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CADTH Reimbursement Recommendation

Brexucabtagene Autoleucel (Tecartus)

Indication: For the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia

Sponsor: Gilead Sciences Canada Inc.

Final recommendation: Reimburse with conditions

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

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

Summary

What Is the CADTH Reimbursement Recommendation for Tecartus?

CADTH recommends that Tecartus be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Tecartus should only be covered to treat adult patients who have B-cell precursor ALL whose disease never achieved remission from previous treatments, returned within 1 year after the first remission, returned or did not respond after 2 or more treatments, or returned or did not respond after an allogeneic stem cell transplant (alloSCT).

What Are the Conditions for Reimbursement?

Tecartus should only be reimbursed for patients who have not already received a chimeric antigen receptor (CAR) T-cell therapy, are in relatively good health, do not have leukemia in the central nervous system (CNS), and the cost of Tecartus is reduced. Tecartus should be prescribed and administered by clinicians with expertise in leukemia and cellular therapy or SCT in a hospital setting with adequate resources to perform the procedure and manage side effects.

Why Did CADTH Make This Recommendation?

- In adult patients with relapsed or refractory B-cell precursor ALL, evidence from a clinical trial demonstrated that treatment with Tecartus may be associated with meaningful improvements in remission rates compared to past studies for other treatments, as well as the time until patients experienced disease relapse or died.
- Tecartus may be an effective treatment option for patients who are seeking new treatments with a high complete remission rate, and this treatment may prolong survival.
- Based on CADTH's assessment of the health economic evidence, Tecartus does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Tecartus is estimated to cost the public drug plans approximately $17 million over the next 3 years.

Summary

Additional Information

What Is B-Cell Precursor ALL?

B-cell precursor ALL is a rare, aggressive leukemia in adults in which too many B-cell lymphoblasts (immature white blood cells) are found in the bone marrow and blood. It is estimated that 1,148 people living in Canada have relapsed or refractory B-cell precursor ALL.

Unmet Needs in B-Cell Precursor ALL

Patients with B-cell precursor ALL have a poor prognosis and limited treatment options. Furthermore, not all patients benefit from currently available treatments. Additional treatments that can prolong survival, cure the disease, and improve quality of life are needed.

How Much Does Tecartus Cost?

Treatment with Tecartus is expected to cost approximately $533,500 per infusion.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that brexucabtagene autoleucel be reimbursed for the treatment of adult patients with relapsed or refractory B-cell precursor ALL only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase I and II, open-label, single-arm study (ZUMA-3) demonstrated that treatment with brexucabtagene autoleucel resulted in added clinical benefit for adult patients with relapsed or refractory B-cell precursor ALL. Outcomes evaluated from the phase II part of the ZUMA-3 trial demonstrated that one-time treatment with brexucabtagene autoleucel may be associated with benefits in response rates, overall survival (OS), and relapse-free survival (RFS). The overall complete remission (OCR) rate based on central assessment was 70.9% (95% confidence interval [CI], 57% to 82%), which was higher than the prespecified historical control rate of 40%. At 21 months of follow-up, the median OS was 25.4 months (95% CI, 16.2 to not estimable [NE]), and the median RFS based on central assessment was 11.6 months (95% CI, 2.7 to 20.5). Overall, the OS, RFS, and OCR results were deemed clinically meaningful by clinical experts when compared with expected outcomes in adult patients with relapsed or refractory B-cell precursor ALL.

Patients identified a need for more effective treatments that prolong survival, improve quality of life, and have fewer side effects. Furthermore, patients indicated that there is a need for easier access to CAR T-cell therapy. Given the totality of the evidence, pERC concluded that brexucabtagene autoleucel may meet some of the needs identified by patients, such as prolonged survival and a high complete remission rate.

The committee considered analyses conducted by CADTH that evaluated the cost-effectiveness of brexucabtagene autoleucel relative to inotuzumab ± tyrosine kinase inhibitors (TKIs), blinatumomab ± TKIs, and salvage chemotherapy. Given the uncertainty associated with the comparative treatment effects and the limitations with the modelling approach, CADTH could not estimate a robust single base-case estimate of cost-effectiveness for brexucabtagene autoleucel. Based on the sponsor's submitted price for brexucabtagene autoleucel and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio ranged from $164,545 to $679,053 per quality-adjusted life-year based on the possible range of brexucabtagene autoleucel's extrapolated OS benefits. In all reanalyses, a price reduction would be required for brexucabtagene autoleucel to achieve an incremental cost-effectiveness ratio of $50,000 per quality-adjusted life-year.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Brexucabtagene autoleucel should be reimbursed in adult patients aged 18 years or older	The ZUMA-3 study enrolled patients who had relapsed or refractory B-cell precursor ALL, defined as 1 of the following: primary refractory	—

Reimbursement condition	Reason	Implementation guidance
with relapsed or refractory B-cell precursor ALL, defined as 1 of the following: 1.1. primary refractory disease 1.2. first relapse if first remission ≤ 12 months 1.3. relapsed or refractory disease after 2 or more lines of systemic therapy, or 1.4. relapsed or refractory disease after alloSCT.	disease, first relapse if first remission ≤ 12 months, relapsed or refractory disease after 2 or more lines of systemic therapy, relapsed or refractory disease after alloSCT provided patient is at least 100 days from stem cell transplant and off of immunosuppressive medications for at least 4 weeks.	
2. Patients with Ph+ B-cell precursor ALL may receive brexucabtagene autoleucel if they are intolerant to TKI therapy, or have relapsed or refractory disease despite treatment with at least 2 different TKIs.	Patients with Ph+ B-cell precursor ALL were enrolled in the ZUMA-3 trial if they were intolerant to TKI therapy, or if they had relapsed or refractory disease despite treatment with at least 2 different TKIs.	—
3. Patients must have good performance status.	The ZUMA-3 trial enrolled patients who had an ECOG performance status of 0 or 1.	—
4. Brexucabtagene autoleucel should not be initiated in patients with uncontrolled CNS disease.	The ZUMA-3 trial excluded patients with CNS 3 disease (detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 WBCs per mm^3 with or without neurologic changes) or CNS 2 disease (detectable cerebrospinal blast cells in a sample of CSF with < 5 WBCs per mm^3 with neurologic changes). Patients with CNS 1 disease (no detectable leukemia in the CSF) or CNS 2 disease without clinically evident neurologic changes were included in the ZUMA-3 study.	—
Renewal		
5. Treatment with brexucabtagene autoleucel is a one-time therapy. Brexucabtagene autoleucel should not be reimbursed in patients who have had a previous CAR T-cell therapy.	Brexucabtagene autoleucel is provided as a single-dose, one-time treatment as per the Health Canada product monograph. There is no evidence that patients previously treated with CAR T-cell therapy can benefit from brexucabtagene autoleucel. In the ZUMA-3 study, re-treatment was infrequent (n = 2) and patients who experienced re-treatment did not respond to the second dose of brexucabtagene autoleucel.	—
Prescribing		
6. Brexucabtagene autoleucel should be prescribed by clinicians with expertise in the management of leukemia and cellular	This is meant to ensure that brexucabtagene autoleucel is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	pERC acknowledges that the availability of specialized centres with adequate infrastructure and resources to administer CAR T-cell

Reimbursement condition	Reason	Implementation guidance
therapy or stem cell therapy. Brexucabtagene autoleucel should be administered in specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with CAR T-cell therapy.		therapy in Canada is a barrier that needs to be addressed.
Pricing		
7. A reduction in price	CADTH undertook a price reduction analysis using the sponsor's model based on an alternative set of assumptions around overall survival. These analyses, with differing overall survival estimates, found that a 71% to 88% price reduction for brexucabtagene autoleucel is needed to achieve an ICER of $50,000 per QALY gained. As outstanding uncertainty remains, it was noted that higher price reductions may be required.	—

ALL = acute lymphoblastic leukemia; alloSCT = allogeneic stem cell transplant; CAR = chimeric antigen receptor; CNS = central nervous system; CSF = cerebrospinal fluid; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Ph+ = Philadelphia chromosome positive; QALY = quality-adjusted life-year; TKI = tyrosine kinase inhibitor; vs. = versus; WBC = white blood cell.

Discussion Points

- Since there was uncertainty with the clinical evidence given the single-arm study design of ZUMA-3, pERC deliberated on brexucabtagene autoleucel considering the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the rarity and severity of relapsed or refractory B-cell precursor ALL in adult patients, the committee concluded that while the available evidence of efficacy and safety comes from a noncomparative phase II trial, brexucabtagene autoleucel has the potential to reduce morbidity and mortality associated with the disease.
- pERC discussed the natural history and poor prognosis of relapsed or refractory B-cell precursor ALL in adult patients, and acknowledged the need for effective treatments in a patient population that has limited treatment options. pERC noted that the efficacy outcomes (e.g., survival, response rates) used in the ZUMA-3 study are important to patients and relevant to clinicians. pERC noted that uncertainties remain regarding the magnitude of the clinical benefit from treatment with brexucabtagene autoleucel because of the noncomparative design of the ZUMA-3 study and focus on the modified intention-to-treat (mITT) population (i.e., patients who received brexucabtagene autoleucel) for the analyses. Although the full study population enrolled in the ZUMA-3 trial generally represents the patients in Canada with relapsed or refractory B-cell precursor ALL, the mITT population represents a select population, which may limit the generalizability of the results.

- Patients and clinicians indicated that health-related quality of life (HRQoL) is an important outcome in the treatment of relapsed or refractory B-cell precursor ALL. Although patients need new treatments to improve quality of life, it is uncertain whether this expectation is met by brexucabtagene autoleucel. HRQoL was assessed in the ZUMA-3 study using the 5-level EQ-5D (EQ-5D-5L). The results could not be interpreted due to the amount of missing data. As such, pERC was uncertain about the effects of brexucabtagene autoleucel on HRQoL.
- pERC considered the comparative evidence from a sponsor-submitted matching-adjusted indirect comparison (MAIC) and a retrospective matched cohort study (SCHOLAR-3), and noted that the MAIC and SCHOLAR-3 study had considerable methodological limitations. pERC discussed the MAIC results that suggested OS and event-free survival (EFS) may be prolonged with brexucabtagene autoleucel when compared to blinatumomab, inotuzumab, or chemotherapy. However, definitive conclusions related to the survival benefits of brexucabtagene autoleucel cannot be drawn from this MAIC analysis due to methodological limitations (e.g., heterogeneity, not all prognostic factors and effect modifiers could be adjusted for, small sample size, small evidence base) causing substantial risk of bias in the results. Similarly, data from the SCHOLAR-3 trial suggested that the response rate (e.g., complete remission) in patients treated with brexucabtagene autoleucel in the ZUMA-3 study was higher than those observed in patients who received standard of care in historical trials. However, interpretation of the comparative results from the SCHOLAR-3 trial is limited by the potential for selection bias and unaccounted for confounding despite the propensity score matching approach used in that analysis. Therefore, the statistical inference from the SCHOLAR-3 study findings has low reliability and validity. Due to the limitations of the MAIC and the SCHOLAR-3 study, pERC was unable to draw conclusions on the comparative efficacy of brexucabtagene autoleucel versus other treatments for relapsed or refractory B-cell precursor ALL.
- pERC discussed the immaturity of the OS data for brexucabtagene autoleucel, and that there is currently insufficient evidence to support brexucabtagene autoleucel being a curative treatment. The uncertainty in long-term efficacy was seen in the economic analysis, through the sponsor's use of a naive indirect comparison that was unable to control for varying rates of alloSCT and any other potential confounders. No definitive conclusions could be made by pERC in regard to brexucabtagene autoleucel being curative, and it is difficult to interpret the long-term efficacy of brexucabtagene autoleucel with the confounding impact of alloSCT.
- pERC noted that the harms associated with the brexucabtagene autoleucel infusion are consistent with its mechanism of action and that there were no unexpected safety signals observed. pERC noted that the observed benefits of brexucabtagene autoleucel need to be weighed against the associated harms such as cytokine release syndrome (CRS) and neurologic adverse events (AEs). Although patients desire new treatments that have reduced side effects, it is uncertain whether this expectation is met by brexucabtagene autoleucel. The MAIC and the SCHOLAR-3 study did not assess harms; therefore, the safety of brexucabtagene autoleucel compared to other treatments for relapsed or refractory B-cell precursor ALL remains unknown.

- pERC noted that uncertainties remain regarding the implementation of CAR T-cell therapy and the systems needed to optimize timely access and deliverability of brexucabtagene autoleucel in the real-world setting. Furthermore, patients identified the need for improved access to CAR T-cell therapies. Brexucabtagene autoleucel must be administered at specialized treatment centres with the infrastructure and resources required to administer brexucabtagene autoleucel and treat AEs. However, a limited number of centres in Canada have the expertise and resources to deliver CAR T-cell therapy and it is unlikely that qualified centres will be available in all jurisdictions. Therefore, out-of-province care may be needed for administration of brexucabtagene autoleucel. pERC considered that some patients may be unable to travel outside the province or country to receive therapy.
- pERC discussed ethical and equity considerations related to brexucabtagene autoleucel, including those related to disparities in incidence, treatment, and outcomes of ALL, as well as its physical and psychosocial impacts and access challenges, especially those for racialized populations. Ethical issues were also noted in the context of access to brexucabtagene autoleucel, and how, similar to other CAR T-cell therapies in Canada, the considerable resourcing needs of these therapies can lead to geographic access challenges and related burdens due to travel and absence from work for patients and their caregivers. These challenges may be amplified in racialized populations or for those of from socioeconomically disadvantaged populations. Due to these and other access barriers that can be present, there is a need to develop equitable, transparent, and standardized criteria for CAR T-cell therapy eligibility across the country.

Background

ALL is a rare form of leukemia in adults. It accounts for approximately 5% of all adult leukemia cases in Canada. Among these ALL cases, 80% are of B-cell lineage and the B-cell precursor ALL is found in 75% of adult ALL. About 50% of the patients who have B-cell precursor ALL have relapsed or refractory disease. The estimated prevalence and incidence of relapsed or refractory B-cell precursor ALL is 1,148 and 58 people, respectively, based on an estimated population in 2021 in Canada. Although more than 80% of adult patients with newly diagnosed ALL will achieve a complete remission (CR) with intensive induction chemotherapy, the majority of these patients will ultimately relapse and their prognosis is poor.

For patients with relapsed or refractory B-cell precursor ALL, treatment options include cytotoxic chemotherapy regimens, targeted therapies, alloSCT, and emerging CAR T-cell therapies.

Brexucabtagene autoleucel is a CD19-directed genetically modified autologous T-cell immunotherapy that binds to CD19-expressing cancer cells and normal B-cells. Brexucabtagene autoleucel has been approved by Health Canada for the treatment of adult patients with relapsed or refractory B-cell precursor ALL. The sponsor's reimbursement request is the same as the Health Canada indication. Brexucabtagene autoleucel is available as an IV infusion (target dose of 1×10^6 CAR-positive viable T-cells per kg of body weight, with a maximum of 1×10^8 CAR-positive viable T-cells for patients weighting 100 kg or more).

Sources of Information Used by the Committee

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

- a review of an ongoing, phase I and II, open-label, single-arm study in patients with relapsed or refractory B-cell precursor ALL
- patient perspectives gathered by 1 patient group, the Leukemia and Lymphoma Society of Canada (LLSC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with ALL
- input from 2 clinician groups, including Cell Therapy Transplant Canada and the Ontario Health Cancer Care Ontario (OH-CCO) Complex Malignant Hematology Group
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to brexucabtagene autoleucel.

Ethical Considerations

To identify ethical considerations relevant to the use of brexucabtagene autoleucel for the treatment of adult patients with relapsed or refractory B-cell precursor ALL, input provided by patient groups, clinician groups, and provincial drug programs were reviewed along with information collected through direct engagement with clinical experts and relevant literature.

- Ethical considerations arising in the context of relapsed and refractory ALL highlight impacts on patients as well as disparities in diagnosis, treatment, and treatment outcomes among racialized or socioeconomically disadvantaged populations. Challenges associated with accessing and enduring current second-line treatments, particularly alloSCT, were noted as potential barriers to treatment. Accessing alloSCT may be particularly challenging for those who are racialized given this population's systemic underrepresentation in transplant registries.
- Ethical considerations arising in the evidence used to evaluate brexucabtagene autoleucel highlight limitations related to the absence of long-term effectiveness and safety data and representativeness of trial participants in the ZUMA-3 trial.
- Ethical considerations related to the use of brexucabtagene autoleucel highlight challenges related to the location of specialized CAR T-cell treatment centres and the geographic, financial, and referral barriers faced by patients who do not live near these treatment centres. Cell use, ownership, and challenges around informed consent were also highlighted as considerations in the context of CAR T-cell manufacturing and delivery.
- Ethical considerations for health systems related to the implementation of brexucabtagene autoleucel involve challenges of sustainability to the health care system due to the high cost of CAR

T-cell therapies and the related challenge of navigating limited capacity (e.g., resources and costs to health system) to keep up with the demand for new CAR T-cell therapies.

Stakeholder Perspectives

Patient Input

Patient input for the review of brexucabtagene autoleucel was provided by the LLSC. An online survey was distributed by the LLSC between August 15 and September 21, 2022. A total of 22 individuals across Canada responded to the survey. Two respondents reported experience with brexucabtagene autoleucel.

The majority of the survey respondents indicated that typical symptoms include fatigue or weakness, followed by loss of appetite or weight loss, bone or joint pain, headaches, blurred vision, nausea, or vomiting, which had a significant impact on their ability to work, exercise, and continue everyday activities. This was followed by the ability to travel and pursue activities and hobbies, and intimate relationships. The majority of the survey responses indicated that interruption of life goals and accomplishments (e.g., career and schooling) was a psychological and social factor of the disease that had a significant impact on their quality of life. This was followed by stress, anxiety, worry, feeling isolated, problems concentrating, loss of sexual desire, and financial impacts.

The outcomes that were considered most important to patients when making decisions related to treatment were the degree of certainty that ALL would respond to treatment and improve quality of life. These outcomes were followed by coverage by insurance and drug plans and prolonged survival. Of note, the LLSC indicated that reduced side effects and easier accessibility were frequently mentioned as an improvement that respondents would like to see in any new treatment for ALL.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts indicated that for many adult patients with ALL, the most important treatment goal is to cure the disease and improve their HRQoL. The clinical experts indicated that the prognosis for these patients is poor. Once targeted therapy of blinatumomab or inotuzumab, or SCT have been used and have failed or if such treatments cannot be used, options available to the patients in this situation are limited, which represents an unmet need for effective treatments for B-cell precursor ALL.

The experts stated that brexucabtagene autoleucel can be used in patients who are ineligible for treatment with inotuzumab or blinatumomab, or who have relapsed once or twice after prior treatment with inotuzumab or blinatumomab. The clinical experts indicated that it would be beneficial if all these treatments were available for the patients with relapsed or refractory ALL, which is a difficult-to-treat disease. The experts also agreed that brexucabtagene autoleucel is expected to cause a shift in the current treatment paradigm if it is approved and reimbursed, particularly for patients aged 25 years and up. It was noted that another CAR T-cell therapy, tisagenlecleucel, has been approved by Health Canada for the treatment of patients 3 to

25 years with B-cell precursor ALL who are refractory, have relapsed after SCT or are otherwise ineligible for SCT, or have experienced second or later relapse.

Per the clinical experts, patients with a higher percentage of blasts in bone marrow at baseline or presence of CNS leukemia may have poor response to CAR T-cell therapy. The clinical experts noted that more clinical evidence is needed to identify the subsets of patients with relapsed or refractory B-cell precursor ALL who would be best suited for the treatment with brexucabtagene autoleucel.

The experts indicated that in clinical practice, patients are evaluated and followed in a similar manner described in the ZUMA-3 study. Bone marrow biopsies, the level of remission, and complete blood counts are routinely conducted to assess treatment response. In practice, complete blood counts are assessed during patient's routine visits, while bone marrow biopsy is less frequently performed, unless unusual results from other examinations are observed, or when brexucabtagene autoleucel is used as a bridge to an eventual alloSCT and the clinician wants to know if remission has been achieved at the end of the treatment.

The clinical experts reported that meaningful responses to treatment with brexucabtagene autoleucel include prolonged OS, minimal residual disease negative rate, improved HRQoL, better performance status, and the durability of treatment response.

The experts indicated that treatment with brexucabtagene autoleucel needs to be provided by hematologists and/or oncologists who have experience treating leukemia with cellular therapy or SCT.

Clinician Group Input

Two clinician groups provided input for the review of brexucabtagene autoleucel: Cell Therapy Transplant Canada, which was represented by 4 clinicians, and OH-CCO Complex Malignant Hematology Group, which was represented by 2 clinicians. The OH-CCO Drug Advisory Committees provide evidence-based clinical and health system guidance on drug-related issues.

The clinician group input is consistent with the input provided by the experts consulted by CADTH for the brexucabtagene autoleucel review. They also pointed out that with the currently available targeted therapies such as blinatumomab or inotuzumab, few patients have a long-term remission with these therapies alone, and alloSCT has remained the only curative option for patients with relapsed or refractory disease, but not every patient is eligible to receive this treatment. The clinician group suggested that the patients who are best suited for brexucabtagene autoleucel are adult patients with relapsed or refractory B-cell precursor ALL with morphological disease in the bone marrow (> 5% blasts).

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Relevant comparators for brexucabtagene autoleucel include blinatumomab, inotuzumab, and salvage multidrug chemotherapy. Patients with Ph+ disease are treated with TKIs (e.g., dasatinib and ponatinib). For patients between the age of 18 to 25, tisagenlecleucel may be another comparator; however, it is only available in some jurisdictions across Canada. Tisagenlecleucel is funded for patients who are refractory, have relapsed after alloSCT or are otherwise ineligible for SCT, or have experienced second or later relapse.	This was a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
If brexucabtagene autoleucel is recommended for reimbursement, should patients be required to be ineligible for alloSCT and/or other therapies?	pERC and the clinical experts noted that treatment selection in this patient population should be individualized, and flexibility should be allowed to provide the optimal treatment(s) to patients. The clinical experts indicated that patients with refractory or relapsed Ph+ B-cell precursor ALL may be eligible to receive brexucabtagene autoleucel if their disease has not failed to respond to 2 different TKIs. pERC and the clinical experts agreed that being ineligible for alloSCT and/or other therapies should not be included as a criterion for patients to be treated with brexucabtagene autoleucel.
Is there sufficient evidence to support re-treatment with brexucabtagene autoleucel in case of disease relapse in the future?	pERC and the clinical experts noted there is no evidence to support re-treatment with brexucabtagene autoleucel in the case of disease relapse in the future. Furthermore, pERC noted that there is no evidence to support the use of brexucabtagene autoleucel after prior treatment with tisagenlecleucel.
Which exclusion criteria from ZUMA-3 should be applied in determining eligibility for brexucabtagene autoleucel, if recommended for reimbursement?	The clinical experts indicated that patients with inadequate renal, hepatic, pulmonary, or cardiac function should not be eligible for treatment with brexucabtagene autoleucel. pERC and the clinical experts agreed it is reasonable for patients with HIV infection or hepatitis B to be eligible if the viremia is undetectable and the patients can restart their antiviral therapy soon after or stay on antiviral therapy throughout the brexucabtagene autoleucel treatment. pERC and the experts also indicated that hepatitis C infection should not be considered an exclusion criterion because hepatitis C is potentially curable. pERC agreed with the experts, who indicated that patients with prior noncellular CD19-targeted therapy could be eligible for the treatment with brexucabtagene autoleucel. pERC and the experts agreed that patients with uncontrolled or active CNS disease should be excluded.
Considerations for prescribing of therapy	
Access would be limited to jurisdictional capacity. Although the manufacturer is planning to roll out	This was a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
additional centres across Canada, there are current capacity limitations (e.g., health human resources, bed limitations). As more CAR T-cell products are implemented, it is anticipated that the capacity may not be able to meet the demand. Out-of-province or out-of-country care may still be needed. There may be issues with access and prolonged stay in (or near) specialized centres, especially for patients from remote areas. Financial support for travel and accommodation would be needed.	
The ZUMA-3 study noted that patients who had complete remission could resume TKIs 2 months after brexucabtagene autoleucel infusion and that these patients contributed to the derivation of duration of remission. To what extent did the use of TKIs contribute to the remission?	The clinical experts suggested that the added contribution to maintaining remission from the subsequent TKIs after brexucabtagene autoleucel infusion likely would have been small. The rationale to use subsequent TKIs for patients with Ph+ B-cell ALL is in line with the current guidance on the management of this subtype of B-cell precursor ALL. pERC agreed that the use of TKIs after brexucabtagene autoleucel infusion may be appropriate based on the knowledge of mutation status, prior TKI exposure, and tolerance.
Generalizability	
Should brexucabtagene autoleucel be used in patients with an ECOG PS > 1?	The clinical experts noted that in clinical practice, patients with an ECOG PS of 2 may be treated with brexucabtagene autoleucel. pERC indicated that patients with good PS can be considered for CAR T-cell therapy.
Funding algorithm	
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	This was a comment from the drug programs to inform pERC deliberations.
For patients between 18 and 25 years of age, under what clinical circumstances would brexucabtagene autoleucel be preferred over tisagenlecleucel and vice versa?	pERC and the clinical experts noted that there is a lack of evidence to answer this question; therefore, they could not recommend criteria for the choice of brexucabtagene autoleucel vs. tisagenlecleucel.
Care provision issues	
There will be significant resource use for patient preparation, including leukapheresis, cell processing, and use of bridging and lymphodepleting chemotherapy. People working in specialized centres need to be trained and accredited by the manufacturer. There is a high resource burden to obtain and maintain certification (including developing various protocols and supporting yearly audits). There is a need to coordinate patient care and product preparation with an external manufacturer. There are now specialized centres administering multiple CAR T-cell therapies; managing various protocols for preparation and delivery of each product type poses an administrative burden.	This was a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
System and economic issues	
The drug plans noted there is a need for data collection to understand long-term outcomes. What outcomes should be measured, what constitutes treatment success, and what stopping rules should be considered?	pERC and the clinical experts indicated that overall survival and event-free or relapse-free survival, as well as taking into account late toxicities (e.g., infections and second malignancies) are outcomes for measuring treatment success.
The drug plans noted the following system and economic issues: • Travel expenses for eligible patients are additional costs to be considered. • In some jurisdictions, the cost of CAR T-cell therapy may be through other areas of the ministry rather than the drug programs. • High upfront costs of this gene therapy may require special payment arrangements. • Patient privacy and patient cell ownership concerns exist due to the fact that CAR T-cell therapy is manufactured by a US-based company outside of Canadian jurisdiction. This is also the case for the other publicly funded CAR T-cell therapies.	This was a comment from the drug programs to inform pERC deliberations.

ALL = acute lymphoblastic leukemia; all SCT = allogenic stem cell transplant; CAR = chimeric antigen receptor; CNS = centra nervous system; ECOG = Eastern Cooperative Oncology Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Ph+ = Philadelphia chromosome positive; PS = performance status; TKI = tyrosine kinase inhibitor; vs. = versus.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One clinical study (ZUMA-3) is included the CADTH systematic review. The ZUMA-3 study (N = 71) is an ongoing phase I and II, open-label, single-arm study that is evaluating the efficacy and safety of brexucabtagene autoleucel in patients with relapsed or refractory B-cell ALL. The primary end point is OCR rate (defined as CR + CR response with incomplete hematologic recovery [CRi]) by central assessment. Secondary end points include OS, RFS, duration of response, minimal residual disease negative rate, subsequent alloSCT rate, and HRQoL. A total of 55 of the 71 patients enrolled received brexucabtagene autoleucel and were included in the primary efficacy and safety analyses. Data up to 21 months of follow-up were available at the time of this review with a data cut-off date of July 23, 2021. For patients treated in phase II of ZUMA-3, the median actual follow-up time from the brexucabtagene autoleucel infusion was 20.5 months (range, 0.3 months to 32.6 months). The mean age of patients was 42 years. The majority of patients were male (60%), white (67%), and had an astern Cooperative Oncology Group (ECOG) performance status of 1 (71%). Overall, 27% of patients were Philadelphia chromosome positive (Ph+); 45%, 22%, and 42% of the patients had prior blinatumomab, inotuzumab, or alloSCT, respectively; 33% of the study population had primary refractory disease and 78% had relapsed or refractory leukemia to second-line or greater line therapy. The mean percentage of blasts in bone marrow at baseline was 33%. Extramedullary disease at baseline was

reported in 11% of the patients. All patients had CNS 1 disease (no detectable leukemia in the cerebrospinal fluid) before entering the study.

Efficacy Results

At the data cut-off of July 23, 2021, based on the 21-month follow-up data in phase II of the ZUMA-3 trial, the median OS measured with the Kaplan-Meier method was 25.4 months (95% CI, 16.2 months to NE) in the overall patient population. The median OS was 26.0 months (95% CI, 21.9 months to NE) for those who had achieved CR or CRi, and was 2.4 months (95% CI, 0.7 months to NE) for all other patients who did not achieve CR or CRi. The median OS was not reached (95% CI, 25.4 months to NE) for patients with CR.

Another survival outcome, RFS, was defined as the length of time from the brexucabtagene autoleucel infusion date to the date of disease relapse or death from any cause. The median RFS was 11.6 months (95% CI, 2.7 months to 20.5 months) in the overall population. Among patients with CR or CRi, the median RFS was 15.5 months (95% CI, 11.6 months to NE). The median RFS was 22.1 months (95% CI, 11.6 months to NE) for patients with CR and 11.7 months (95% CI, 1.8 months to NE) for those with CRi.

The OCR rate (including CR and CRi) per central assessment was the primary outcome of the ZUMA-3 trial. For patients in the phase II mITT analysis set in the trial, the OCR rate was 70.9% (39 of 55 patients; 95% CI, 57% to 82%), with a CR rate of 56.4% (31 of 55 patients; 95% CI, 42% to 70%), which was higher than a prespecified historical overall response rate of 40% identified for adult patients with ALL who received standard of care treatment.

Eleven patients (20%) received subsequent alloSCT. Among them, 10 (18%) achieved OCR and 8 (15%) achieved CR.

The median EQ-5D visual analogue scale (VAS) score was 70.0 (range, 5 to 100; n = 51) at screening and increased over time: 80.0 (range, 20 to 100; n = 41) at day 28, 80.0 (range, 50 to 100; n = 26) at month 3, 85.0 (range, 40 to 100; n = 25) at month 6, 87.5 (range, 70 to 100; n = 14) at month 12, [redacted].

Harms Results

At the data cut-off date of July 23, 2021, all 55 patients in the safety analysis set in the phase II component of the ZUMA-3 trial reported at least 1 AE. The most commonly reported AEs included pyrexia (95%), hypotension (67%), anemia (53%), nausea (38%), sinus tachycardia (38%), headache (36%), chills (33%), and decreased platelet count (33%). Serious AEs were reported in 41 patients (75%). The most commonly reported serious AEs were hypotension (29%), pyrexia (27%), and hypoxia (13%). In total, 25 of 55 patients (45%) had died as of the data cut-off date. Eleven patients (20%) had died due to AEs, including 4 (7%) who died due to disease progression within 3 months after the brexucabtagene autoleucel and 7 (1%) who died due to AEs other than disease progression. Brexucabtagene autoleucel is administered as a one-time single infusion; no patients discontinued treatment due to treatment-emergent AEs in the ZUMA-3 trial.

In terms of notable harms, CRS was the most commonly reported notable harm in the study population. A total of 49 patients (89%) had CRS, and 13 (24%) had worst-grade 3 or higher CRS. No patient had grade

5 CRS. Pyrexia, hypotension, sinus tachycardia, chills, and hypoxia were typically reported notable harms. Thirty-three patients (60%) had at least 1 neurologic AE. Frequently reported neurologic AEs in the study population were tremor, confusional state, and encephalopathy.

According to the clinical experts consulted by CADTH, the safety profile of brexucabtagene autoleucel is consistent with other CAR T-cell therapy, and no unexpected safety signals are observed from the included studies.

Critical Appraisal

The single-arm, noncomparative study design for the ZUMA-3 trial is 1 of the key limitations of this evidence. Although the primary efficacy outcome, OCR per central assessment in the mITT analysis set (70.9%), was higher than the prespecified historical control rate of 40%, without a control arm, it is not possible to assess the relative efficacy and safety of brexucabtagene autoleucel versus currently available treatments for patients with relapsed or refractory B-cell precursor ALL based on the results of the ZUMA-3 study. As well, the study design increases the possibility for bias in the estimation of treatment effects due to the potential for confounding related to selection bias, fluctuations in health status, and unidentified prognostic factors.

Another limitation of the ZUMA-3 trial is the relatively small sample size and a selective study population. Although 71 patients were enrolled, only 55 patients received treatment with brexucabtagene autoleucel and were included in the primary analyses. Furthermore, 18 patients (33%) had an important protocol deviation. This as-treated population potentially introduces selection bias because it deviates from the intent-to-treat principle, which could bias the effect estimate away from the null hypothesis, favouring brexucabtagene autoleucel. It is not possible to determine the magnitude of the potential overestimation of the treatment effect based on the available data and conducted analyses from this 1 study.

The follow-up time was likely sufficient for assessing response and safety outcomes associated with brexucabtagene autoleucel. Although the median OS was estimable, the upper limit of the 95% CI was not, suggesting that the follow-up duration was not long enough to fully capture the effects on OS; thus, these results are considered immature.

No conclusion can be drawn for HRQoL outcomes because the analyses on EQ-5D VAS scores had considerable missing data throughout the study time points; [redacted].

After response to infusion of brexucabtagene autoleucel, 20% of the patients received subsequent alloSCT. Some patients may have received other subsequent treatments, such as chemotherapy or TKIs, for the purpose of consolidating the treatment effect from CAR T-cell therapy. Data on subsequent treatments other than alloSCT were not reported. The survival results (OS and RFS) should be considered in the context of subsequent treatments because it may be difficult to tell which treatment has more impact on a patient's survival, especially when there is a lack of comparative data in the ZUMA-3 study.

According to the clinical experts consulted by CADTH, the study population of the ZUMA-3 study generally represents the patients in the Canadian population with relapsed or refractory B-cell precursor ALL who would be receiving brexucabtagene autoleucel. However, the clinical experts noted that patients seen in

clinical practice would include those with poorer performance status (the ZUMA-3 trial only included patients with and ECOG performance status of 0 or 1) and more comorbidities.

According to the clinical experts consulted by CADTH, the efficacy outcomes used in this study are clinically relevant and important for the treatment of relapsed or refractory B-cell precursor ALL. Because ZUMA-3 was an open-label trial, all patients knew about the treatment they received. This would have some impact on patient-reported outcomes such as HRQoL, but would be less likely to affect objective outcomes such as remission rate and OS.

Indirect Comparisons

Description of Studies

The sponsor-submitted indirect treatment comparison (ITC) included a systematic literature review and an unanchored MAIC that compared brexucabtagene autoleucel to targeted therapies (blinatumomab and inotuzumab) or chemotherapy in patients with relapsed or refractory B-cell precursor ALL. Three studies were included in this ITC: ZUMA-3, INO-VATE, and TOWER. The outcomes assessed in the ITC were OS and EFS.

Efficacy Results

The results from the sponsor-submitted ITC suggested that the median OS was longer for brexucabtagene autoleucel than for comparators. The estimated hazard ratios (HRs) for OS ranged from [redacted] for the comparisons to inotuzumab, blinatumomab, chemotherapy, and pooled chemotherapy, respectively. [redacted] for the ZUMA-3 phase II mITT population for the comparisons with inotuzumab and blinatumomab.

The median EFS was longer for brexucabtagene autoleucel than for comparators. The estimated HRs for EFS ranged from [redacted] for the comparisons to inotuzumab, blinatumomab, chemotherapy, and pooled chemotherapy, respectively. Statistical significance depended on the study population the HRs were estimated for (e.g., mITT).

Harms Results

Harm outcomes were not assessed in this ITC.

Critical Appraisal

The authors of the ITC conducted a thorough review of the study design, inclusion and exclusion criteria, patient population characteristics, and outcomes measured in the included clinical trials and identified a number of differences in study design and patient's baseline characteristics across the studies that could potentially threaten the validity of an ITC. The rationale for conducting a MAIC was provided. A limitation of the MAIC is that a MAIC can only adjust for heterogeneity that is directly related to differences in baseline patient characteristics. It is out of scope for a MAIC to account for differences between studies other than patient characteristics, such as those related to differences in study design, definitions of study outcomes, or changes in the management of support of patients over time.

When conducting an unanchored MAIC, identifying all effect modifiers and prognostic factors that could influence the results of the analysis is essential. The technical report indicated that 9 prognostic factors were

identified and confirmed by the clinical experts consulted by the sponsor before the ITC analysis. However, not all factors could be used in the ITC because the complete list prevented the models from converging.

Considerable reductions in the effective sample size were observed during the weighting process. For example, when comparing brexucabtagene autoleucel with inotuzumab for the outcome of OS, the sample size in the phase II ZUMA-3 mITT population reduced [redacted]. This suggests significant heterogeneity between the ZUMA-3 trial and the comparator trials, and could lead to greater uncertainty of the validity of the comparison, as well as poor precision. The results for comparisons with major reductions in effective sample size may not be reliable.

The outcome measures (OS and EFS) assessed in this study were clinically important. Other clinically relevant outcomes were not included in this report, such as treatment response rate, HRQoL, and safety outcomes. Outcome definitions varied across the studies, as well, requiring modifications to the outcome definitions from the ZUMA-3 study to increase similarity with those used in the comparator studies.

Other Relevant Evidence

This section includes a summary of 1 additional relevant study, SCHOLAR-3, which was included in the sponsor's submission to CADTH and considered to provide additional comparative effectiveness data for brexucabtagene autoleucel from the ZUMA-3 trial versus matched historical cohorts.

Description of Studies

SCHOLAR-3 was a retrospective matched cohort study that included adult patients with relapsed or refractory B-cell precursor ALL and compared the patients who received brexucabtagene autoleucel in the modified intent-to-treat (mITT) analysis set from the ZUMA-3[12] phase II study with 2 propensity score-matched historic cohorts of patients (N = 89). The comparator regimens were blinatumomab, inotuzumab ozogamicin, or standard of care (SOC) chemotherapy regimens.

Historic clinical trials were identified within the Medidata Enterprise Data Store database. Eligible historic clinical trials were phase I and II, II, or III, multicentre, multinational, open-label, single-arm or parallel assignment and randomized trials that were conducted between 2010 to 2017.

Two cohorts were created to account for relevant previous treatment experience. The first cohort consisted of patients previously treatment naive to blinatumomab and inotuzumab at enrolment (synthetic control arm 1 [SCA-1]). The second cohort consisted of patients experienced with blinatumomab or inotuzumab (synthetic control arm 2 [SCA-2]).

The inclusion criteria used in the SCHOLAR-3 trial were generally consistent with the inclusion criteria used in the ZUMA-3 trial. Overall, a relatively broader patient population was enrolled in the SCHOLAR-3 trial than in the ZUMA-3 trial. Although response definitions across all historic clinical trials were harmonized to the same definitions used in the ZUMA-3 study, definitions for alloSCT rate, RFS, and OS in the SCHOLAR-3 trial were not completely aligned with the corresponding definitions used in the ZUMA-3 study.[11]

For the ZUMA-3 study, the data cut-off date for the primary analysis was September 9, 2020, and the data cut-off date for the 21-month follow-up analyses and sensitivity analysis that used the full analysis set was

on July 23, 2021. The method for creating the matched historic cohorts of patients to the full analysis set population was consistent with the previously described method.[13] The effectiveness outcomes of OCR, RFS, and OS were analyzed; OCR is designated as the primary outcome for the comparison with SCA-1, while only OS was analyzed for SCA-2 as a result of limited data availability. The secondary effectiveness outcome results were considered as supportive evidence.

Effectiveness Results

The primary outcome analyses were the focus for this review given the limitations of the SCHOLAR-3 study, including the lack of adjustment for multiplicity. For OCR at week 24, the estimated difference in the percentage of patients in the ZUMA-3 mITT population (17 out of 20 patients) compared with patients in SCA-1 (7 out of 20 patients) was 50% (95% CI, 17.9 to 73.7; odds ratio = 10.5; 95% CI, 2.3 to 48.7). The comparison of OS between the ZUMA-3 mITT (N = 29; median follow-up = 24 months) and SCA-2 (N = 20; median follow-up = 24 months) populations suggested that patients in the ZUMA-3 study had a longer median OS (15.90 [95% CI, 3.19 to 26.02] months versus 4.76 [95% CI, 2.66 to 12.35] months; HR = 0.55; 95% CI, 0.26 to 1.13). The results from the sensitivity analysis were generally consistent with this 21-month follow-up updated analysis.

Harms Results

Safety outcomes were not evaluated in the SCHOLAR-3 trial.

Critical Appraisal

Internal Validity

As with the MAIC approach used for the ITC, ensuring homogeneity and accounting for potential confounding, effect modifiers, and prognostic factors is key to the validity of comparisons using external comparison groups. It was noted that duration of first remission of less than 12 months and complex karyotype were not included as factors used in the propensity matching in the SCHOLAR-3 study but were considered valid in the ITC by the clinical experts consulted by the sponsor and by CADTH for this review. Additionally, the heterogeneity of the historic clinical study designs that were included, and the dissimilar baseline characteristics between the ZUMA-3 trial population and that of the historical studies highlights that there is likely confounding of the treatment effect estimates due to known and unknown confounders that could not be adjusted for. It should also be noted that a sensitivity analysis using a matching method other than the primary matching method was not conducted, and as such, the reliability and validity of the results were reduced.

The interpretation of the comparative effectiveness results, specifically the secondary outcomes, in the SCHOLAR-3 study is limited by the sampling approach that was used in the construction of the synthetic control arms. In particular, the data pool for SCA-2 (i.e., those with treatment experience with blinatumomab or inotuzumab) included patients who were previously treatment naive to blinatumomab and inotuzumab and had an on-study treatment switch from blinatumomab or inotuzumab to other SOC treatments. The baseline for these patients was redefined as the first day of the new treatment. Although the number of prior lines of therapy was a prognostic factor used in the propensity score matching, the data pool for SCA-2

was a heterogenous population as patients entered the data pool with different treatment histories (i.e., it included historical patients who were and were not truly treatment experienced with blinatumomab or inotuzumab). Moreover, the data pool for SCA-1 (i.e., those who were treatment naive to blinatumomab and inotuzumab) did not include all eligible historic patients who were treatment naive to blinatumomab and inotuzumab; the impact, if any, of this sampling approach on the results is unknown. The interpretation of the comparative effectiveness results is further limited by the recruitment of patients from both the active and control arms of the historic clinical trials that reflected approved SOC treatments in the Europe Union.

There was no formal hypothesis stated (e.g., superiority), no power or sample size considerations, and no adjustments for multiple comparisons. As such, the statistical inference from the results of this study has low reliability and validity. Additionally, relatively small numbers of patients were included in the analysis sets; according to the preliminary feasibility assessments, it was anticipated that approximately 490 patients were eligible to participate in the study, yet a total of 89 patients formed the primary ZUMA-3 mITT versus SCA-1 and SCA-2 comparisons.

External Validity

In the SCA-1 cohort, 45% of patients were treated with blinatumomab and 55% of patients were treated with SOC chemotherapy; no patients received inotuzumab, which was identified as a relevant comparator by the clinical experts consulted by CADTH for this review.

In the SCA-2 cohort, the majority (90%) of patients were treated with SOC chemotherapy. The clinical experts consulted by CADTH for this review indicated that there is no backbone chemotherapy identified as many options are available, depending on previous treatment experience; moreover, most regimens have been stable since 2010.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by PSM
Target population	Adult patients with relapsed or refractory B-cell precursor ALL
Treatment	Brexu-cel (Tecartus)
Dose regimen	Single-dose cell suspension for infusion containing a target dose of 1×10^6 CAR T-cells per kilogram of body weight, with a maximum of 1×10^8 CAR T-cells for patients weighing 100 kg and more
Submitted price	$533,523.10 per infusion
Treatment cost	$533,523.10 (one-time dose)

Component	Description
Comparators	Blinatumomab ± TKIs (dasatinib or ponatinib) Inotuzumab ± TKIs (dasatinib or ponatinib) Salvage chemotherapy (FLAG-IDA or hyper-CVAD)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (59 years)
Key data sources	The ZUMA-3 trial, the INO-VATE trial (blinatumomab vs. chemotherapy), and the TOWER trial (inotuzumab vs. chemotherapy)
Submitted results	• The ICER for brexu-cel vs. salvage chemotherapy was $58,178 per QALY (incremental costs = $587,667; incremental QALYs = 7.83). • Blinatumomab ± TKI and inotuzumab ± TKI were extendedly dominated[a] by brexu-cel.
Key limitations	• Treatment comparators were modelled using a naive indirect comparison, which introduced substantial uncertainty into the determination of comparative clinical efficacy and the magnitude of any relative benefits associated with brexu-cel. • The sponsor's choice of OS extrapolation for brexu-cel overestimated long-term survival, according to clinical experts consulted during this review. In addition, OS estimates presented a high degree of uncertainty due to data immaturity and the influence of subsequent treatments, including the rate of treatment with alloSCT. • CADTH noted a lack of face validity with EFS and OS extrapolations for comparator treatments. First, the clinical experts consulted for this review indicated that the long-term extrapolation of OS for comparators is likely underestimated and inconsistent with their clinical experience, thus overestimating the brexu-cel benefit. In addition, OS estimates for inotuzumab were substantially higher than for blinatumomab, although indirect comparison studies revealed no statistical difference in OS between the 2 comparators. • Results from the sponsor's model suggest that brexu-cel is associated with higher QALYs observed in the postprogression health state vs. the other comparators. However, there was no clear mechanism by which brexu-cel would continue to provide clinical benefit after disease relapse vs. other therapies. Therefore, this approach produced a biased postrelapse survival benefit that favours brexu-cel. • The duration of treatment was incorporated in the model using average treatment duration for blinatumomab and ponatinib, while the maximum number of cycles was used for inotuzumab and salvage chemotherapy. The use of different approaches to account for the treatment duration of comparators hinders comparability of drug acquisition costs and likely overestimated the cost of inotuzumab and salvage chemotherapy. • The sponsors did not consider re-treatment with brexu-cel in subsequent treatment options, despite it occurring in 4% of patients in the ZUMA-3 trial. Of note, the drug acquisition cost of brexu-cel was $533,523. This omission underestimated subsequent treatment drug acquisition costs, thus favouring brexu-cel.
CADTH reanalysis results	• CADTH was unable to derive a robust single base-case estimate of cost-effectiveness, as key limitations associated with the immaturity of OS data, the use of naive indirect comparisons, and the supposed postprogression survival benefit for brexu-cel could not be addressed. CADTH noted that these limitations likely favour brexu-cel; therefore, any reanalyses performed by CADTH likely underestimated the true ICER. • CADTH's reanalysis addressed the lack of face validity of long-term OS for comparators, the lack of a consistent approach when incorporating comparator's treatment duration, the omission of re-treatment with brexu-cel, and the assumption of a cure point of 2 years. In addition, CADTH

Component	Description
	reanalyses explored the uncertainties associated with long-term treatment efficacy (due to the absence of long-term evidence), by selecting 2 alternative extrapolation curves to inform the OS for brexu-cel: ◦ Reanalysis 1 — OS extrapolation curve with a 5-year and 25-year OS of 26% and 6%, respectively: ICER of $164,545 per QALY gained (incremental costs = $436,206 and incremental QALYs = 2.65 vs. salvage chemotherapy), a 71% price reduction is needed to achieve an ICER < $50,000 per QALY ◦ Reanalysis 2 — OS extrapolation curve with a 5-year and 25-year OS of 21% and 0%, respectively: ICER of $679,053 per QALY gained (incremental costs = $276,672 and incremental QALYs = 0.41 vs. inotuzumab ± TKIs), an 88% price reduction is needed to achieve an ICER < $50,000 per QALY

ALL = acute lymphoblastic leukemia; alloSCT = allogeneic stem cell transplant; brexu-cel = brexucabtagene autoleucel; CAR = chimeric antigen receptor; EFS = event-free survival; FLAG-IDA = fludarabine, cytarabine, idarubicin, filgrastim; hyper CVAD = alternating courses of cyclophosphamide, vincristine, doxorubicin, and dexamethasone with courses of methotrexate, and cytarabine; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; TKI = tyrosine kinase inhibitor; vs. = versus.

[a]Extendedly dominated means in a sequential analysis, when 1 intervention has a higher ICER than the next more costly comparator.

Budget Impact

CADTH identified the following key limitations: the treatment duration was overestimated and inconsistently calculated for comparators; subsequent treatment costs, including re-treatment with brexucabtagene autoleucel, were omitted; and bridging and consolidating chemotherapy costs for patients receiving brexucabtagene autoleucel were omitted.

CADTH's base-case revisions included a change in treatment duration for comparators and the incorporation of bridging and consolidation drug acquisition costs.

Based on CADTH's base case, the expected budget impact for funding brexucabtagene autoleucel for the treatment of adult patients with relapsed or refractory B-cell precursor ALL is expected to be $4,408,819 in year 1, $5,962,938 in year 2, and $7,128,931 in year 3, with a 3-year budget impact of $17,500,689.

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: February 8, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None