Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

epcoritamab (Epkinly)

Indication: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma, primary mediastinal B-cell lymphoma or follicular lymphoma Grade 3B after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T cell therapy.

Sponsor: AbbVie Corporation

Recommendation: Time-limited Reimbursement

This recommendation is time-limited and contingent on a reassessment of additional evidence.

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that epcoritamab (Epkinly) be reimbursed for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma, primary mediastinal B-cell lymphoma or follicular lymphoma Grade 3B after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T cell therapy for a time-limited period while additional evidence is generated and only if the conditions listed in

Table 1 are met.

Rationale for the Recommendation

Evidence from one ongoing phase I/II open-label, single arm study (EPCORE NHL-1; which included 157 patients with R/R LBCL) suggested that treatment with epcoritamab may result in clinically meaningful improvements in median overall survival (OS, 18.5 months [95% CI, 11.7 to [redacted]) and progression-free survival (PFS, 4.4 months [3.0 to 8.8]). Additional landmark analyses of OS and PFS at 12- [redacted] and 18-months [redacted] were supportive of the survival analyses. Epcoritamab was associated with a clinically meaningful complete response (CR) rate of [redacted], and durable response (median duration of response [DOR], [redacted] [9.7 to [redacted]). The results of the EPCORE NHL-1 study suggested no detriment in health-related quality of life (HRQoL).

Patients identified a need for additional treatments that result in longer disease remission and improved survival, disease symptom control, and improvement in HRQoL. Furthermore, patients indicated a need for easier access to new treatments that can be received closer to home and are aligned with their preferred treatment goals. Based on the evidence reviewed, pERC concluded that epcoritamab may meet some of these needs including potentially extending disease remission and survival, as well as providing an alternative treatment that may be more tolerable for some patients in this palliative setting compared with regimens that include the use of cytotoxic chemotherapy; no definitive conclusion could be reached regarding the effects of epcoritamab on HRQoL.

Using the sponsor submitted price for epcoritamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) as estimated by CADTH for epcoritamab was $120,435 per quality-adjusted life-year (QALY) gained compared with salvage chemotherapy in patients who had not previously received CAR-T therapy. This analysis was based on the hazard ratio (HR) of [redacted] from the sponsor-submitted indirect treatment comparison (ITC) for epcoritamab versus rituximab-based chemoimmunotherapy (R-CIT; costs informed by the R-GemOx regimen) but did not include a post-progression benefit for patients who received epcoritamab. At this ICER, epcoritamab is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for patients with R/R LBCL after at least two prior lines of therapy. A price reduction is required for epcoritamab to be considered cost-effective at a $50,000 per QALY gained threshold.

pERC noted that Health Canada has mandated the sponsor to complete the ongoing EPCORE DLBCL-1 phase III study and confirm that epcoritamab improves the OS of DLBCL patients compared to investigator's choice of either BR or R-GemOx. Given the considerable uncertainty in the magnitude of clinical benefit and cost-effectiveness, pERC recommends time-limited reimbursement of epcoritamab, with a reassessment of the comparative efficacy and cost-effectiveness when the results of the phase 3 EPCORE DLBCL-1 study are available from the sponsor. pERC noted that this approach would help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness, safety, and cost-effectiveness. The time-limited reimbursement strategy allows the integration of future clinical trial evidence to help shape stronger health policy and drug funding decisions where longer-term follow-up data is required. The sponsor has confirmed that the EPCORE DLBCL-1 results will be filed with CADTH in accordance with the timelines and requirements for a reassessment as described in the *CADTH Procedures for Time-Limited Reimbursement Recommendations*.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult (≥ 18 years) patients with both of the following: 1.1. Relapsed or refractory DLBCL, not otherwise specified, DLBCL transformed from indolent lymphoma, HGBCL, PMBCL or FLG3b 1.2. Have received two or more lines of systemic therapy and have previously received CAR T-cell therapy; declined, are ineligible to receive, or cannot receive CAR-T cell therapy.	In the EPCORE NHL-1 trial, treatment with epcoritamab monotherapy demonstrated a clinical benefit for patients with DLBCL, not otherwise specified, DLBCL transformed from indolent lymphoma, HGBCL, PMBCL or FLG3b who relapsed after or failed to respond to at least two prior systemic treatment regimens. The Health Canada approved indication is limited to patients who have previously received or are unable to receive CAR-T cell therapy.	As outlined in the Product Monograph for epcoritamab, all patients must receive a premedication regimen involving prednisolone or equivalent, diphenhydramine or equivalent, and acetaminophen to minimize the risk of CRS.
Discontinuation		
2. Treatment with epcoritamab should be discontinued upon the occurrence of any of the following: 2.1. Objective disease progression 2.2. Unacceptable toxicity	In the EPCORE NHL-1 study, treatment with epcoritamab was discontinued if a patient experienced disease progression, or intolerable or serious adverse events, which is aligned with clinical practice.	—
3. Patients should be initially assessed clinically at least every 3 months until disease progression, with imaging based on local standards.	In the EPCORE NHL-1 trial, response was evaluated through assessment of PET-CT scans using the Lugano criteria. Based on clinical expert opinion, patients would undergo interim imaging every 3 months to confirm response using Lugano criteria.	—
Prescribing		
4. Epcoritamab should be prescribed by clinicians (hematologists or oncologists) with expertise in the management of LBCL.	This is to ensure that epcoritamab is prescribed only for appropriate patients and adverse effects (e.g., CRS) are managed in an optimized and timely manner.	Based on expert opinion, patients should be treated in a facility familiar with aggressive histology lymphomas and with experience managing CRS/ICANS. Additionally, tocilizumab should be available to treat severe or life-threatening CRS.
5. Epcoritamab should not be reimbursed when given in combination with other systemic anticancer drugs.	There is no evidence to demonstrate a benefit of epcoritamab in combination with other anticancer drugs in the target population.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price.	The ICER for epcoritamab is $120,435 per QALY gained when compared with rituximab based chemoimmunotherapy (costs informed by the R-GemOx regimen), in patients who had not previously received CAR-T therapy, but did not include a post-progression benefit for patients who received epcoritamab. A price reduction of 60% would be required for epcoritamab to achieve an ICER of $50,000 per QALY gained compared to rituximab based chemoimmunotherapy (not including Pola-BR).	—
Feasibility of Adoption		
7. The organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with epcoritamab: 7.1. Access to specialized inpatient facilities for monitoring patients after the full dose of epcoritamab	The lack of availability of the required admissions or ambulatory monitoring facilities may limit access to epcoritamab.	The Product Monograph states that patients should remain within proximity of a healthcare facility and be monitored for signs and symptoms of CRS and ICANS, or alternatively consider hospitalization for 24 hours following administration of the first full dose of 48 mg (Day 15 of Cycle 1).
Time-limited reimbursement		
8. This recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty.	pERC noted that Health Canada has mandated the sponsor to complete the ongoing EPCORE DLBCL-1 phase III study and confirm that epcoritamab improves the OS of DLBCL patients compared to investigator's choice of either BR or R-GemOx.	The sponsor has stated that the clinical study report for EPCORE DLBCL-1 is currently targeted to completion in [redacted] and the results targeted for submission to Health Canada in [redacted]. The sponsor has confirmed that the EPCORE DLBCL-1 results will be filed with CADTH in accordance with the timelines and requirements for a reassessment as described in the *CADTH Procedures for Time-Limited Reimbursement Recommendations.* Based on a [redacted] completion date, the reassessment should be filed with CADTH no later than [redacted]. In accordance with CADTH's procedures, the sponsor must keep CADTH informed of any revisions to the anticipated timelines for the EPCORE DLBCL-1 trial.

BR = bendamustine plus rituximab; CAR-T = chimeric antigen receptor T-cell therapy; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; FLG3b = follicular lymphoma Grade 3B; HGBCL = high grade B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; ICER = incremental cost-

effectiveness ratio; LBCL = large B-cell lymphoma; OS = overall survival; pERC = pCODR Expert Review Committee; PET-CT = positron emission tomography-computed tomography; PMBCL = primary mediastinal B-cell lymphoma; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life-year; R-CIT = rituximab-based chemoimmunotherapy; R-GemOx = rituximab, gemcitabine, and oxaliplatin.

Discussion Points

- **Non-comparative data:** pERC discussed the poor prognosis for patients with R/R LBCL and the need for effective therapies in this patient population alongside the uncertainty of the evidence given the lack of a comparator in the EPCORE NHL-1 trial. pERC agreed with clinical experts that the ORR rate, which was the primary end point of the EPCORE NHL-1 trial, and median and landmark CR, OS, PFS, and DOR observed in the EPCORE NHL-1 trial appeared compelling, durable, and clinically meaningful for patients in an otherwise palliative setting.
- **Unmet medical need:** The committee acknowledged that patients highlighted the need for additional treatments that are easier to access and noted that epcoritamab may meet this need. Although the treatment landscape for R/R LBCL may be changing with the availability of CAR T-cell therapy as a second line therapeutic option (for patients with early relapse or refractory disease), pERC considered that not all patients would be able to access CAR T-cell therapy for various logistical and non-medical reasons, and that this should not disqualify patients from receiving epcoritamab. pERC discussed the subgroup of patients in the EPCORE NHL-1 trial who received prior CAR-T (n = 61 [38.9%]), noting that the CR rate in this subgroup ([redacted]) was comparable with the overall CR rate ([redacted] from the trial. Based on input from clinical experts, an unmet need for patients in the third or fourth-line setting was also identified. pERC noted that epcoritamab may meet this need as an option for patients who have received intensive therapies such as CAR- T or a stem cell therapy who are more likely to experience hematologic toxicity with polatuzumab vedotin with bendamustine and rituximab (Pola-BR) or R-CIT.
- **Comparison versus Pola-BR:** pERC discussed a submitted indirect treatment comparison that compared epcoritamab to Pola-BR by a matching adjusted indirect comparison (MAIC). Results for the MAICs varied across the comparisons for epcoritamab versus Pola-BR. The sponsor claimed significant improvements in PFS, OS, CR rate, and ORR in the overall LBCL population and no significant difference in PFS, OS, or CR rate in the population without prior CAR T-cell therapy. The committee considered the analyses of epcoritamab versus Pola-BR to be associated with significant uncertainty due to small sample sizes and heterogeneity across the studies and patient populations.
- **Comparison versus R-CIT:** The sponsor's indirect comparison suggested that treatment with epcoritamab was superior to CIT for patients with no prior exposure to CAR T-cell therapy; however, there are important limitations with MAIC that pose challenges with evaluating and quantifying the potential added benefit of the treatment (i.e., the small effective sample size [[redacted]] and the heterogeneity across the populations [different study designs, lack of reporting and adjustment for potentially relevant patient characteristics, and differences in the CIT regimens used in SCHOLAR-1]). pERC noted that the clinical experts consulted by CADTH felt that it was plausible that treatment with epcoritamab could be superior to R-CIT for the target patient population on the basis that these patients have already demonstrated disease progression following exposure to an R-CIT regimen (typically R-CHOP) and that the potential toxicity of R-CIT regimens at this stage of disease can limit their clinical utility. pERC noted the challenge remains with quantifying any additional benefit due to limitations of the available indirect comparisons. The committee also noted that R-CIT specifically excludes Pola-BR.
- **Care provision issues:** pERC noted treatments that require inpatient and outpatient delivery of therapy and transitions of care are extremely complicated and not always feasible.
- **Economic evaluation:** pERC discussed the sponsor submitted economic evaluation and noted concerns with the sponsor's modelling approach. These concerns with the modelling approach, along with the uncertainty associated with the comparative clinical efficacy, led to uncertainty associated with the incremental cost-effectiveness estimates of epcoritamab. In accordance with pERC's assessment of evidence comparing epcoritamab and Pola-BR and discussion regarding their place in therapy and sequencing, there is no robust clinical evidence to suggest the total drug cost of epcoritamab should exceed the total drug cost of Pola-BR paid by CADTH-participating drug plans. pERC discussed the uncertainty associated with the post-progression survival benefit for patients receiving epcoritamab, and felt that there was insufficient evidence to support a post-progression benefit associated with epcoritamab. As such, pERC considered the ICER and price reduction (i.e., 60%) derived from the

CADTH scenario analysis where the post-progression survival benefit of epcoritamab was removed, to be more relevant for the assessment of epcoritamab versus R-CIT.

- **Consideration for a time-limited reimbursement recommendation:** Based on the preliminary assessment by CADTH, epcoritamab met the criteria to be considered by pERC for a time-limited reimbursement recommendation. In accordance with the *CADTH Procedures for Time-Limited Reimbursement Recommendations*, the pERC deliberated on the existing gaps in the evidence and the sponsor's evidence-generation plans.

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of Non-Hodgkin's Lymphoma (NHL), accounting for approximately 30% to 40% of all NHL cases in Canada. Diffuse large B-cell lymphomas are a heterogeneous group of aggressive B-cell malignancies that differ in clinical presentation, molecular features, prognosis, and treatment options. The Canadian Cancer Society estimated that 11,400 Canadians were diagnosed with NHL in 2022, with 3000 dying from the disease. For patients who are not chemosensitive and who are ineligible for autologous SCT, who relapse post-SCT or post-CAR-T, the prognosis is poor and there is no standard treatment approach to treatment. Available options are currently limited to palliative chemotherapies including rituximab plus gemcitabine and oxaliplatin (R-GemOx) and polatuzumab vedotin with bendamustine and rituximab (Pola-BR), or clinical trials with novel drugs.

Epcoritamab is a humanized IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.

Epcoritamab is administered via SC injection at a step-up dose of 0.16 mg/0.8 mg/48 mg according to the following schedule:

- Cycle 1: 0.16 mg (priming dose) on Day 1, 0.8 mg (intermediate dose) on Day 8, 48 mg (full dose) on Day 15.
- Cycles 2 and 3: 48 mg once per week over a 28-day period (Days 1, 8, 15, and 22 of the 28-day cycle).
- Cycles 4 through 9: 48 mg once every two weeks (Days 1 and 15 only of each cycle).
- Cycle 10 onwards: 48 mg once every 4 weeks (Day 1 only of each 28-day cycle)

Epcoritamab was issued a Notice of Compliance with Conditions (NOC/c) by Health Canada for use in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma, primary mediastinal B-cell lymphoma or follicular lymphoma Grade 3B after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T cell therapy. Health Canada issued an NOC/c for epcoritamab with the following key confirmatory requirements regarding efficacy:

- The sponsor should commit to submitting a clinical trial to provide confirmatory evidence of efficacy in the setting of R/R DLBCL. Specifically, the primary analyses of Study GCT3013-05: A Randomized, Open-Label, Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in Relapsed/Refractory Diffuse Large B-cell Lymphoma (EPCORE DLBCL-1) should be submitted to Health Canada as an SNDS-C.
- The primary efficacy objective of the EPCORE DLBCL-1 phase III study is to demonstrate that epcoritamab monotherapy improves the OS of DLBCL patients compared to investigator's choice of either bendamustine plus rituximab (BR) or the combination of R-GemOx. The sponsor should acknowledge that authorization may be revoked if the trial fails to show an OS benefit for epcoritamab over investigator's choice of therapy. The sponsor should provide an estimated date of completion of the primary analyses for the study as well as an estimated date for the submission of the study to Health Canada.

Sources of Information Used by the Committee

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

- a review of 1 phase I/II, single-arm, open label trial (EPCORE NHL-1) in adult patients with R/R LBCL who have relapsed after or failed to respond to at least 2 prior systemic therapies; and an indirect comparison submitted by the sponsor.
- patients' perspectives gathered by 2 patient groups, Lymphoma Canada (LC) and The Leukemia & Lymphoma Society of Canada (LLSC)
- 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 LBCL
- input from 3 clinician groups, including Lymphoma Canada, Ontario Health Hematology Cancer Drug Advisory Committee, and the LLSC Nurses Network;
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient groups, Lymphoma Canada (LC) and The Leukemia & Lymphoma Society of Canada (LLSC) responded to CADTH's call for patient input for the current review of epcoritamab. Lymphoma Canada is a national Canadian registered charity that empowers the lymphoma community through education, support, advocacy, and research. LLSC is a national organization dedicated to finding a cure for blood cancers and supporting patients and their families by funding life-enhancing research and providing educational resources, services, and support.

LC gathered Information for this submission via a survey that was launched from October 3 to November 20, 2023, targeting patients living with LBCL. The LC survey data included 33 respondents. Also, LC information used a France submission that was based on a survey regarding the use of Epcoritamab for diffuse LBCL conducted by Ensemble Leucémie Lymphomes Espoir (ELLyE) with 9 survey respondents, supported by results of the Lymphoma Coalition's 2022 survey that included the experience of patients with DLBCL (n = 171). LLSC conducted four 1 on 1 interviews in November 2023; two interviewees were DLBCL patients, and two were caregivers. 3 interviewees reside in Canada, and 1 interviewee resides in the United States.

According to input from both groups, living with LBCL is associated with extreme fatigue, body aches, nausea, shortness of breath and lack of energy, as well as stress and worry, all of which have a significant impact on day-to-day activities and patients' quality of life.

Patient groups identified a need for additional second and third-line treatment options, and they described having difficulties regarding the management of treatment regimens and side effects. Current available treatments have significant mental and psychological tolls on patients and their loved ones, are associated with immense financial burdens, and negatively impact their ability to work, travel long distances, and participate in daily activities. Expectations, according to both inputs, for new treatments to be more effective and less invasive with fewer side effects. Patients are seeking to have a choice in their treatment decisions and a variety of options that offer a longer life span, longer remission, and better quality of life.

Patients indicated that epcoritamab could offer hope and relief to LBCL patients who require a third-line treatment option, and the SC route of administration could mean a less time in hospitals per visit, which can improve the quality of life of patients and caregivers.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH stated that the goal of treatment at this stage is palliative and generally includes maintaining HRQoL through relieving lymphoma-related symptoms, delaying disease progression, and balancing the toxicities of therapy. There is no standard of care in this setting, but options include chemotherapy (e.g., Pola-BR or R-CIT), radiation, and

potential enrolment in clinical trials. The clinical experts stated that there is an unmet need for safe and effective treatments for patients who are not eligible for curative treatment, or whose lymphoma has progressed after second-line treatment consisting of SCT or CAR-T, as there are limited treatment options for disease control, and currently available options are often associated with significant toxicity that limits their usefulness and applicability. Additionally, prognosis of LBCL relapsing post-transplant and post-CAR-T is limited, and poor bone marrow function may prevent patients from receiving or tolerating further cytotoxic therapy. The clinical experts also noted that there is a significant group of patients who may be eligible for intensive treatments but are unable to access them due to barriers based on location. Many patients are unable to travel with caregivers to specialized cellular therapy centres and choose not to have this treatment as they wish to be treated closer to home. As such, there is an additional unmet need for treatments that patients can access and receive closer to home.

After failure of first line R-CHOP (curative intent), treatment for second line consists of salvage rituximab-based chemotherapy and autologous SCT for transplant eligible chemosensitive patients (curative intent), and third line therapy consisting of CAR-T (curative intent). There is no standard of care following these treatment options and transplant ineligible patients in second and third line tend to receive palliative rituximab-based chemotherapy (e.g., Pola-BR or R-GemOx), radiation, and clinical trials. The clinical experts highlighted that there is a planned shift to use CAR T-cell therapy as second line therapy for primary refractory or early relapsed DLBCL pending funding in Canada. The clinical experts emphasized that cytopenias are a major problem of palliative cytotoxic treatment options.

Acknowledging that the Health Canada-approved indication for epcoritamab limits usage to patients “who have previously received or are unable to receive CAR T-cell therapy”, the clinical experts consulted by CADTH highlighted that epcoritamab could be beneficial treatment option for patients:

- for use post-CAR T-cell therapy; or
- for patients that are ineligible to received CAR T-cell therapy; or
- for patients who are eligible to receive CAR T-cell therapy, but could not receive the treatment (e.g., logistical challenges or patient choice).

The experts noted that these patients would be identified in routine practice by clinicians familiar with the treatment of lymphoma patients undergoing surveillance for relapse (clinical and/or imaging). The experts could not identify a specific subgroup of patients that would demonstrate an enhanced benefit, or a reduced benefit from epcoritamab treatment. The experts highlighted that repeat biopsy is not always required in cases of suspected relapsed of DLBCL but is recommended in setting of a late relapse or if the patient had prior history of indolent lymphoma and it was unclear which lymphoma had relapsed.

The clinical experts stated that response to treatment would include standard assessment of lymphoma response using the Lugano criteria. Patients would undergo interim imaging every 3 months to confirm response, which would either lead to ongoing treatment or discontinuation. Patients are also assessed for lymphoma-related symptoms at each visit, however, the clinical experts noted that these outcomes are more subjective but do factor into patients’ decisions for continuation of therapy. The experts also noted that the frequency of these assessments may vary across Canada. In terms of meaningful response to treatment, the clinical experts stated that a response of 6 months or more with improved symptoms can be considered meaningful. The experts did not consider temporary shrinking of tumours beneficial to patients and believed that a meaningful partial or complete response should have a duration of at least 6 months, otherwise epcoritamab should be discontinued. Additionally, with a current median overall survival (OS) of 6 months in this population, the experts considered a benefit of at least 6 months and 3 months over current standard of care to be clinically meaningful for OS and progression-free survival (PFS), respectively.

The clinical experts suggested that treatment with epcoritamab should be discontinued upon overt disease progression or lack of response to treatment. The experts noted that adverse events (AEs) may vary, and resolution of severe AEs can still allow for resumption of therapy, so this is more variable and should be left to physician judgement and patient request before discontinuation.

The clinical experts indicated that patients with R/R DLBCL are typically under the care of hematologists or oncologists who are familiar with the treatment of lymphoma patients. They also noted that the monitoring and treatment of these patients must be

conducted at tertiary centers also with the means to monitor and treat cytokine release syndromes (CRS), which may require some initial training of site staff before implementation.

Clinician Group Input

Three clinician groups, Lymphoma Canada (LC, 3 clinicians contributed to the input), Ontario Health (CCO, 7 clinicians contributed to the input) Hematology Cancer Drug Advisory Committee, and LLSC Nurses Network (6 clinicians contributed to the input), responded to CADTH's call for clinician group input.

According to the clinician groups, there are poor and limited treatment options for patients with R/R DLBCL. LC indicated that for patients who are eligible for aggressive curative intensive therapies, options such as autologous stem cell transplantation (ASCT) and CAR-T therapy are considered. Those who have disease progression post-CAR T-cell therapy or are unfit for CART for medical and/or social reasons have the greatest unmet need for treatment as they do not have another curative intent therapy readily available.

In contrast, those who are not eligible for curative ASCT-based or CAR T-cell therapy approaches are managed with palliative approaches such as Pola-BR or the anti-CD19 antibody tafasitamab in combination with lenalidomide CADTH notes that tafasitamab in combination with lenalidomide received a do not reimburse recommendation and is not currently reimbursement by the participating drug programs. A small percentage of patients might have pursued allogeneic stem cell transplant, but the vast majority of patients in this setting were managed with a variety of palliative chemotherapy regimens, radiation therapy or clinical trials. Multiple novel agents (ibrutinib, lenalidomide, tafasitamab, selinexor) do not have Health Canada approvals or provincial funding for R/R DLBCL.

Clinician groups noted there is an unmet need for safe and effective treatments for patients who are not eligible for CAR T-cell therapy or those who have failed second-line treatment. LC and LLSC Nurses Network added that there are limited treatment options for disease control, and currently, available options are often associated with significant toxicity of past treatments, side effects, and both mental and physical treatment fatigue. LC stated that while ASCT or CAR-T are considered effective for some patients, patients are unable to access them due to barriers based on location, and only a select number of sites are equipped to offer CAR T-cell therapy.

The most important goals of treatment for DLBCL, according to clinician groups, are to prolong survival, delay disease progression, and improve symptoms, which in turn can improve the quality of life of patients and caregivers. Clinician groups agreed, in regard to the indication, that epcoritamab can be used in third line or beyond if the patient was previously treated with CAR T-cell therapy or ineligible for CAR T-cell therapy. LC and LLSC Nurses Network stated that this treatment, as an off-the-shelf product could alleviate regional access issues, and the subcutaneous injection, could possibly become a more feasible and well-favoured option than currently available treatments.

According to the clinician groups, improved survival (PFS, OS), blood work, less presence of cancer cells in their bone marrow, and improvement in disease symptoms are outcomes used to determine whether a patient is responding to treatment. LC added that a clinically meaningful response would be PR or CR, which is typically determined using CT and or PET scans.

The clinician groups agreed that discontinuation of therapy should be considered in patients with disease progression or toxicity and that epcoritamab can be given in any inpatient and outpatient setting that has the ability to admit and monitor patients who are receiving anti-cancer therapy and should have the expertise in managing CRS and neurotoxicity.

Drug Program Input

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

Table 2. Responses to Questions from the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
Based on the preliminary evidence provided by the sponsor (e.g., phase II EPCORE NHL-1 trial), could the clinical experts please comment on how the efficacy and safety of epcoritamab compares to: • Pola-BR • CAR T-cell therapy (tisagenlecleucel, axicabtagene ciloleucel) • R-CIT	The clinical experts and pERC agreed that there was heterogeneity across the different clinical studies for each of these regimens, making it challenging to draw conclusions regarding the comparative clinical benefit of each regimen. However, the clinical experts noted the following: • CAR T-cell therapy would generally be the preferred option for patients who are sufficiently fit to receive the treatment given that it can be a curative regimen and there is longer-term follow-up data in comparison with bispecific antibodies such as epcoritamab. • The clinical experts noted the importance of managing treatment-related toxicity in these heavily pretreated patients and that this may limit usage of Pola-BR and/or R-CIT for some patients.
Considerations for initiation of therapy	
EPCORE-NHL-1 included patients who had received prior CAR T-cell therapy (38.9% of the LBCL population), but it was not requirement for inclusion in the trial. The Health Canada-approved indication for epcoritamab states that patients must have received prior CAR-T or be unable to receive CAR-T therapy. Could the clinical experts please comment on what scenarios make a patient "unable to receive CAR T-cell therapy?	The clinical experts consulted by CADTH noted that eligibility for CAR T-cell therapy is determined by patient factors (e.g., age, cardiac function, renal function, liver function), tumour factors (e.g., rate of tumour progression; extent of extranodal involvement), and issues related to CAR T cell manufacturer and health system capacity. However, pERC noted that there is no evidence to support CAR-T therapy post Epcoritamab.
In a scenario with access to either CAR-T or epcoritamab in a patient who already received 2 prior lines of systemic therapy, what would guide treatment selection?	The clinical experts and pERC agreed that CAR T-cell therapy would generally be the preferred option for patients who are sufficiently fit to receive the treatment given that it can be curative regimen and there is longer-term follow-up data in comparison with bispecific therapies, such as epcoritamab. The clinical experts and pERC also noted that treatment with CAR-T cell therapy is resource-intensive and this can lead to equity and access issues depending on health care system considerations. Additional treatment options, such as epcoritamab, are required for patients who are not candidates for CAR T-cell therapy.
The programs noted that glofitamab (Columvi) is undergoing review by CADTH for a similar indication (i.e., treatment of adult patients with R/R DLBCL NOS, DLBCL arising from follicular lymphoma, or PMBCL, who have received two or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T cell therapy or have previously received CAR-T cell therapy). Drug programs noted that consistency with initiation criteria in the same therapeutic space can be beneficial from a formulary management perspective.	For consideration by CADTH expert committee.

Drug program implementation questions	Response
Considerations for prescribing of therapy	
Depending on the last dose given and the length of any treatment interruptions, the priming schedule may need to be given again once treatment is resumed. Could the clinical experts please comment on the complexity of the dosage schedule and the potential need to repeat the priming and intermediate doses in the event of an interruption?	The clinical experts noted to pERC that monotherapy with epcoritamab could be considered less complicated than many of the alternative regimens, that often involve the IV administration of multiple drugs. The main issue with epcoritamab is the potential need to hospitalize patients at the timing of administering the first full dose of the drug (as hospital capacity issues can be on ongoing challenge within the health care system).
Epcoritamab is administered via SC injection which may offer efficiencies for health care providers and improved quality of life for patients; however, IV access is still required during treatment if supportive care may be required following the administration epcoritamab.	The clinical experts noted to pERC that the fixed-dose SC administration for epcoritamab would offer efficiencies for both patients and health care providers compared with the IV administration required for the existing comparator options. In addition, epcoritamab is given as monotherapy and all comparator regimens are as administered as combinations. This may reduce the time required for patients to be within the cancer treatment centres, offering improvements in quality of life for patients and their caregivers as well as reductions in time for healthcare providers to administer the treatments. pERC however noted that treatment with glofitamab intravenous infusion is recommended for a maximum of 12 cycles while there is no maximum treatment duration recommended for epcoritamab.
Generalizability	
Could the clinical experts please comment on if the EPCORE NHL-1 trial data can be generalized to the following patients: • CNS lymphoma or patients with CNS involvement. • Patients previously treated with another bispecific antibody. • Patients with prior allogeneic stem cell transplant or solid organ transplant.	The clinical experts and pERC noted that these patients were excluded from the EPCORE NHL-1 trial and there is no evidence to support the use of epcoritamab in these circumstances.
EPCORE-NHL-1 included patients who had received prior CAR T-cell therapy, but it was not a required inclusion criterion. Only 38.9% of the EPCORE-NHL-1 patient cohort received prior CAR T-cell therapy, and of those patients [redacted] experienced progressive disease within the first 6 months following CAR T-cell therapy. The Health Canada-approved indication for epcoritamab indicates patients must have received prior CAR T-cell therapy or be unable to receive CAR T-cell therapy. Could the clinical experts please comment if there is a clinical rationale for why patients should be required to have prior CAR T-cell therapy or be unable to receive CAR T-cell therapy to be eligible for epcoritamab?	The clinical experts consulted by CADTH do not believe there is a clinical rationale for why patients should be required to have prior CAR T-cell therapy or be unable to receive CAR T-cell therapy to be eligible for epcoritamab. The clinical experts noted that epcoritamab has been shown to be clinically beneficial for patients who could be considered candidates for CAR T-cell therapy. Acknowledging the absence of studies directly comparing epcoritamab against CAR T-cell therapies, the clinical experts consulted by CADTH noted that CAR T-cell therapy would generally be the preferred option for patients who are sufficiently fit to receive the treatment given that it can be curative regimen and there is longer-term follow-up data.
Care provision issues	
Due to risk of cytokine release syndrome, patients require close monitoring, appropriate supportive care interventions, and hospital admission for certain doses of epcoritamab (i.e., first full dose on Week 3). This represents an increase in resource use of inpatient facilities and increased administrative	For consideration by expert committee regarding organizational feasibility of adoption by the health system. The clinical experts consulted by CADTH noted that reserving a hospital bed for patients who are going to receive treatment with epcoritamab is logistically difficult. In a typical Canadian

Drug program implementation questions	Response
efforts to coordinate inpatient and outpatient settings for epcoritamab on a weekly basis once patients initiate treatment. Use of T-cell engager therapies increases risk of infections, which can be serious and complex. Additional resources may be required to address infectious complications.	hospital setting, the wards are likely to be fully occupied or near fully occupied. In addition, the clinical experts noted that the planned hospitalization would require co-ordination between the outpatient infusion clinics and the inpatient hospital wards. The clinical experts consulted by CADTH noted that patients treated with epcoritamab may also require immunoglobulin infusion support.
Patients experiencing CRS (usually Grade 2 or higher) will require supportive care medication with tocilizumab. If there is concurrent ICANS (and CRS), the product monograph recommends alternatives to tocilizumab 'if possible' (such as anakinra or siltuximab) to manage the toxicity, and potentially further treatment with anakinra. Impact of the costs and acquisition of these therapies adds additional budget impact and logistical complexities. Funding of these therapies needs to be incorporated as part of any implementation to ensure that sites can manage CRS and/or ICANs.	For consideration by expert committee regarding organizational feasibility of adoption by the health system. The clinical experts consulted by CADTH noted that access to these drugs is essential for the safe administration of epcoritamab.
The priming and intermediate doses of epcoritamab require further dilutions of the commercial 5 mg/mL product which represents a time-intensive preparation for Pharmacy staff. The full dose of epcoritamab is a simpler preparation for Pharmacy staff. The priming and intermediate doses use a vial of 5 mg/mL strength (blue vial cap) and further dilution to achieve the intended doses. The full doses use a vial of 60 mg/mL strength (orange vial cap). This introduces a "look-alike, sound-alike" scenario for having two strengths of epcoritamab and careful attention to storage and vial selection will be paramount to safe and appropriate delivery of this therapy.	No response required. For pERC consideration.
System and economic issues	
Drug programs noted that the product monograph recommends that patients be monitored for signs and symptoms of CRS and ICANS for 24 hours after the first full dose of epcoritamab (i.e., 48 mg administered on Day 15 of Cycle 1). The monograph recommends that patients should remain within the proximity of a healthcare facility and be monitored for signs and symptoms of CRS and ICANS, or alternatively consider hospitalization.	For consideration by expert committee regarding organizational feasibility of adoption by the health system. The clinical experts consulted by CADTH noted that, in the event there are no options for 24-hour outpatient monitoring available (e.g., insufficient treatment facility available), patients will likely require short admissions while the treatment is administered. This would likely be the case until criteria are available that would allow proactive identification of those who are at high risk of adverse events with the treatment or until better prophylactic regimens are developed to minimize the risk CRS and/or ICANs.
Epcoritamab is available in two vial strengths: • 4 mg in 0.8 mL for the priming and intermediate doses • 48 mg in 0.8 ml for the full doses. The drug programs noted that these are single use vials and wastage will be incurred during the priming and intermediate dosing given the fixed vial size of 4 mg.	The clinical experts consulted by CADTH agreed that wastage would occur within the pharmacies that are preparing the drug for administration. The clinical experts noted that wastage is an inefficient use of health care resources and that the sponsor could consider marketing alternative dosage strengths that would limit wastage.

Drug program implementation questions	Response
Would the clinical experts agree that there is likely to be wastage given the vial sizes for epcoritamab?	
The budget impact to anticancer and supportive care budgets is of concern. The approved indication indicates prior CAR T-cell therapy is required or patients are “unable” to receive CAR T-cell therapy). PAG notes prior CAR T-cell therapy was not a required inclusion criterion in the EPCORE-NHL-1 trial. Affordability of requiring CAR T-cell therapy (or being “unable” to receive CAR T-cell therapy) prior to epcoritamab is of significant concern.	For consideration by expert committee regarding economic feasibility of adoption.
The intensive monitoring required with early doses of epcoritamab presents increased resource use costs. Not all jurisdictions will have the capacity to admit patients. Additionally, drug costs for inpatient versus ambulatory use may be borne from different drug budgets, depending upon jurisdiction.	For consideration by expert committee regarding organizational feasibility of adoption by the health system. pERC agreed with the clinical experts who noted that the lack of availability of the required admissions or ambulatory monitoring facilities may limit uptake of this treatment.
Commentary on Time-limited Recommendation	
The phase 3 EPCORE-DLBCL-1 trial is comparing epcoritamab to investigator’s choice of chemoimmunotherapy (either BR or R-GemOx). The drug programs have indicated that BR is currently reimbursed in most jurisdictions for relapsed indolent lymphomas. R- GemOx is not a common regimen in Canadian jurisdictions for relapsed LBCL. Could the clinical experts please comment on the clinical relevance of R-GemOx as a comparator for the phase 3 trial.	The clinical experts consulted by CADTH expressed concerns regarding the choice of comparator in EPCORE DLBCL-1 (i.e., BR or R-GemOx), as it was felt that the efficacy data from EPCORE NHL-1 were compelling and that BR and R-GemOx would be associated with significant toxicities for patients. The experts noted that patients at this stage of disease would likely have already received R-CIT earlier in the course of disease and shown to be refractory to the treatment, as such they expressed concerns regarding clinical equipoise in the trial with a belief that those randomized to BR or R-GemOx would be receiving an inferior treatment option. The clinical experts noted that more appropriate comparator(s) would be the newer therapies that have recently emerged in the second- and third-line setting, such as Pola-BR and CAR T-cell therapy. pERC acknowledged that more appropriate comparators could have been considered in the phase 3 EPCORE-DLBCL-1, but noted that this trial may help in confirming and quantifying the potential added clinical benefit with epcoritamab compared with R-CIT and would provide a more robust foundation for an indirect comparison against more relevant comparators (e.g., Pola-BR). In their comments on the draft report, the sponsor clarified that at the start of the EPCORE-DLBCL-1 study (January 2021), neither CAR T-cell therapy nor Pola-BR were widely used. Therefore, R-CIT was considered the most appropriate comparator and that chemoimmunotherapy remains a treatment option used in Canadian practice for the treatment of relapsed or refractory LBCL.

BR = bendamustine plus rituximab; CAR-T = chimeric antigen receptor T-cell therapy; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; IV = intravenous; LBCL = large B-cell lymphoma; PAG = Provincial Advisory Group; PMBCL = primary mediastinal B-cell lymphoma; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; R/R = relapsed or refractory; R-CIT = rituximab-based chemoimmunotherapy; R-GemOx = rituximab, gemcitabine, and oxaliplatin; SC = subcutaneous

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, Phase I/II, open-label, single arm study (EPCORE NHL-1) was included in this review. The review for epcoritamab was based on the dose expansion phase of the study, which consisted of 157 patients with R/R LBCL who have relapsed after or failed to respond to at least 2 prior systemic treatment regimens. Patients were excluded if they had a known primary CNS lymphoma or known CNS involvement. Patients were also excluded if they received CAR T-cell therapy within 30 days or an ASCT within 100 days prior to first dose of epcoritamab. Patients with any prior allogenic HSCT were excluded. Eligible patients received treatment with epcoritamab monotherapy at the step-up recommended doses: priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg (C1D15, C1D22, and the Q4W thereafter until unacceptable toxicity or disease progression). The primary endpoint was ORR rate, with secondary or exploratory endpoints of CR, DOR, PFS, OS, HRQoL, and safety.

The majority of patients in the LBCL ITT population had DLBCL (88.5%) with smaller subgroups who had HGBCL (5.7%), PMBCL (2.5%), or FL grade 3B (3.2%). Patients had received 2 (29.9%), 3 (30.6%), or 4 or more prior lines of antilymphoma therapy (39.5%), and a majority were refractory to their last prior therapy (82.8%). Prior CAR-T cell therapy was reported for 38.9% of patients and 19.7% had received prior stem cell transplant.

Efficacy Results

Table 2 summarizes results for the efficacy end points from the EPCORE NHL-1 trial using the most recent data cutoff date (April 21, 2023).

- **OS:** [redacted] patients died, resulting in a median OS of 18.5 months (95% CI, 11.7 to [redacted]). The estimated proportion of patients who remained alive at 12 and 18-months was [redacted] and [redacted] respectively.
- **PFS:** [redacted] patients experienced a PFS event (disease progression or death) based on the Lugano criteria. The median PFS was 4.4 months (95% CI, 3.0 to 8.8). The estimated percentage of patients remaining progression free at 12 and 18 months was [redacted] and [redacted] respectively. Overall results for the 18 patients in the cohort of other LBCL subtypes were similar to those for the LBCL and DLBCL cohorts.
- **CR**: The CR rate based on Lugano criteria was [redacted] when determined by the IRC and [redacted] when determined by the investigator. The median DOCR was [redacted] when assessed by IRC and [redacted] when assessed by the investigators.
- **ORR:** The ORR (CR + PR) in patients with LBCL was 63.1% (95% CI, 55.0% to 70.6%) with [redacted] and [redacted] patients achieving best response of CR and PR, respectively.
- **DOR:** For patients who had achieved PR or CR [redacted] the median DOR was [redacted] when assessed by IRC using Lugano Criteria. The estimated percentage of patients remaining in response at 12 and 18 months was [redacted] and [redacted] respectively. The median DOR was [redacted] when assessed by the investigators using Lugano Criteria.
- **FACT-Lym Total Score:** 140 patients completed the FACT-Lym and the mean (SD) score at baseline was 118.4 (25.47). At Cycle 5 Day 1 (n = 66) and Cycle 7 Day 1 (n = 52), the mean change from baseline in total score was [redacted] respectively. At the end of treatment assessment (n = 54), the mean change from baseline in total score was [redacted].
- **FACT-G Total Score:** 140 patients completed the FACT-G and the mean (SD) score at baseline was 76.2 (16.86). At Cycle 5 Day 1 (n = 66) and Cycle 7 Day 1 (n = 52), the mean change from baseline in total score was [redacted] respectively. At the end of treatment assessment [redacted] the mean change from baseline in total score was [redacted]

- **FACT-LymS:** The sponsor evaluated six questions from the FACT-Lym that were related to the symptoms of lymphoma (P2 [body pain], BRM3 [fever], ES3 [night sweats], GP1 [lack of energy], BMT6 [tires easily], and C2 [weight loss]). 140 patients completed the FACT-LymS and the mean (SD) score at baseline was 42.2 (9.98). At Cycle 5 Day 1 (n = 66) and Cycle 7 Day 1 (n = 52), the mean change from baseline in total score was [redacted] and [redacted] respectively.

Harms Results

As of the data cutoff date (April 21, 2023), [redacted] patients with LBCL had experienced at least 1 TEAE. A total of [redacted] patients experienced grade 3 or higher TEAEs. The most frequent (at least 20% of patients) TEAEs by preferred term (PT) were CRS (80 [51.0%]), pyrexia (not attributed to CRS; [redacted]), fatigue ([redacted] neutropenia ([redacted] nausea ([redacted] anemia ([redacted] and diarrhea ([redacted] The most common grade 3 or 4 TEAEs (≥5%) by PT in patients with LBCL (N=157) were neutropenia ([redacted] patients), anemia ([redacted] patients), neutrophil count decreased ([redacted] patients), COVID-19 ([redacted] patients), and thrombocytopenia ([redacted] patients). Serious TEAEs were reported in [redacted] patients. The most frequent (≥2%) serious TEAEs by PT in patients with LBCL were CRS ([redacted] COVID-19 ([redacted] patients); COVID-19 pneumonia ([redacted] patients); pleural effusion ([redacted] pneumonia ([redacted] patients); and pyrexia (not attributed to CRS), sepsis, ICANS, and febrile neutropenia ([redacted] patients each). [redacted] patients experienced at least 1 TEAE that led to treatment discontinuation and [redacted] of patients had at least 1 TEAE that led to delayed dosing.

CRS: 80 (51.0%) patients had at least 1 CRS event. The majority of these were grade 1 events (50 of 80 patients) and occurred most frequently after the first full dose of epcoritamab (65 of 80 patients). Grade 2 and grade 3 events occurred in 25 and 5 of 80 patients, respectively. There were no grade 4 or 5 events. The CRS symptoms resolved in [redacted] patients.

Immune Effector Cell-Associated Neurotoxicity: Events of ICANS were reported in 10 (6.4%) patients; 7 (4.5%) patients had grade 1 ICANS, 2 (1.3%) patients had grade 2 ICANS, and 1 (0.6%) patient had grade 5 (fatal) ICANS. [redacted] patients experienced events of ICANS that led to dose delay and in [redacted] patient this event led to treatment discontinuation.

Clinical Tumour Lysis Syndrome: 2 (1.3%) patients experienced events of CTLS, both were grade 3 in severity. [redacted].

Critical Appraisal

EPCORE NHL-1 is an ongoing phase I/II, multicenter, open-label, single-arm study of epcoritamab. EPCORE NHL-1 was conducted as part of a clinical trial program including the ongoing comparative phase 3 trial, EPCORE-DLBCL-1. The single arm trial was justified considering that the study was designed as an early phase I/II study where an internal comparator group is not required, as well as the severity of illness for patients at this stage (i.e., those with refractory or relapsed illness following at least 2 lines of prior systemic therapy). However, the decision to conduct a single-arm study also has implications for the overall strength and interpretability of the results. As a single-arm study, there is an increased risk of bias in the estimation of treatment effects due to the potential for confounding related to natural history and prognostic factors. The potential influence of selection bias is also difficult to ascertain in a single-arm study. Additionally, time to event endpoints cannot be adequately assessed in a single-arm trial because all patients received the same treatment. As such, the effect of epcoritamab on time-to-event endpoints such as PFS, OS, and DOR are uninterpretable and can only be considered as exploratory and supportive.

Health Canada issued an NOC/c for epcoritamab based on promising results from EPCORE-NHL1. In absence of a comparator group in the EPCORE NHL-1, assessing the comparative clinical value of epcoritamab relies on indirect comparisons (unanchored MAICs) which rely on numerous assumptions about the comparability of treatment groups thereby increasing the uncertainty related to the comparative efficacy. The uncertainty in the comparative efficacy of epcoritamab versus relevant comparators was acknowledged by Health Canada who have specified that the sponsor must provide phase 3 trial results showing that epcoritamab improves the overall survival of DLBCL patients compared to investigator's choice of either BR or R-GemOx. In addition to the single-arm design, the study was administered in an open-label manner in EPCORE NHL-1, whereby the investigator and the study participants were aware of their treatment status, potentially increasing the risk of detection bias and performance bias. As such, the open-label trial design limits interpretability of the subjective study outcomes such as tumour response, PROs including HRQoL, and AEs. However, to mitigate the impact of this bias, PFS and ORR were assessed by both IRC and the investigator using the Lugano classification criteria for the response.

The EPCORE NHL-1 study was an international, multicenter study and the clinical experts consulted by CADTH had no concerns regarding generalizability of the study results to the Canadian setting. The clinical experts consulted by CADTH noted that the baseline characteristics were a reasonable reflection of the patient population for whom epcoritamab could be considered an appropriate treatment in Canadian clinical practice. The proportion of patients with an ECOG performance status of 2 was relatively low (3.2%) and the clinical experts noted that this could be greater in clinical practice. The clinical experts noted that 40% of patients with prior CAR-T exposure is a reasonable reflection of the target population in Canada (though noting this would vary across jurisdictions) and that the overall proportion of patients with stem cell transplant could be slightly lower than could be anticipated in routine Canadian practice for patients who have failed 2 or more lines of systemic therapy. The treatment regimen used in EPCORE NHL-1 aligns with recommendations within the Health Canada-approved product monograph for epcoritamab (i.e., priming dose of 0.16 mg; intermediate dose of 0.8 mg; and then a full dose of 48 mg thereafter). The clinical experts consulted by CADTH noted that dosing of epcoritamab and medications used for the management of adverse events throughout the peri-treatment period are reflective of the regimen would be administered in Canadian practice.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials (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 CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

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: median OS, median PFS, change from baseline in HRQoL, and clinical response (CR, ORR, median DOR). For time-to-event outcomes, landmark analyses at 12- and 18-months were also of interest.

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 is 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 target of the certainty of evidence assessment was the presence of a clinically important improvement in survival (OS and PFS) and HRQoL, which were considered the most important outcomes to treatment by the clinical experts consulted by CADTH, and the clinician group and patient group inputs. According to the clinical experts consulted by CADTH, clinically important thresholds for the outcomes of OS and PFS were a benefit of at least 6 months and 3 months over current standard of care for OS and PFS, respectively. Additionally, response to treatment (CR, ORR, DOR) was included in the certainty of evidence assessment based on the potential translation to long-term survival outcomes.

Table 2: Summary of Findings for Epcoritamab for Patients with R/R DLBCL

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
Survival				
OS Follow-up (median): 25.1 months (95% CI, 24.0 to 26.0)	157 (1 single arm trial)	**Median (95% CI) OS:** 18.5 (11.7 to [redacted]) **12-Month OS Rate (95% CI):** [redacted] **18-Month OS Rate (95% CI):** [redacted]	Very Low[b, c]	The evidence is very uncertain about the effects of epcoritamab on OS versus any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
PFS (IRC-Assessed) Follow-up (median): 22.3 months (95% CI, 22.0 to 23.0)	157 (1 single arm trial)	**Median (95% CI) PFS:** 4.4 (3.0 to 8.8) **12-Month PFS Rate (95% CI):** [redacted] **18-Month PFS Rate (95% CI):** [redacted]	Very Low[b, c]	The evidence is very uncertain about the effects of epcoritamab on PFS versus any comparator.
HRQoL				
FACT-Lym Follow up (median): NR	157 (1 single arm trial)	**Total Score:** Mean (SD) CFB to Cycle 5: [redacted] Mean (SD) CFB to Cycle 7: [redacted]	Very Low[b, c, d, e]	The evidence is very uncertain about the effects of epcoritamab on FACT-Lym versus any comparator.
FACT-G Total Score Follow up (median): NR	157 (1 single arm trial)	**Total Score:** Mean (SD) CFB to Cycle 5 [redacted] Mean (SD) CFB to Cycle 7: [redacted]	Very Low[b, c, d, e]	The evidence is very uncertain about the effects of epcoritamab on FACT-G versus any comparator.
FACT-Lym Symptoms Follow up (median): NR	157 (1 single arm trial)	**Total Score:** Mean (SD) CFB to Cycle 5: [redacted] Mean (SD) CFB to Cycle 7: [redacted]	Very Low[b, c, d, e]	The evidence is very uncertain about the effects of epcoritamab on FACT-Lym Symptoms versus any comparator.
Clinical Response to Treatment				
CR (95% CI) (IRC-Assessed) Follow up (median): 20.8 months (95% CI, 20.4 to 21.1)	157 (1 single arm trial)	[redacted]	Low[e]	Epcoritamab may result in a large CR rate, although the evidence is still uncertain.
ORR (IRC-Assessed) Follow up (median): 20.8 months (95% CI, 20.4 to 21.1)	157 (1 single arm trial)	63.1% (95% CI: 55.0, 70.6)	Low[e]	Epcoritamab may result in a large ORR, although the evidence is still uncertain.
DOR (IRC-Assessed) Follow up (median): 20.8 months (95% CI, 20.4 to 21.1)	157 (1 single arm trial)	**Median (95% CI) DOR:** [redacted] **12-Month Event-Free Rate (95% CI):** [redacted] **18-Month Event-Free Rate (95% CI):** [redacted]	Very Low[b, c]	The evidence is very uncertain about the effects of epcoritamab on DOR versus any comparator.

CFB = change from baseline; CI = confidence interval; CR = complete response; DOR = duration of response; FACT-G = Functional Assessment of Cancer Therapy - General; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; HRQoL = health-related quality of life; IRC = independent review committee; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SD = standard deviation.

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a] In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is started at very low.

[b] In the EPCORE NHL-1 trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[c] Rated down 1 level for serious imprecision due to the absence of or very low number of events and small sample size.

[d] Rated down 1 level for serious risk of bias due to potential for bias arising from the open-label nature of the study and the subjective nature of the outcome.

[e] Despite the study limitations resulting in the certainty of evidence starting as 'very low', the outcomes of CR and ORR are demonstrative of an anti-tumour effect, which is supported by regulatory authorities (FDA, Health Canada, EMA). As such, given the effect size, which was believed to be large and clinically important, the CADTH review team considered the certainty of this evidence to be higher. Note that the outcome could be rated down 1 level for serious indirectness as a surrogate outcome (ORR) was used as the primary outcome in the place of OS and PFS.

Indirect Comparisons

Description of Studies

One sponsor-submitted ITC was summarized and critically appraised by CADTH. The MAICs focused on 3 patient populations: (1) overall LBCL population; (2) LBCL with no prior CAR-T cell therapy; and (3) LBCL with no prior CAR-T cell therapy but considered eligible to receive CAR-T. The indirect comparisons of interest for the CADTH review were epcoritamab versus Pola-BR and rituximab-based chemoimmunotherapy (R-CIT). The sponsor submitted ITC included comparisons against three CAR-T regimens: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel). Given that the Health Canada-approved indication for epcoritamab states that the drug is only approved for use in patients "who have previously received or are unable to receive CAR-T cell therapy", CADTH does not consider CAR-T cell therapies to be relevant comparators for the current review. The approach is consistent with applications that have been filed in the same therapeutic area. Outcomes evaluated in the MAIC included OS, PFS, ORR, and CR.

Efficacy Results

Epcoritamab versus polatuzumab vedotin with rituximab, with or without bendamustine (Pola-B/R) (Overall LBCL Population)

In the adjusted overall LBCL patient population, the sponsor reported that epcoritamab was associated with significant improvements in both PFS ([redacted]) and OS ([redacted]) compared to Pola-B/R. The sponsor also reported a significant improvement with epcoritamab versus Pola-B/R in both CR rate ([redacted]) and ORR ([redacted]).

Epcoritamab versus Pola-BR (Patients without Prior CAR T-cell therapy)

Compared with Pola-BR in the analysis for patients with prior CAR T-cell therapy, the sponsor reported no significant difference in PFS ([redacted]), OS ([redacted]), or CR rate [redacted]). The sponsor reported that epcoritamab was associated with an improvement in ORR versus Pola-BR ([redacted]).

Epcoritamab versus CIT (Patients without Prior CAR T-cell therapy)

PFS was unable to be reported for the comparison versus R-CIT in the LBCL with no prior CAR-T population. Compared to CIT, the sponsor reported that epcoritamab was associated with significant improvements in OS ([redacted]); CR rate ([redacted]); and ORR ([redacted]).

Critical Appraisal

Given the lack of direct evidence comparing epcoritamab to relevant treatments in the R/R DLBCL third-line setting, the sponsor's decision to conduct an ITC (i.e., unanchored MAIC) was justified. There were important differences in the design of the included studies and the cohorts evaluated that limit the ability to draw strong conclusions about the efficacy of epcoritamab compared with Pola-BR and R-CIT. The EPCORE NHL-1 study of epcoritamab was a phase I/II, single-arm study, whereas the GO29365 study was a comparative phase Ib/II randomized, open-label study; SCHOLAR-1 was a retrospective research study; and Liebers et al., 2021 was a real-world study. In addition, all of the comparisons involved the use of subgroup data from one or both of the studies included in the indirect comparison.

In addition to differences in study design, there were notable differences in the eligibility criteria of the included studies, which resulted in heterogeneity in baseline characteristics across populations. The sponsor provided a comprehensive list of likely prognostic factors and treatment-effect modifiers (identified through consultation with clinical experts). However, adjustment of all these factors could not be achieved due to differences in reporting across the various studies and a lack of access to patient-level data (other than for those enrolled in the EPCORE NHL-1 trial). It is unclear if the lack of adjustment for differences in baseline characteristics (particularly those which may be prognostic factors such as primary refractory disease) would have an impact on the results of the MAIC. A key limitation of the sponsor-submitted MAICs, which is a limitation inherent to all unanchored MAICs, is that it assumes that all effect modifiers and prognostic factors are accounted for in the model. This assumption is largely considered

impossible to meet, according to the NICE DSU Technical Guidance report on the methods for population-adjusted indirect comparisons.

Overall, CADTH conclude that there were multiple limitations of the sponsor-submitted MAICs, including differences in inclusion and exclusion criteria, heterogeneity in baseline characteristics across studies, as well as notable reductions in sample sizes due to matching and weighting, there was significant uncertainty about the overall generalizability of the results to the Canadian population. Additionally, wide 95% CIs led to imprecision and uncertainty in the results.

CADTH notes that Haute Autorité de Santé (HAS) in France similarly concluded that no formal conclusions can be drawn from the sponsor's MAICs, citing methodological limitations including, uncertainty regarding the quality of the data (particularly the RWE), significant heterogeneity between the populations included in the different studies, and residual differences across the various treatments after weighting. However, NICE in the UK acknowledged that, despite the uncertainty associated with the sponsor's MAICs, epcoritamab was likely to be more effective than R-CIT based on the sponsor's MAIC. Clinical experts consulted by NICE noted that it was plausible epcoritamab was more effective than Pola-BR; however, the NICE expert committee noted that there was too much uncertainty with the indirect comparison and concluded that an assumption of equal efficacy would be more appropriate to inform the economic evaluation.

Long-Term Extension Studies

Not applicable.

Studies Addressing Gaps in the Evidence From the Systematic Review

Not applicable.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partition Survival Model
Target population	Adult patients with R/R DLBCL, not otherwise specified, DLBCL transformed from indolent lymphoma, HGBCL, PMBCL or FLG3b after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T therapy
Treatment	Epcoritamab
Dose Regimen	In cycle 1, a priming dose of 0.16 mg is given on day 1, a 0.8 mg intermediate dose on day 8, followed by 48 mg doses on days 15 and 22. For cycles 2 and 3, 48 mg doses of epcoritamab are provided on days 1, 8, 15 and 22. For cycles 4 to 9, 48 mg doses are administered on days 1 and 15. A 48 mg dose is administered on day 1 of each cycle thereafter until disease progression or unacceptable toxicity.
Submitted Price	Epcoritamab: • 4 mg in 0.8 mL, solution for subcutaneous injection: $550.75 per vial • 48 mg in 0.8 mL, solution for subcutaneous injection: $6,609.00 per vial
Submitted Treatment Cost (per 28-day cycle)	Cycle 1: $14,320 Cycles 2 and 3: $26,436 Cycles 4 to 9: $13,218 Cycles 10 and beyond: $6,609
Comparators	Pola-BR Key scenario analyses: • R-CIT[a] • CAR-T therapies (lisocabtagene maraleucel [liso-cel], axicabtagene ciloleucel [axi-cel], and tisagenlecleucel [tisa-cel])
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs and LYs

Component	Description
Time horizon	Lifetime (30 years)
Key data sources	EPCORE-NHL-1 trial data was used to inform progression free survival (PFS) and overall survival (OS) for epcoritamab, with matching-adjusted indirect comparisons (MAIC) informing the comparative efficacy of relevant comparators
Key limitations	• Clinical expert feedback received by CADTH noted that rituximab-based chemoimmunotherapy (R-CIT) is likely to be the more appropriate comparator in the population eligible for epcoritamab, due to the restricted public funding status of Pola-BR in jurisdictions across Canada, and that Pola-BR would likely have been used in patients prior to the patient receiving CAR-T therapy. The available evidence for R-CIT, however, is in patients who had not previously received CAR-T therapy. Given the wording of the indication, CAR-T was not considered a relevant comparator. • In the absence of direct head-to-head comparative evidence comparing epcoritamab to Pola-BR and R-CIT, clinical efficacy was informed by the sponsor's submitted MAICs. Due to methodological limitations in the MAICs, substantial uncertainty exists in the comparative clinical effectiveness of epcoritamab versus either Pola-BR or R-CIT. This uncertainty in the comparative clinical evidence underpins the economic analysis. • The sponsor assumed that patients in this population who remained progression free 3 years after initiating treatment were considered functionally cured and no longer at risk of progression for the remainder of the model time horizon. This definition did not align with clinical expert expectations for functionally cured patients in clinical practice where functional cure may be defined for patients who are progression free after several years after completing treatment and who have a negative PET scan. As epcoritamab is an ongoing treatment until disease progression or unacceptable toxicity, there remains significant uncertainty as to whether epcoritamab has a curative effect on patients with R/R DLBCL. • The sponsor applied hazard ratios obtained from the submitted unanchored MAICs to the survival curves of epcoritamab from the EPCORE-NHL-1 trial. Clinical expert feedback noted that the sponsor's survival estimates for R-CIT were underestimated, which was a result of the modelling method utilized by the sponsor. • The sponsor's model does not adequately capture the causal relationships between patient characteristics, the probability of progression, and death. Results from the sponsor's model predicted that epcoritamab is associated with longer survival after disease progression compared with current treatment. There is no evidence of a clear mechanism by which epcoritamab would provide clinical benefit to patients with progressive disease. This is aligned with clinical-expert feedback received by CADTH. • CADTH identified several other limitations that may bias results in favour of epcoritamab (including the sponsor's application of RDI and time to treatment discontinuation), and increased uncertainty (poor modelling practices which limited a thorough auditing of the model).
CADTH reanalysis results	• CADTH conducted pairwise reanalyses for epcoritamab versus pola-BR and R-CIT. Additionally, CADTH removed the 3-year functional cure assumption, used the Weibull distribution to inform OS in the analysis versus R-CIT, assumed equal efficacy between epcoritamab versus pola-BR, and set the RDI of included treatments to 100%. • In the CADTH reanalysis comparing epcoritamab to R-CIT in patients who had not previously received CAR-T therapy, epcoritamab was more costly ($300,784 versus $150,374) and more effective (2.21 versus 0.50 QALYs), resulting in an ICER of $87,735 per QALY gained. A price reduction of approximately 45% is required for epcoritamab to be considered cost-effective at a $50,000 per QALY willingness-to-pay threshold. The ICER is likely an underestimate due to the data limitations and inherent biases in the model structure that favour epcoritamab, which are observed in the CADTH scenario analyses including the analyses exploring alternative hazard ratios versus R-CIT or where the post-progression benefit of epcoritamab was removed. • The results of the CADTH reanalysis comparing epcoritamab to Pola-BR (based on the assumption of equal efficacy) found that epcoritamab was more costly ($278,990 versus $251,696). As such, there is insufficient clinical evidence to justify a price premium for epcoritamab relative to the total cost of Pola-BR.

DLBCL = diffuse large B-cell lymphoma; FLG3b = follicular lymphoma Grade 3B; HGBCL = high grade B-cell lymphoma; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparisons; OS = overall survival; PFS = progression free survival; PMBCL = primary mediastinal B-cell lymphoma; pola-BR = polatuzumab vedotin in combination with bendamustine and rituximab; QALY= quality-adjusted life-year; RDI = relative dose intensity; R/R = relapsed or refractory.

[a] In the submitted economic evaluation, rituximab-based chemoimmunotherapy was informed using the cost of the rituximab, gemcitabine, and oxaliplatin (R-GemOx) regimen.

Budget Impact

CADTH identified the following key limitations with the sponsor's BIA: uncertainty in the proportion of patients who relapse and receive third line treatment, uncertainty in the proportion of patients who relapse after CAR-T therapy, inappropriate exclusion of pre-medication drug costs associated with epcoritamab, and uncertainty in using R-GemOx as a proxy for all chemoimmunotherapies costs. The CADTH reanalysis updated the proportion of patients who relapse and receive third-line treatment, incorporated pre-medication drug costs associated with epcoritamab and informed the cost of chemoimmunotherapies as an average between R-GemOx and R-GDP. In the CADTH base case, the budget impact of reimbursing epcoritamab is $3,478,047 in year 1, $14,752,278 in year 2, and $25,799,166 in year 3. Therefore, the three-year total budget impact is $44,029,491.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, 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 10, 2024

Regrets:

Three expert committee members did not attend.

Conflicts of interest:

One expert committee member did not participate due to considerations of conflict of interest.