Canadian Journal of Health Technologies

CADTH

August 2021 Volume 1 Issue 8

CADTH Reimbursement Recommendation

Brexucabtagene Autoleucel (Tecartus)

Indication: For the treatment of adult patients with relapsed or refractory mantle cell lymphoma after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor

Sponsor: Gilead Sciences Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Tecartus?

CADTH recommends that Tecartus should be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (R/R MCL) after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor if certain conditions are met.

What are the conditions for reimbursement?

Tecartus should only be reimbursed if prescribed as a one-time therapy by experienced specialists in centres delivering cellular therapies, and the cost of Tecartus is reduced.

Which patients are eligible for coverage?

Tecartus should only be covered to treat patients with R/R MCL who have received treatment with a BTK inhibitor (ibrutinib or acalabrutinib) and are in a clinically reasonable health status to tolerate the treatment.

Why did CADTH make this recommendation?

- Evidence from 1 clinical trial demonstrated that Tecartus was associated with clinically meaningful and durable response rates, prolonged survival, and had side effects consistent with other CAR T-cell therapies, thereby meeting the needs of patients with R/R MCL.
- Based on public list prices, Tecartus is not considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to currently reimbursed alternatives. The economic evidence suggested a 99% price reduction is needed for Tecartus to be considered cost-effective at a $50,000 per QALY threshold. A high amount of uncertainty was identified with the cost-effectiveness estimates due to the lack of robust comparative or long-term data.
- The 3-year budget impact to the health care system was estimated to be $46 M, though high uncertainty with this estimate was identified.

Additional Information

What is mantle cell lymphoma?

Mantle cell lymphoma is an aggressive subtype of B-cell non-Hodgkin lymphoma that affects the lymphatic system. In Canada, there are approximately 500 to 600 new cases of MCL diagnosed each year. MCL occurs more frequently in men and is usually diagnosed in patients who are 60 to 70 years old.

Unmet needs in relapsed or refractory mantle cell lymphoma

Patients with R/R MCL whose disease relapse or progress after treatment with a BTK inhibitor have a limited life expectancy and only a few treatment options. Effective treatments extending survival and improving quality of life are needed.

How much does Tecartus cost?

Treatment with Tecartus is expected to have a one-time cost of $533,523 per patient. Additional costs associated with pre- and post-infusion management (i.e., leukapheresis, bridging therapy, conditioning chemotherapy) and administration will also apply.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that brexucabtagene autoleucel should be reimbursed for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (R/R MCL) after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase II, single-arm, open-label study (ZUMA-2, n = 68) demonstrated that treatment with brexucabtagene autoleucel was associated with fast and durable remission through a clinically meaningful objective response rate (ORR) of 93% (95% confidence interval [CI], 83.8, 98.2) and proportion of patients achieving a complete response (CR) to treatment (67% [95% CI, 53.3, 78.3]). Further, neither median progression-free survival (PFS) or median overall survival (OS) were reached (95% CIs, 9.6, NE; and NE, NE, respectively) with 16.8 months follow up. These survival rates are not typically observed in patients with R/R MCL. Brexucabtagene autoleucel was also associated with a significant but manageable toxicity profile, as expected with Chimeric Antigen Receptor (CAR) T-cell therapy. However, pERC acknowledged that there was uncertainty in the magnitude of clinical benefit given the phase II single-arm, open-label, non-randomized, non-comparative design of the ZUMA-2 study. Although patients value new treatments for R/R MCL to improve health-related quality of life (HRQoL), given the amount of missing data, pERC was uncertain about the HRQoL benefit for brexucabtagene autoleucel. Brexucabtagene autoleucel could potentially meet the patient identified values of faster remission, longer life, control of disease and symptoms and providing another treatment option.

The sponsor submitted a matching-adjusted indirect comparison (MAIC) that compared the efficacy of brexucabtagene autoleucel to standard of care (SOC) in terms of OS, PFS, and tumour response outcomes. pERC noted that the uncertainty in the results of the sponsor-submitted unanchored MAIC were compounded by the inclusion of lower quality comparator trials and clinical heterogeneity across studies. Due to the limitations of the indirect treatment comparisons, pERC was unable to draw any conclusions on the comparative efficacy of brexucabtagene autoleucel.

The cost-effectiveness of brexucabtagene autoleucel compared with standard of care (SOC) is highly uncertain given the lack of robust comparative evidence, and limitations with the modelling approach. As such, a base-case cost-effectiveness estimate was unable to be determined in patients with R/R MCL whose disease progressed after treatment with an anthracycline or bendamustine therapy, an anti-CD20 antibody, and a BTK inhibitor. The committee considered exploratory analyses conducted by CADTH and determined that the incremental cost-effectiveness ratio (ICER) was likely closer to the upper range of these results ($422,000), and that brexucabtagene autoleucel is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold. At a $308,000 per QALY ICER, a 99% price reduction would be required to achieve cost-effectiveness at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Brexucabtagene autoleucel should be reimbursed for adult patients (aged 18 years or older) who have all of the following: 1.1. ECOG PS of 0 or 1 1.2. Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14) 1.3. Relapsed or refractory disease, defined by 1 of the following: 1.3.1. Disease progression after last regimen (relapsed) 1.3.2. Failure to achieve a PR or CR to the last regimen (refractory)	This condition reflects the eligibility criteria and place in therapy from the ZUMA-2 trial, as well as guidance from clinical experts.
2. Patients may have received up to 5 prior regimens for MCL. Prior therapy must have included all of the following: 2.1. Anthracycline or bendamustine-containing chemotherapy 2.2. Anti-CD20 monoclonal antibody therapy 2.3. BTK inhibitor	This condition reflects the prior therapies required in the ZUMA-2 trial.
3. Treatment with brexucabtagene autoleucel should not be initiated in patients with: 3.1. ECOG PS ≥ 2 3.2. Multiple comorbidities which are uncontrolled	This condition reflects the exclusion criteria for the ZUMA-2 trial.
Renewal	
4. Treatment with brexucabtagene autoleucel is a 1-time therapy	There is currently no evidence available for repeating treatment with brexucabtagene autoleucel.
Prescribing	
5. Brexucabtagene autoleucel must be administered by experienced specialists in centres delivering cellular therapies with a multidisciplinary team of qualified medical personnel and appropriate capacity to provide urgent ICU care.	Patients undergoing cellular therapy require tertiary care management to ensure that the treatment is administered most effectively and that patients receive optimal care.
6. Brexucabtagene autoleucel should not be used in combination with other treatments for MCL.	There is no evidence to support combining brexucabtagene autoleucel therapy with any other treatment for MCL.
Pricing	
7. Price reduction	The cost-effectiveness of brexucabtagene autoleucel is highly uncertain. CADTH undertook a price reduction analysis based on an exploratory analysis which used data from the MAIC for brexucabtagene autoleucel and removed the cure component. This analysis indicated that a 99% reduction in price is required to achieve an ICER of $50,000 per QALY.

BTK = Bruton's tyrosine kinase; CNS = central nervous system; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICU = intensive care unit; MAIC = matching-adjusted indirect comparison; MCL = mantle cell lymphoma; PR = partial response.

Implementation Guidance

1. Place of brexucabtagene autoleucel in therapy
    - Clinical experts noted that brexucabtagene autoleucel therapy best fits into treatment of relapsed or refractory MCL following failure of a BTK inhibitor. In the ZUMA-2 trial, most patients received brexucabtagene autoleucel treatment following ibrutinib. The clinical experts indicated for patients who are intolerant to ibrutinib, brexucabtagene autoleucel may be administered following treatment with acalabrutinib. pERC noted that intolerance to both (or all) BTK inhibitors is rare; however, in such cases, the use of brexucabtagene autoleucel should be discussed on a case-by-case basis.
    - The clinical experts consulted by CADTH stated that there is currently no evidence available to suggest any benefit of retreatment or sequencing of treatment for brexucabtagene autoleucel; therefore, pERC agreed that switching to brexucabtagene autoleucel is not warranted unless there is disease progression on patients' current therapy.
    - pERC discussed the time-limited need to cover brexucabtagene autoleucel in patients who are on other therapies for R/R MCL, including immunochemotherapies and salvage chemotherapy. Patients currently receiving third- or fourth-line therapy with ibrutinib or acalabrutinib following progressive MCL could be considered for brexucabtagene autoleucel at relapse, given the short duration of expected benefit with the former therapies. pERC noted that switching to brexucabtagene autoleucel should be considered in these patients if they show any signs of relapsing disease following treatment with a BTK inhibitor. Patients should be monitored with frequent imaging to estimate the best time to switch to brexucabtagene autoleucel.
    - pERC noted that for the transplant-eligible younger patients, autologous stem cell transplant (SCT) would be the preferred first-line approach; however, implementation of brexucabtagene autoleucel will likely result in this therapy being given before consideration of allogeneic SCT. Brexucabtagene autoleucel can potentially replace allogeneic SCT.
    - In the ZUMA-2 trial, lymphodepleting chemotherapy (LDC) consisting of fludarabine and cyclophosphamide was administered for 3 days before brexucabtagene autoleucel infusion. Bridging therapy was administered, based on the clinical discretion of the investigator for disease control, after leukapheresis, and was completed at least 5 days before the initiation of LDC. pERC noted that patients who are unable to tolerate fludarabine in the LDC regimen can be considered for brexucabtagene autoleucel. pERC agreed with the clinical experts who consulted with CADTH that bendamustine can be used for LDC in these patients.
2. Priority setting for scarce resources
    - Brexucabtagene autoleucel must be administered at specialized treatment centres. However, a limited number of centres in Canada have the expertise and resources to deliver this treatment 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. Therefore, the committee suggested that the jurisdictions may need to consider developing interprovincial and international (with the US) agreements to ensure equitable access for eligible patients and their caregivers, including consideration of financial and logistic support for required travel and short-term relocation.

- pERC noted that, upon implementation of brexucabtagene autoleucel reimbursement, considerations of distributive and procedural justice may arise where the demand for CAR T-cell therapies (including brexucabtagene autoleucel) exceeds manufacturing and administration capacities, which may be constrained by access to highly-trained personnel and facilities capable of assessing patients' eligibility for therapy, collecting, shipping, and handling cells, as well as administering the therapy. pERC recognized that jurisdictions would need to establish equitable and fair priority setting criteria for patient access to CAR T-cell therapies with key stakeholders, including patients, that are clear, transparent, and based on rationales that are publicly defensible, and with an appeals mechanism.

Discussion Points

- pERC discussed the evidence from 1 phase II, single-arm, open-label trial (ZUMA-2, n = 68) that showed treatment with brexucabtagene autoleucel was associated with fast and durable remission through a clinically meaningful ORR and high proportion of patients who achieved a CR. The median PFS and OS was not reached after a median of 16.8 months follow- up in patients treated with brexucabtagene autoleucel. pERC acknowledged that these survival outcomes are higher than expected in patients with advanced MCL. Brexucabtagene autoleucel was associated with a manageable toxicity profile. However, pERC noted that the observed benefits of brexucabtagene autoleucel need to be weighed against the associated harms including serious cytokine release syndromes (CRS) and neurologic adverse events (AEs).
- Inputs received from patient and clinician groups highlighted that R/R MCL is a rare cancer with a poor prognosis and lack of effective treatment options. pERC concluded that brexucabtagene autoleucel could potentially address patients' unmet needs for a durable treatment that alleviates symptoms, has manageable side effects, and prolongs survival, although the impact on quality of life and delays in disease progression is uncertain.
- Although results of MAIC suggest that brexucabtagene autoleucel may be associated with meaningful improvements in ORR, PFS, and OS, no conclusions on the comparative efficacy of brexucabtagene autoleucel can be drawn due to limitations that are inherent to unanchored indirect comparisons, inclusion of lower quality comparator trials and clinical heterogeneity across studies.
- Clinical experts consulted by CADTH noted that the ZUMA-2 trial may represent a population of patients who are generally healthier than in clinical practice settings. It was noted that the Eastern Cooperative Oncology Group (ECOG) performance status of patients included in the ZUMA-2 trial may be lower than what is seen in clinical practice. Additionally, the proportion of patients who received bridging therapy in the trial was considered by the clinical experts to be lower than the proportion of patients who would require bridging therapy in their clinical practice. pERC agreed that these factors may affect the generalizability of the trial results to the Canadian setting.
- pERC discussed ethical concerns driven by the high cost of brexucabtagene autoleucel, limited number of centres that are authorized to administer the therapy, and geographic constraints on access. It was noted that patients from remote areas would need to have a prolonged stay at or near specialized centres; and that relocation and interprovincial travel will be required for some patients to access this therapy. Travel costs for patients and their caregivers and the requirement for time spent away from work may disproportionately

affect certain populations. Furthermore, pERC agreed with clinical experts that some provinces do not have capacity to assess patients' eligibility for treatment with brexucabtagene autoleucel, which would result in substantive out-of-pocket costs for patients travelling out of province to be assessed for their eligibility for treatment with brexucabtagene autoleucel. For implementation purposes, pERC agreed that there is a need to advocate for equitable patient access not based on ability to pay, and requiring patient support programs or reimbursement for lodging, travel, and other expenses so that all patients in need have timely access to therapy.

Background

Brexucabtagene autoleucel is approved by Health Canada for the treatment of adult patients with relapsed or refractory MCL after 2 or more lines of systemic therapy including a BTK inhibitor. Brexucabtagene autoleucel is an autologous T-cell product manufactured from leukapheresis and administered after LDC, and bridging therapy, as necessary. It is available as a single infusion bag containing a suspension of anti-CD19 CAR T-cells in approximately 68 mL. The target dose is 2×10^6 CAR T-cells per kilogram (kg) of body weight (range: 1×10^6 – 2×10^6 CAR T-cells/kg), with a maximum of 2×10^8 CAR T-cells for patients 100 kg and above.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- A review of 1 phase II clinical trial of brexucabtagene autoleucel in patients with R/R MCL
- Patients' perspectives gathered by a patient group, Lymphoma Canada
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Three clinical specialists with expertise diagnosing and treating patients with R/R MCL
- Input from 2 clinician groups, including Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee and 7 clinicians whose input was coordinated by Lymphoma Canada
- A review of the pharmacoeconomic model and report submitted by the sponsor
- A review of relevant ethical issues related to brexucabtagene autoleucel from published literature.

Patient Input

One patient group, Lymphoma Canada, provided input for the review of brexucabtagene autoleucel, based on information gathered through an anonymous online survey of patients with MCL that was circulated between October 2020 and January 2021. In total, 33 patients provided input on their experience with MCL.

Patients reported that the symptoms of MCL, such as enlarged lymph nodes, fatigue, and gastrointestinal symptoms, aches and pains, and high or low white blood count, had the greatest impact on their quality of life and affected their ability to travel, exercise, concentrate, perform daily activities like household chores, and perform regular duties like working or volunteering. Patients' mental and emotional well-being was negatively affected, and many patients experienced stress, anxiety or worry, and difficulty sleeping.

All patients surveyed rated faster remission and longer life as the most important outcomes for a new therapy. Other important outcomes included control of disease and symptoms, improved quality of life and improved blood counts. Having choice in their treatment selection was rated as very important with a large majority of patients agreeing that there is a need for more effective therapy options.

Most patients would accept a treatment with known, and potentially serious adverse effects, if it was recommended by their doctor. The majority of patients were willing to tolerate adverse effects of a new treatment if they were short-term.

Drug Plan Input

Input was obtained from drug programs (Ministries of Health and/or cancer agencies) participating as part of the CADTH pan-Canadian Oncology Drug Review Provincial Advisory Group (PAG). PAG identified the following key implementation factors:

- place of brexucabtagene autoleucel in treatment of R/R MCL and sequencing with other relevant treatments
- priority setting for scarce resources.

Clinical Evidence

Clinical Trials

The CADTH systematic review included 1 phase II trial, ZUMA-2 (N = 74), which was a single-arm, open-label, multicenter study assessing the efficacy and safety of brexucabtagene autoleucel in patients with R/R MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and/or acalabrutinib).

Key eligibility criteria included pathologically confirmed MCL, with documentation of either cyclin D1 overexpression, or presence of t(11;14) that is relapsed or refractory (R/R) defined by disease progression after the last regimen, or failure to achieve a partial response (PR) or a complete response (CR) to the last treatment regimen. Patients were required to have prior treatment with up to 5 regimens that included all of the following: anthracycline or bendamustine-containing chemotherapy, anti-CD20 antibody, and ibrutinib or acalabrutinib. Therapy with a BTK inhibitor was not required to be the last line of therapy before trial entry, and patients were not required to have disease that was refractory to BTK inhibitor therapy. Patients were also required to have an ECOG performance status of 0 or 1, an absolute

neutrophil count ≥ 1,000/μL, platelet count ≥ 75,000/μL, and an absolute lymphocyte count ≥ 100/μL. Patients were excluded if they had a history of allogeneic, or autologous SCT within 6-weeks of study drug infusion or had a history of CNS or cardiac disorders.

The key limitations of the ZUMA-2 trial included the lack of a comparator arm which can lead to bias in the estimation of treatment effects of brexucabtagene autoleucel, and an open-label design which can increase the risk of bias in reporting of outcomes that are subjective in measurement and in interpretation such as response, HRQoL, and AEs. The risk of bias due to the open-label design may be unavoidable given the rarity of the indication and unmet need in a population where placebo-controlled randomized trials are not methodologically or ethically feasible.

Outcomes

Outcomes of interest to this review assessed in the ZUMA-2 trial included:

- **ORR** was the primary efficacy end point of ZUMA-2, defined as the incidence of CR or PR using central assessment of PET–CT (PET/CT) scans per the Lugano lymphoma staging classification. Scans were conducted 4 weeks post-treatment and repeated every 3 months, and as needed for patients that displayed symptoms suggestive of disease progression. Evaluations of bone marrow were also needed to confirm CR.
- **Duration of Response (DOR)** was evaluated only for patients who had an objective response (CR or PR) and was defined as the time from the first objective response to disease progression or death, using disease assessments (central and investigator assessment).
- **PFS** was defined as the time from the brexucabtagene autoleucel infusion date to the date of disease progression or death from any cause using both central assessment and investigator assessment. In the full analysis set, PFS was defined as the time from the enrolment date to the date of disease progression or death from any cause.
- **OS** was defined as the time from the brexucabtagene autoleucel infusion to the date of death from any cause. In the full analysis set, OS was defined as the time from enrolment to the date of death from any cause.
- **HRQoL** was assessed using the EQ-5D questionnaire at screening (for baseline scores), Week 4 (± 3 days), Month 3 (± 1 week), and Month 6 (during the long-term follow-up period).

Efficacy

The primary efficacy outcome of the ZUMA-2 trial was ORR using central assessment. Two data cut-off dates were included; the July 24, 2019 data cutoff representing a 12.3-month median follow up, and December 31, 2019 that was focused on results at a longer-term median follow up of 16.8 months.

As of the July 24, 2019 data cut-off date, the primary end point of ZUMA-2 was met. The ORR was 93% (95% CI, 83.8%, 98.2%) with 67% (95% CI, 53.3%, 78.3%) of patients achieving a CR. As of the December 31, −2019 data cut-off date, the ORR was 92% (95% CI, 81.6%, 97.2%), with 67% (95% CI, 53.3%, 78.3%) of patients achieving a CR. The median time to response (CR or PR) was 1.0 month (range: 0.8 to 3.1 months) and the median time to achieve a CR was 3.0 months (range: 0.9 to 9.3 months). At both data cutoffs, ORR was significantly greater than the pre-specified historical control of 25% ($P < 0.0001$), as the lower limit of the 95% CI

for ORR exceeded higher historical control margins. At both data cuts, pre-specified subgroup analyses for ORR were consistent with the primary analyses.

Key secondary outcomes included DOR, PFS, and OS. As of the July 24, 2019 data cutoff, and a median follow-up time for DOR of 8.6 months, the median DOR was not reached. In patients who achieved a PR, the median DOR was 2.2 months (95% CI, 1.4 months, not evaluable). With a median follow-up time for DOR of 14.1 months at the December 31, 2019 data cutoff, the median DOR was still not reached (95% CI,13.6 months to not estimable).

As of the July 24, 2019 data cutoff, the median PFS and median OS were not reached (PFS 95% CI, 9.2 to not evaluable; OS 95% CI, 24.0, not evaluable). The 6-, 12-, and 24-month PFS rate estimates were 77.0%, 60.9%, and 56.9%, respectively; and the corresponding OS rates were 86.7%, 83.2%, and 66%, respectively. As of the December 31, 2019 data cutoff, the median PFS and OS remained unreached (PFS 95% CI, 9.6, not evaluable; OS 95% CI, not evaluable, not evaluable). Kaplan–Meier estimates of PFS rate at 6 months and 12 months were similar to the primary data cut at 76.8% and 62.2%, respectively. The 24- and 33-month PFS rate estimates were 55.5% and 50.5%, respectively. Kaplan–Meier estimates of OS were comparable to the primary data cutoff with rates of 86.7%, and 83.3% at 6- and 12 months, and were 68.8% in the 24- and 36-month estimates.

HRQoL was measured by the EQ-5D in the ZUMA-2 trial. A total of 62 patients (91%) completed the questionnaire at study screening, however only 42 (62%) completed the questionnaire at 6 months. The proportion of patients experiencing moderate to severe health problems increased in the first month following infusion with brexucabtagene autoleucel for all EQ-5D subscales; however, longitudinal changes in HRQoL cannot be interpreted due to the decreasing numbers of patients reporting for HRQoL assessments over time. Overall, the median visual analogue scale (VAS) score improved by 5 points from 85.0 to 90.0 from screening to month 6 and by 12 points from 78.0 at week 4 to 6 months. An improvement of 7 to 12 points on the VAS in patients with advanced cancer is considered a clinically meaningful difference; however, given the missing data at later time points, interpretations in change over time cannot be made.

Harms

At least 1 treatment emergent AE was reported in all patients, of which 99% had AEs that were Grade 3 or higher (16% Grade 3, 76% Grade 4, and 6% Grade 5). The most common Grade 3 or higher AEs at the primary data cutoff were anemia (50%), decreased neutrophil count (50%), and decreased white blood cell (WBC) count (40%). In the updated analysis, the most common Grade 3 or higher treatment emergent AEs were also decreased neutrophil count (53%), anemia (51%), and decreased WBC count (41%). Grade 3, 4, and 5 serious adverse events (SAEs) were recorded in 29%, 19%, and 6% of patients, respectively. The most common Grade 3 or higher SAEs were encephalopathy (18%), hypotension (12%), and hypoxia (12%). Two patients had Grade 5 SAEs of B-cell lymphoma, who died due to disease progression. At the December 31, 2019 data cutoff, Grade 3, Grade 4, and Grade 5 SAEs were similar to the primary analysis and were observed in 31% and 19%, and 6% of patients, respectively. The most common Grade 3 or higher SAEs were encephalopathy (16%), pneumonia (which increased to 13% from 7%), and hypotension (12%).

Notable harms evaluated in the ZUMA-2 trial included CRS, and neurologic events. CRS occurred in 91% of patients with the most common Grade 3 or higher CRS symptoms including hypotension (25%), hypoxia (19%), and pyrexia (11%). The median time to onset of

CRS was 2 days after the brexucabtagene autoleucel infusion, with a median duration of 11 days (range = 1 to 50 days). As of the July 24, 2019 data cutoff, CRS had resolved in all 62 patients. Neurologic AEs occurred in 63% of patients, with 22% and 9% of patients reporting Grade 3 and 9% of patients reporting Grade 4 neurologic events, respectively; no patients reported a Grade 5 neurologic event. The most common Grade 3 or higher neurologic events were encephalopathy (19%), confusion (12%), and aphasia (4%). Median onset of a neurologic event following brexucabtagene autoleucel infusion was 7 days, and in patients whose neurologic events had resolved, the median duration of neurologic events was 12 days (range = 1 to 567 days). Three patients had neurologic events beyond 200 days that were attributed to lymphodepleting chemotherapy and brexucabtagene autoleucel.

Overall, there were 18 deaths in the ZUMA-2 trial (26%), 16 (24%) of which were attributed to progressive disease, while 2 (3%) were reported to be due to AEs including organizing pneumonia and staphylococcal bacteremia, both deemed related to lymphodepleting chemotherapy, and 1 patient (1%) with an unknown cause of death. The majority of deaths occurred more than 3 months after the brexucabtagene autoleucel infusion (14 of 18 deaths).

Indirect Evidence

In the absence of head-to-head studies, the sponsor submitted indirect treatment comparisons (ITC) that compared the efficacy of brexucabtagene autoleucel to SOC treatments. The evidence base for the ITC was identified through a systematic literature review to identify studies reporting on treatment outcomes for the post-BTK inhibitor R/R MCL population. The systematic literature review identified 9 uncontrolled, mainly retrospective, open-label studies that provided outcome data in patients with relapsed or refractory MCL who received the study treatment(s) following BTK inhibitor therapy. The SOC trials used lenalidomide-based treatments, venetoclax, R-BAC (rituximab, bendamustine, cytarabine), RiBVD (rituximab IV, bendamustine, velcade subcutaneous [SC] bortezomib, dexamethasone IV), or mixed treatments (various chemo-immunotherapies or systemic therapies).

Absolute treatment effects of SOC treatments, in terms of OS, PFS, and tumour response (ORR, CR, and PR), were estimated using a meta-analysis of studies identified from the systematic literature review. The efficacy of brexucabtagene autoleucel, relative to SOC, was estimated using a MAIC. For the MAIC analysis, a logistic propensity score model was used to match individual patient-level data for brexucabtagene autoleucel from the ZUMA-2 trial with the aggregate study-level data from the SOC studies identified in the literature review, so that the weighted mean baseline characteristics of the ZUMA-2 patients matched the pooled mean characteristics of the SOC studies. The following baseline patient characteristics were included in the MAIC as covariates: number of prior therapies, prior autologous stem cell transplantation, duration on prior BTK inhibitor therapy, response to prior BTK inhibitors, Ki67 proliferation index, and blastoid morphology variant. The primary MAIC analyses reported a hazard ratio (HR) of 0.18 (95% CI, 0.09 to 0.38;4 studies; effective sample size: 36.2) for OS, HR of 0.50 (95% CI, 0.31 to 0.76, 2 studies, effective sample size 16.3) for PFS, and an odds ratio of 7.91 (95% CI, 2.35 to 26.62, 8 studies, effective sample size 29.5) for ORR. The sponsor-submitted MAIC did not assess safety outcomes for brexucabtagene autoleucel.

The key limitation of the MAIC is the assumption that absolute outcomes can be predicted from the covariates included in the model. This assumption is largely considered impossible to meet and failure of this assumption leads to an unknown amount of bias in the unanchored estimate. For the sponsor-submitted ITC, some prognostic factors were excluded from the

model or may have been incompletely specified due to missing data from the clinical trials. Effective sample size was small for all outcomes (16 to 36). which suggests poor population overlap and unstable estimates. The results for the tumour response outcome lacked precision and showed wide 95% CIs. Uncertainty in the results of the unanchored MAIC are compounded by the inclusion of lower quality comparator trials and clinical heterogeneity across studies. Due to the limitations of the ITC, no conclusions on the comparative efficacy of brexucabtagene autoleucel can be drawn from the MAIC.

Economic Evidence

Cost and Cost-Effectiveness

The submitted price of brexucabtagene autoleucel is $533,523 per infusion (target dose of 2×10^6 CAR T-cells per kg, with a maximum of 2×10^8 cells). This does not include costs associated with leukapheresis, bridging therapy, and conditioning chemotherapy (i.e., LDC) which are typically required for patients receiving treatment with brexucabtagene autoleucel. This is assumed to be a one-time infusion and one-time cost.

The sponsor submitted a cost-utility analysis comparing brexucabtagene autoleucel with best supportive care (BSC), defined as a blended comparator which included rituximab, bendamustine, and bortezomib, in patients with relapsed/refractory MCL whose disease progressed after treatment with anthracycline or bendamustine therapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and/or acalabrutinib). The submitted model was a partitioned survival mixture-cure model (PSMCM) with 3 states, pre-progression, post-progression, and death. All patients entered the model in the pre-progression health state. The proportion of patients in each health state at any point in time was based on direct modelling of OS and PFS curves, which the sponsor extrapolated over the time horizon of the analysis using parametric methods. The sponsor incorporated a cure component; patients whose disease did not progress within the first 5 years were considered functionally cured (e.g., experiencing long-term remission and survival). The key efficacy data for brexucabtagene autoleucel were derived from the single-arm ZUMA-2 trial of the treatment in patients with MCL, while the key data used to inform BSC were obtained from a sponsor-commissioned meta-analysis of published retrospective studies and qualitative interviews with clinical experts; no direct or indirect comparative information was used to inform the sponsor's base case. Health state utility values were derived from the published literature. The analysis was undertaken from the perspective of the Canadian public health care system and adopted a lifetime time horizon (i.e., 50 years).

CADTH identified several key limitations with the submitted analysis:

- The clinical efficacy of brexucabtagene autoleucel is uncertain. ZUMA-2 is an open-label, single-arm phase II study limited by a small sample size and short duration of follow up. The study design resulted in an inability to control for confounding and unblinded assessment of subjective outcomes which may inhibit the interpretation of the results.
- Although follow-up time in ZUMA-2 was considered appropriate to assess response to treatment, it was not considered mature for assessing survival outcomes. Thus, the extrapolated benefits are associated with high uncertainty and the choice of a PSMCM with a 5-year functional cure point may not have been appropriate.

- Although the sponsor commissioned an MAIC comparing data from ZUMA-2 with the trials identified in sponsor-commissioned meta-analysis, the MAIC results submitted by the sponsor lacked face validity due to heterogeneity in the patient populations of ZUMA-2 and the studies cited to inform BSC. The sponsor's model was based on a naive comparison, which is associated with its own potentially erroneous assumptions, such as conditional constancy. No conclusions can be drawn regarding the comparative clinical effectiveness of brexucabtagene autoleucel and BSC.
- Relevant costs associated with brexucabtagene autoleucel were underestimated or excluded from the analysis. Bridging therapy and leukapheresis were underestimated, while costs associated with tests to determine patient eligibility were not incorporated and neither were costs associated with the use of IV immunoglobulin (IVIG).

The limitations with the clinical trial data, such as the inability to control for confounding and the unblinded assessment of subjective outcomes that may inhibit the interpretation of the results, and the lack of robust comparative data meant that no conclusions could be drawn regarding the comparative clinical effectiveness of brexucabtagene autoleucel with currently available treatments. As such, a CADTH base case could not be derived. Corrections were made to the sponsor's analysis involving an updated cost of leukapheresis and more accurate assumptions around use of bridging therapy; and CADTH undertook a series of exploratory analyses involving alternate efficacy assumptions, alternate parametric modelling approaches for OS and PFS, and alternate cost assumptions. These reanalyses indicate that the ICER of brexucabtagene autoleucel compared to BSC was likely to be higher than the base-case ICER estimated by the sponsor ($89,557 per QALY). The ICERs were most sensitive to clinical efficacy and modelling assumptions, and changes to the time horizon, with results ranging from $104,570 to $422,416 per QALY. In an analysis in which the cure component of the model was removed and weighted data from ZUMA-2 was used to inform the comparative effectiveness, the ICER for brexucabtagene autoleucel compared to BSC was $308,034. Based on this analysis, a price reduction of more than 99% would be required to achieve an ICER of $50,000 per QALY based on this combination analysis.

Budget Impact

The sponsor estimated the incremental budget impact of reimbursing brexucabtagene autoleucel to be $39,386,468 and $45,524,260 over 3 years from a drug plan and health care system perspective, respectively. CADTH identified limitations with the submitted budget impact analysis and undertook reanalyses which estimated the incremental budget impact of reimbursing brexucabtagene autoleucel to be $39,386,468 (unchanged from sponsor's when considering a drug plan perspective) and increasing to $46,439,484 (health care system perspective) over 3 years. CADTH noted the budget impact is sensitive to market share assumptions and consideration of assessment costs for eligibility for brexucabtagene autoleucel that will underestimate the budget impact if not included.

Ethical Considerations

Empirical and normative literature related to the use of brexucabtagene autoleucel and other CAR T-cell therapies as well as experiences of refractory MCL were reviewed for ethical content, using methods of qualitative description to highlight ethical considerations and themes. Nine publications met the inclusion criteria and were included in the report; none

directly reported on the use of brexucabtagene autoleucel for refractory MCL, but instead explored MCL incidence and outcomes, cost and value, risks and benefits of CAR T-cell therapies in vulnerable populations, and decision-making capacity.

Findings indicate several domains of disparity in MCL incidence and outcomes based on age, gender, race, socioeconomic status, as well as differential access to effective upfront therapies and treatment options. These findings necessitate implementation strategies to enhance equitable patient access to therapy and consideration of differential treatment strategies for different groups.

Patients eligible for CAR T-cell therapies often have few therapeutic options and thus are willing to pursue high-risk treatments, highlighting a need to consider and identify the appropriate balance of risks and benefits for patients receiving these therapies.

Members of the pCODR Expert Review Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: May 13, 2021

Regrets: None

Conflicts of interest: None