than the null hypotheses used for the PAS (40% and 20%, respectively). With a median follow-up for PFS of [REDACTED] months, the median PFS was 4.8 (95% CI, 4.3 to 7.3) months. With a median survival follow-up of 18.8 months, the median OS was 14.0 (95% CI, 11.1 to 21.1) months. The estimated survival rates at 6 and 12 months were 70.2% (95% CI, 65.0% to 74.8%) and 54.0% (95% CI, 48.5% to 59.2%), respectively. Only 7 of 269 patients were never hospitalized. Nineteen patients (7.1%) were admitted to the intensive care unit (ICU), with a variable duration from 2 to 88 days.

HRQoL outcomes improved during treatment with liso-cel, although not all HRQoL domains reached statistical significance as compared to a minimally important difference and were not included in the adjustment for multiplicity.

Harms Results

The most frequently reported treatment-emergent AEs were neutropenia (169 of 269 patients; 62.8%), anemia (129 of 269 patients; 48.0%), and fatigue (119 of 269 patients; 44.2%), followed by CRS (113 of 269 patients; 42.0%). CRS was also the most frequently reported serious AE (occurring in 44 of 269 patients; 16.4%), but grade 3 or higher CRS occurred in only 6 of 269 patients (2.2%). The second most frequently reported treatment-emergent serious AE was encephalopathy ([REDACTED]), which is the most frequent symptom of investigator-identified neurologic toxicity. All other treatment-emergent SAEs were reported in less than 5% of patients. Grade 3 or higher CRS occurred in 6 of 269 subjects (2.2%); grade 3 or higher investigator-identified neurologic toxicity in 27 of 269 patients (10.0%), while no grade 5 CRS or investigator-identified neurologic toxicity AEs were reported. Admission to

the ICU occurred infrequently. During initial hospitalization, 19 of 269 patients (7.1%) were admitted to the ICU; the median number of ICU days was [REDACTED]. Considering all hospitalizations through the end of the study, [REDACTED] were admitted to the ICU; the median number of ICU days for those patients who were hospitalized was 8 days (range = 1 to 56 days).

Critical Appraisal

The main limitation of the TRANSCEND study stems from the single-arm design and lack of comparator groups. In lieu of an available direct comparator, the investigators evaluated the primary end point of ORR against a null hypothesis (in the PAS population) of ORR of 40% or less, with an alternate hypothesis of greater than 40% and an effect size of 25% (ORR = 65%). The hypothesis testing and adjustment for multiplicity was evaluated only for the PAS population, which can instill uncertainty in the effect estimates for other sets, such as the leukapheresed set (intention to treat) and the DLBCL-treated set. An open-label design may also increase uncertainty in patient-reported outcomes (HRQoL), which introduces bias due to the inherent subjectivity of the outcome in an unblinded assessor (patients and investigators). Furthermore, HRQoL outcomes were evaluated as secondary end points with no adjustment for multiplicity and with decreasing sample sizes at later time points of evaluation, decreasing precision due to a diminishing number of patients available to be analyzed. Any magnitude of effect that the anticancer interventions (bridging therapies) could have on the outcomes evaluated in the TRANSCEND study in patients receiving liso-cel is unknown. Sensitivity analyses based on assessing the leukapheresed set, by per-protocol analysis, disease histology, and response determined by the investigator, were supportive of the robustness of results. No subgroup effects were informative because the sample size was small and only in the PAS population.

Issues of generalizability of the results originate from the differences in the population of patients included in the TRANSCEND study, which can be considered relatively young (mean age of 60.1 years in the DLBCL-treated set compared with a mean age of 65 years from clinical guidelines and reviews) and with fewer baseline risks (only 4 patients in the DLBCL-treated population was classified with ECOG PS = 2). This agreed with the input from the clinical experts consulted by CADTH, when considering the similarities between the populations from the TRANSCEND study and those likely to be encountered in clinical practice in Canada. However, the impact of these issues in the full implementation of the intervention is uncertain. Other issues of generalizability are the low number of patients with FL3B, DLBCL transformed from indolent lymphomas other than follicular lymphoma, and patients with secondary CNS lymphoma who were included in the TRANSCEND study. These numbers make it difficult to draw conclusions on the effects of liso-cel in these populations. Furthermore, the relatively short follow-up time for the main analysis on the study's PAS population (median of 11.5 months in the DLBCL-treated set at the cut-off date of August 12, 2019) can cause some uncertainty in the effect estimates and in the generalizability of results in long-term outcomes. Additional data from the June 19, 2020 (median follow-up duration = 19.1 months) and January 4, 2021 (mean follow-up duration = 19.9 months) cut-off dates ameliorate these issues.

Indirect Comparisons

Two sponsor-submitted reports with 3 ITCs are included. The first 2 ITCs include comparisons evaluating individual patient data evidence from a single-arm study (TRANSCEND) compared against aggregated data from 2 published sources evaluating

tisa-cel and axi-cel, respectively. In these 2 unanchored MAICs (one of liso-cel against tisa-cel, and the other against axi-cel), patients from these populations had R/R LBCLs and included the lymphoma subtypes that were common among the 3 bodies of evidence (i.e., DLBCL NOS, HGL, and transformed from FL). The second submitted report (ITC-2) includes an ITC as an unanchored MAIC comparing the same individual patient data from the TRANSCEND study against aggregated data from the SCHOLAR-1 study, which includes a population of patients with DLBCL treated with salvage therapies. The lymphoma subtypes included in the ITC-2 (i.e., those common among both bodies of evidence) were DLBCL, PMBCL, and transformed FL.

In the comparison of liso-cel versus tisa-cel, after matching and weighting 6 clinical factors, the primary analysis showed an ORR odds ratio (OR) favouring liso-cel over tisa-cel (OR = 2.77; 95% CI, 1.63 to 4.73; P < 0.001). For CRR, the OR significantly favoured liso-cel over tisa-cel (OR = 1.92; 95% CI, 1.17 to 3.17; P = 0.010). For survival outcomes, the results of the MAICs showed longer median PFS and OS for liso-cel than for tisa-cel. For instance, the liso-cel group had a median PFS of 6.7 months (95% CI, 3.5 to not reached) compared with tisa-cel of 2.8 months (95% CI, 2.3 to 4.2), and the rate of disease progression or mortality was significantly lower for liso-cel than for tisa-cel (hazard ratio [HR] = 0.66; 95% CI, 0.47 to 0.92; P = 0.013). Similarly, for OS, liso-cel had a median OS of 28.9 (95% CI, 19.9, not reached) months compared with 11.7 (7.2 to not reached) for tisa-cel. For this comparison, the rate of mortality was significantly lower for liso-cel than for tisa-cel (HR = 0.66; 95% CI, 0.46 to 0.93; P = 0.019).

For the ITC analyzing the comparison of liso-cel versus axi-cel, the results of the MAICs showed no statistically significant difference for any of the end points (ORR, CRR, PFS, or OS).

The sponsor submitted an ITC evaluating liso-cel versus salvage chemotherapy in an MAIC that evaluated OS, CRR, and ORR. In the base-case analysis that accounted for 7 clinical factors to match and weight, the median OS for TRANSCEND was 21.1 (95% CI, 12.1 to not reached) months, with an effective sample size of 142 (from an original N = 257); The analysis resulted in an HR of 0.47 (95% CI, 0.37 to 0.60) relative to salvage chemotherapy. PFS was not reported in the SCHOLAR-1 study. Unadjusted median OS was 27.3 (95% CI, 16.8 to not reached) months for liso-cel (N = 257) and 6.0 months (95% CI, 5.6 to 6.8) for salvage chemotherapy (N = 603). Adjusted for 7 clinical factors, the CRR for liso-cel was 49.2% with an effective sample size of 142; compared with salvage chemotherapy (CRR = 7.0%; N = 523), the matched and adjusted treatment effect on CRR was greater with an OR of 12.89 (95% CI, 8.04 to 20.68; P < 0.001). No data on harms were available in ITC-2.

For harms, liso-cel had fewer AEs of special interest, such as CRS, neurotoxicity, and neutropenia, compared with axi-cel or tisa-cel. Compared with tisa-cel, liso-cel had lower odds of CRS (OR = 0.52; 95% CI, 0.31 to 0.87) and prolonged cytopenia (OR = 0.43; 95% CI, 0.26 to 0.73); however, the rest of AEs were similar. Relative to axi-cel, liso-cel had lower odds of CRS (OR = 0.03; 95% CI, 0.01 to 0.07), neurotoxicity (OR = 0.16; 95% CI, 0.08 to 0.32), febrile neutropenia (OR = 0.09; 95% CI, 0.03 to 0.28), prolonged thrombocytopenia (OR = 0.34; 95% CI, 0.13 to 0.86), infections (OR = 0.19; 95% CI, 0.07 to 0.47), and any grade 3 or higher AE (OR = 0.04; 95% CI, 0.01 to 0.19). No data on harms were available for the ITC comparing liso-cel against salvage chemotherapy.

Both ITC reports aimed at comparing individual patient data from a single-arm clinical trial (TRANSCEND) against aggregated data from observational studies. For the first report, 1 ITC compared liso-cel against axi-cel (ZUMA-1 study) and another ITC compared liso-cel against tisa-cel (JULIET study). The second report included 1 ITC that compared liso-cel against

salvage chemotherapy (from the SCHOLAR-1 study). All ITCs compared the interventions via an unanchored MAIC. One main limitation of unanchored MAICs is the lack of inclusion of relevant prognostic variables and effect modifiers that are not included in the weighting process. Differences in baseline characteristics of variables between the included studies suggest that other potential unmeasured confounders might be present, and that these can be unevenly distributed between groups. In both ITCs, authors attempted to obtain all possible prognostic variables/effect modifiers to be included in the weighting process of the MAIC. This effort for finding relevant clinical factors was data driven and included a literature search and clinician input. However, as mentioned by the authors, data-driven methods can miss relevant factors and there is no guarantee that all relevant factors were identified. Important differences in the measured variables were detected (e.g., age, International Prognostic Index scores, ECOG PS) which can further increase the risk of bias. The effective sample size decreased in substantial numbers in both ITCs, which indicates the amount of information lost due to the matching and adjustment process, which introduces uncertainty and indicates heterogeneity among the original studies. There were also concerns of probable violations of the proportional hazards assumptions for time to event in end points such as OS in ITC-1. Overall, populations with R/R LBCL in the salvage chemotherapy lot had poor outcomes (e.g., OS close to a median of 6 months). Comparing the interventions used in these populations against newer CAR T-cell therapies might imply differences in baseline risks and uncertainty in the generalizability of effect estimates.

Other Relevant Evidence

An ongoing study (TRANSCEND WORLD) is included as “other relevant evidence” in this report. This is a single-arm, open-label, multi-cohort, multi-centre, phase II clinical trial to test the efficacy and safety of liso-cel in adult patients with DLBCL NOS (de novo or transformed FL), HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology and FL3B (European cohort 1, N = █ leukapheresed patients) and patients with DLBCL who are not eligible for transplant (Japanese cohort 3, N = 14 leukapheresed patients). Both cohorts included █ leukapheresed patients, █ who received JCAR017 (liso-cel) or other nonconforming product, and 37 who eventually received the JCAR017 (liso-cel) product. The median age of this cohort was also relatively young (58 years) and only 4 patients had an ECOG PS of 2.

The study met the primary efficacy end point, with an IRC-assessed ORR of █ in the efficacy evaluable set, thereby rejecting the null hypothesis of ORR of 40% or less (1-sided P value = 0.020). In the set of patients treated with liso-cel, the ORR based on IRC assessment was █. Overall (N = 37), the Kaplan-Meier estimate median PFS was █. The Kaplan-Meier estimate for the median OS was █ and the median follow-up time was 6.39 (95% CI, 3.09 to 9.33) months. Only 1 of the total 37 patients was admitted to the ICU. The most common treatment-emergent AEs were neutropenia █, anemia █, and pyrexia █. The most frequently reported treatment-emergent serious AEs were CRS █ and aphasia █. The deaths █ observed in the enrolled set of patients █ were primarily due to progression of disease █. The most frequent notable harms, known to be associated with CAR T-cell therapies, were CRS █, prolonged cytopenia █, investigator-identified neurologic toxicity █, and hypogammaglobulinemia █.

Limitations are in line with the TRANSCEND study and include a lack of control group that makes it challenging to make conclusions about efficacy and safety. Other methodological limitations are the small sample size and short follow-up period. An open-label design may also introduce bias in interpreting results. The study population included 1 patient with an

ECOG PS score of 2, and none of the patients had CNS lymphoma at the beginning of the study. Patients may have developed secondary CNS lymphoma during the trial as noted in the study; however, there were no confirmed cases. This selected population could make it difficult to generalize to patients with more severe burden of disease.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree, followed by a PSM with a mixture-cure component
Target population	Adults with R/R LBCL who failed at least 2 prior lines of treatment
Treatment	Lisocabtagene maraleucel (liso-cel; Breyanzi)
Submitted price	\$501,900 per administration
Treatment cost	\$501,900 per administration
Comparators	Axicabtagene ciloleucel (axi-cel; Yescarta) Tisagenlecleucel (tisa-cel; Kymriah) Salvage chemotherapy; modelled as a basket of chemotherapy regimens including GDP, DHAP, ICE, gemcitabine monotherapy, and oral cyclophosphamide-etoposide
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data source	Clinical efficacy data were derived from TRANSCEND (liso-cel), JULIET (tisa-cel), ZUMA-1 (axi-cel), or SCHOLAR-1 (salvage chemotherapy) studies. Relative efficacy was assessed based on naive comparison and 3 pairwise unanchored MAICs.
Submitted results	ICER = \$127,679 per QALY compared with salvage chemotherapy (incremental QALYs = 3.32; incremental costs = \$423,404). Tisa-cel is extendedly dominated (higher ICER and less effective) through salvage chemotherapy and liso-cel. Axi-cel is dominated (more costly and less effective) by liso-cel.
Key limitations	<ul style="list-style-type: none"> The comparative efficacy estimates were derived from the 3 MAICs, which were associated with a high degree of uncertainty due to the inherently different patient populations, heterogeneity in the patients that could be matched, small numbers of included patients for liso-cel in the matched analysis, and lack of key MAIC-weighting parameters. Because multiple MAICs were used to inform the economic comparison, a sequential analysis was not appropriate to compare treatments; pairwise comparisons considering the specific characteristics and data output from each MAIC should have been presented to inform each comparison instead of the single effectiveness estimate for liso-cel assumed by the sponsor. The mixture-cure component of the sponsor's model is associated with substantial uncertainty. Although

Component	Description
	<p>there is the potential for CAR T-cell therapy to be a curative therapy, there is limited long-term evidence to confirm this assumption at this time.</p> <ul style="list-style-type: none"> • The sponsor’s application of trial data to inform pre-treatment inputs bias the results in favour of liso-cel relative to other CAR T-cell therapies. Based on the trial data, the sponsor assumed █ of liso-cel patients make it through the pre-treatment period to receive treatment (and accrue benefits) compared with 90% for axi-cel and 75% for tisa-cel; however, only █ of liso-cel patients accrued costs compared with 90% for axi-cel and 70% for tisa-cel. These inputs were derived from trials with different inclusion criteria, leading to differences that would not be observed in clinical practice. Based on discussions with clinical experts, assuming differences between the proportion of patients that receive treatment based on the type of CAR T cell is highly uncertain. Furthermore, assuming differences between CAR T-cell therapies regarding accrual of drug costs is inappropriate. • Based on the clinical expert feedback, differences in adverse events suggesting that axi-cel is associated with notably higher costs than tisa-cel and liso-cel are likely overestimated. Adverse event costs are expected to be similar across the CAR T-cell therapies.
<p>CADTH reanalysis results</p>	<ul style="list-style-type: none"> • Due to limitations with the clinical evidence and submitted model, CADTH could not determine a base-case cost-effectiveness estimate for liso-cel relative to salvage chemotherapy or other CAR T-cell therapies. • CADTH undertook a series of exploratory analyses which indicated that the results of the model are highly sensitive to assumptions regarding pre-treatment, comparative efficacy and safety, and health state utility values. In these exploratory analyses, the ICERs for liso-cel ranged from \$115,000 per QALY to more than \$13 million per QALY. • There was also a scenario in which liso-cel was not on the cost-effectiveness frontier (i.e., more costly and same or fewer QALYs as other CAR T-cell therapies).

DHAP = cytarabine-dexamethasone-cisplatin; GDP = gemcitabine-dexamethasone-cisplatin; ICE = carboplatin-etoposide-ifosfamide; ICER = incremental cost-effectiveness ratio; LBCL = large B-cell lymphoma; LY = life-year; MAIC = matched-adjusted indirect comparison; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor’s analysis: the sponsor’s assumed market shares do not consider the differences in approved indications for treatments, refractory LBCL patients were not considered, differences in the pre-treatment assumptions between CAR T-cell products are uncertain, and individual CAR T-cell trial results may not reflect current AE experiences in Canadian practice. CADTH reanalyses included considering refractory patients in those eligible for CAR T cells, assuming all CAR T-cell therapies have pre-treatment inputs equivalent to liso-cel, and adjusting AE probabilities to match newer data sources.

Although the sponsor suggested that liso-cel would be associated with a budget impact of \$3,183,747 over the 3-year time horizon, based on the CADTH combined reanalysis, the reimbursement of liso-cel for the indicated population may be associated with a budgetary increase of \$655,908 in year 1, \$4,014,550 in year 2, and \$2,208,224 in year 3, for a total 3-year incremental cost of \$6,878,682 when considering the drug plan perspective.

Ethical Considerations

Literature on ethical considerations related to the use of liso-cel for the treatment of R/R LBCL was reviewed. Empirical and normative publications were reviewed for ethical content, using

methods of qualitative description to highlight ethical considerations and themes. Sixty-one publications met the inclusion criteria and were included in the report; none directly reported on the use of liso-cel for the treatment of R/R LBCL, but instead explored LBCL incidence, treatment and outcomes, clinical trial access, clinical care, barriers to access for CAR T-cell therapies, and resource allocation considerations.

- Ethical issues identified in the context of LBCL include disparities in incidence, treatment, and outcomes of patients with LBCL, especially as they impact groups of people who are racialized, marginalized, or of lower socioeconomic status; disparities in clinical trial access; and considerations relevant to clinical care for LBCL, including challenges related to patient-physician relationships, information provision, and patient understanding.
- Ethical issues identified in the context of CAR T-cell therapies relate to barriers to access for CAR T-cell therapies, including those based on costs, geography, and patient selection. Resource allocation considerations identified the need for increased access and fair patient prioritization processes, opportunities to expand access without sacrificing quality and safety, and implications for health systems regarding the high cost of CAR T-cell therapies.
- Considering the risks and benefits of novel CAR T-cell therapies for individual patients highlights the importance of informed consent and balanced communication between clinicians and patients, as well as mitigating “hype” or the inflation of positive outcomes over potential harms.

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: April 13, 2022

Regrets: 1 expert committee member did not attend

Conflicts of interest: None