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CADTH Reimbursement Recommendation

Zanubrutinib (Brukinsa)

Indication: For the treatment of adult patients with chronic lymphocytic leukemia

Sponsor: BeiGene Canada ULC

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Brukinsa?

CADTH recommends that Brukinsa be reimbursed by public drug plans for the treatment of adult patients with chronic lymphocytic leukemia (CLL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Brukinsa should only be covered to treat adult patients with previously untreated CLL for whom fludarabine-based treatment is inappropriate or patients with relapsed or refractory (r/r) CLL who have received at least 1 prior systemic therapy. Patients receiving Brukinsa should be in relatively good health (i.e., have a good performance status, as determined by a specialist). Patients who have progressed on a Bruton tyrosine kinase (BTK) inhibitor or patients with prolymphocytic leukemia or Richter's transformation should not be eligible for coverage.

What Are the Conditions for Reimbursement?

Brukinsa should only be reimbursed if prescribed by clinicians with expertise and experience in the treatment of CLL and monitoring of therapy and if it is associated with cost savings for drug programs relative to ibrutinib or acalabrutinib. Patients who experience disease progression while taking Brukinsa or who cannot tolerate the drug would not be eligible for continued coverage.

Why Did CADTH Make This Recommendation?

- Evidence from 2 ongoing clinical trials demonstrated that treatment with Brukinsa resulted in improved delay of disease progression for untreated patients with CLL compared with bendamustine-rituximab and improved overall response rate for patients with r/r CLL compared with ibrutinib.
- Despite the limitations with the available evidence, Brukinsa was considered to be similarly as effective as other BTK inhibitors available in Canada (i.e., acalabrutinib and ibrutinib).
- Brukinsa meets patients' needs for more treatment options for CLL that are better tolerated with favourable toxicity profiles compared to current chemoimmunotherapy and BTK inhibitor options.
- Based on public list prices, Brukinsa is estimated to save the public drug plans approximately $4 million over the next 3 years in the eligible population. The cost of Brukinsa must be less than the drug plan cost of ibrutinib and acalabrutinib to ensure cost savings are realized.

Summary

Additional Information

What Is CLL?

CLL is a condition in which there is an excessive growth and buildup of small mature B cells in various parts of the body, such as the blood, bone marrow, lymph nodes, and lymphoid tissue. Patients with CLL may experience symptoms similar to lymphoma, such as fever, chills, night sweats, and unintentional weight loss. Other common signs include fatigue, enlarged lymph nodes, or an enlarged spleen. However, some patients may not show any noticeable symptoms at all. CLL is the most common type of leukemia in Western countries; the 2018 Canadian cancer statistics showed that the incidence of newly diagnosed CLL was 6.0 per 100,000 population (1,725 new cases).

Unmet Needs in CLL

There are no curative treatments for patients with CLL; therefore, patients require continuous ongoing treatment. Patients may also stop responding or relapse on current treatments due to tumour cell resistance. Patients may not tolerate the toxicity and drug interactions of current treatments.

How Much Does Brukinsa Cost?

Treatment with Brukinsa is expected to cost approximately $272 per patient per day ($7,614 per 28-day cycle).

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that zanubrutinib be reimbursed for the treatment of adult patients with chronic lymphocytic leukemia (CLL) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 ongoing phase III, open-label randomized controlled trials (RCTs) (SEQUOIA cohort 1 and ALPINE) demonstrated that treatment with zanubrutinib resulted in added clinical benefit for patients with CLL. The SEQUOIA trial cohort 1 (N = 479) demonstrated a statistically significant difference (P < 0.0001) in progression-free survival (PFS) between the zanubrutinib and bendamustine-rituximab treatment arms in patients with treatment-naive CLL. In the SEQUOIA trial, median PFS had not yet been reached in the zanubrutinib arm, whereas in the bendamustine-rituximab arm, the median PFS was 33.7 months (95% confidence interval [CI], 28.1 months to not estimable [NE]). The hazard ratio (HR) for PFS per independent review committee (IRC) comparing zanubrutinib with bendamustine-rituximab was 0.42 (95% CI, 0.28 to 0.63; P < 0.0001) in favour of zanubrutinib. In patients with r/r CLL, the ALPINE trial (N = 652) demonstrated a statistically significant difference (P = 0.0006) in overall response rate (ORR) between the zanubrutinib and ibrutinib treatment arms (78.3% and 62.5%, respectively; HR = 1.25, 95% CI, 1.10 to 1.41), demonstrating noninferiority as well as superiority of zanubrutinib to ibrutinib. Overall, the frequency of adverse events (AEs) was similar between the treatment arms in the SEQUOIA and ALPINE trials, except for atrial fibrillation and flutter in the ALPINE trial (4.6% and 12.0% for zanubrutinib and ibrutinib arms, respectively) (P = 0.0006). Quality of life results from the SEQUOIA and ALPINE trials were also similar between the treatment arms.

pERC recognized the need for more treatment options for patients with CLL, notably for treatments that are better tolerated with favourable toxicity profiles compared with current chemoimmunotherapy and for Bruton tyrosine kinase (BTK) inhibitor options. Within this context, BTK inhibitors have become the de facto standard of treatment in Canada for patients with CLL, as patients and clinicians recognize the added clinical value of a targeted and oral therapy that is well tolerated in this patient population. Input from patient groups indicated the need for additional treatment options that provide longer remission and survival and improved quality of life with fewer side effects. Given the evidence, pERC concluded that zanubrutinib met some of the needs identified by patients because it provides an additional treatment option for oral administration with the potential for fewer side effects and with no apparent deterioration in quality of life.

At the sponsor-submitted price for zanubrutinib and the publicly listed prices for ibrutinib and acalabrutinib, zanubrutinib was less costly than ibrutinib and acalabrutinib. Because zanubrutinib is considered similarly effective as ibrutinib and acalabrutinib, the total drug cost of zanubrutinib should be less than the total drug cost of either ibrutinib or acalabrutinib.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult (≥ 18 years) patients with CLL who meet 1 of the following criteria: 1.1. previously untreated CLL for whom fludarabine-based treatment is inappropriate 1.2. r/r CLL who have received at least 1 prior systemic therapy.	Evidence from the SEQUOIA and ALPINE trials showed that zanubrutinib demonstrated clinically meaningful benefits for patients with treatment-naive CLL compared with bendamustine-rituximab, and in adult patients with r/r CLL who had received at least 1 prior line of non–BTK inhibitor therapy compared with ibrutinib.	—
2. Patients must have a good ECOG performance status.	No evidence was identified to demonstrate a benefit of zanubrutinib in patients with ECOG PS > 2 at baseline. The SEQUOIA and ALPINE trials only included patients with an ECOG PS of 0, 1, or 2.	—
3. Patients must not have any of the following: 3.1. prior progression on a BTK inhibitor 3.2. prolymphocytic leukemia or Richter's transformation.	No evidence was identified to demonstrate a benefit of zanubrutinib in patients with prior progression on a BTK inhibitor or prolymphocytic leukemia or Richter's transformation because patients with these were not enrolled in the SEQUOIA and ALPINE trials.	The clinical expert consulted by CADTH noted that there is no evidence from clinical trials to suggest that patients who progress on a BTK inhibitor would benefit from treatment with a different covalent BTK inhibitor.
Renewal		
4. Renewal of zanubrutinib should be based on the following assessments: 4.1. blood work and physical examination should be performed every 1 to 3 months at initiation then can be performed less frequently (i.e., 3 to 6 months) at the discretion of the treating physician.	The clinical expert consulted by CADTH and the clinician group input indicated that response to treatment is assessed by changes in peripheral blood counts and physical examinations, which can easily be documented by clinicians looking after patients.	—
Discontinuation		
5. Treatment with zanubrutinib should be discontinued upon the occurrence of any of the following: 5.1. progression of disease according to iwCLL response	No evidence was identified to demonstrate that continuing treatment with zanubrutinib in patients whose disease has progressed is effective.	—

Reimbursement condition	Reason	Implementation guidance
assessment criteria 5.2. unacceptable toxicity.		
Prescribing		
6. Zanubrutinib should only be prescribed by a clinician with expertise and experience in the treatment of CLL and monitoring of therapy.	To ensure that zanubrutinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
7. Zanubrutinib should provide cost savings for drug programs relative to the cost of treatment with either ibrutinib or acalabrutinib for the treatment of adult patients with CLL.	At its submitted price, zanubrutinib was cost saving compared with either ibrutinib or acalabrutinib. This analysis considered publicly available list prices and did not consider potential confidential negotiated prices. The price of zanubrutinib should be negotiated to ensure suggested cost savings are maintained.	—

BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group; iwCLL = International Workshop on chronic lymphocytic leukemia; PS = performance status; r/r = relapsed or refractory.

Discussion Points

- pERC discussed 2 distinct patient groups with CLL in the front line setting: patients who do not have high-risk genetic factors (17p deletion, *TP53* mutation, or unmutated *IGHV*) who are ineligible for fludarabine-cyclophosphamide-rituximab therapy; and patients who do have high-risk factors whose disease will not respond to fludarabine-cyclophosphamide-rituximab. Both groups that may be candidates for BTK inhibitors and/or chemoimmunotherapy combinations (e.g., bendamustine-rituximab, venetoclax-obinutuzumab, chlorambucil-obinutuzumab) as treatment options. However, funding or access to BTK inhibitors is variable across provinces. In this context, for individuals in whom BTK inhibitors are considered appropriate in the frontline setting, zanubrutinib would represent another BTK inhibitor option because it demonstrated superiority in PFS compared to bendamustine-rituximab, although bendamustine-rituximab is rarely used in Canada.
- pERC discussed that according to the clinical expert consulted by CADTH that in patients with r/r CLL, BTK inhibitors would be preferred for those who have already received frontline venetoclax-based therapy or who have high-risk disease. pERC also noted that venetoclax-rituximab might be preferred in patients who have already received a frontline BTK inhibitor. In this context, zanubrutinib would likely represent the preferred BTK inhibitor (over ibrutinib) given the results of ALPINE trial (demonstrating superiority in ORR and PFS and less toxicity compared to ibrutinib). pERC noted the lack of direct comparative evidence of zanubrutinib to acalabrutinib, thus limiting the conclusions regarding the comparative efficacy and safety of zanubrutinib to acalabrutinib.

- The sponsor submitted a network meta-analysis (NMA) and a matching-adjusted indirect comparison (MAIC) of zanubrutinib to relevant comparators in Canada but there were significant limitations of the analyses that could limit interpretability of the comparative efficacy and safety results and compromise the generalizability of the results to patients living in Canada. Among the limitations associated with the NMA was the exclusion of venetoclax-obinutuzumab as a comparator to zanubrutinib in the treatment of CLL. Overall, pERC concluded that limited conclusions could be made on the relative benefit of zanubrutinib compared with existing BTK inhibitors (i.e., ibrutinib and acalabrutinib) or venetoclax-obinutuzumab in patients with CLL who are treatment-naive or have r/r CLL based on the submitted indirect comparative evidence.
- No differences in health-related quality of life (HRQoL) (as measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and 5-Level EQ-5D [EQ-5D-5L]) were observed in the SEQUOIA and ALPINE trials among the zanubrutinib, ibrutinib, and bendamustine-rituximab treatment arms. Overall, pERC agreed that zanubrutinib did not result in deterioration of patients' quality of life. However, pERC noted the limitations in the statistical analyses and lack of identified minimal important difference estimations that no definitive conclusions can be drawn from the HRQoL. Therefore, only limited interpretations could be made on the available quality of life data.
- Input from patient groups stressed the importance of patient choice and additional treatment options that provide longer remission and survival and improved quality of life with fewer side effects. Based on the evidence from the SEQUOIA and ALPINE trials, pERC concluded that zanubrutinib met some needs identified by patients because it provides an additional treatment option for oral administration with the potential for fewer side effects and no apparent deterioration in quality of life.
- pERC discussed the safety profile of zanubrutinib and considered it aligned with the known safety profile of BTK inhibitors. Overall, the incidence of AEs and serious AEs (SAEs) was comparable between treatment arms in the 2 trials with a few exceptions. Zanubrutinib was associated with a higher incidence of hemorrhage and upper respiratory tract infections in the SEQUOIA trial compared to BR. In the ALPINE trial, patients treated with ibrutinib experienced a higher incidence of atrial fibrillation and flutter, key side effects of BTK inhibitors, compared with those treated with zanubrutinib. pERC noted the lack of direct evidence available regarding the comparative efficacy and safety of zanubrutinib to ibrutinib, acalabrutinib, or venetoclax and obinutuzumab in the first-line setting, and to venetoclax and rituximab in the r/r setting, and thus these results may not address the question of the optimal treatment for these patients. pERC also noted that the sponsor's submitted NMA did not evaluate harms, and the limitations with the submitted MAIC on the reporting of AEs varied across included trials. Based on the available evidence, pERC concluded that zanubrutinib has the potential for fewer side effects than comparator treatments.
- pERC discussed the sponsor's submitted cost-minimization analysis comparing zanubrutinib with ibrutinib and acalabrutinib. pERC found the sponsor's assumption of comparable efficacy and safety underpinning the submitted analysis to be appropriate, and the cost savings with zanubrutinib suggested by the sponsor's submitted budget impact assessment to be meaningful. pERC noted that

the submitted analysis only considered publicly available list prices and that the confidential price of ibrutinib and acalabrutinib should be considered to ensure the cost savings suggested by the sponsor are maintained with zanubrutinib.

Background

CLL is characterized by proliferation and accumulation of small mature B cells in the blood, bone marrow, lymph nodes, and lymphoid tissue. Patients may present with B symptoms (features of lymphoma such as fever, chills, night sweats, and unintentional weight loss), fatigue, enlarged lymph nodes, or splenomegaly. Clinical presentation is often asymptomatic. In Western countries, CLL is the most common type of leukemia, with 2018 Canadian cancer statistics showing an incidence of 6.0 per 100,000 population for newly diagnosed CLL (1,725 new cases). Treatment is generally not required for early asymptomatic CLL. Patients with early asymptomatic disease are often followed with a watch-and-wait strategy with routine follow-ups to monitor their disease. When treatments are indicated based on risk factors (i.e., *IGHV* status, 17p deletion, and *TP53* mutation) or disease symptoms, the treatment strategy should be personalized according to risk factors, age, fitness, and patient preferences. For patients with CLL who are treatment-naive, treatment options include fludarabine-cyclophosphamide-rituximab, chemoimmunotherapy combinations (e.g., BR, venetoclax-obinutuzumab, chlorambucil-obinutuzumab), and BTK inhibitors). For patients with r/r CLL, treatment options include BTK inhibitors, a venetoclax-based regimen, and idelalisib plus rituximab. Allogenic stem cell transplant is another potential option in the r/r setting. The most important goals of treatment of patients with CLL is to achieve effective and durable disease control with minimal toxicity and acceptable quality of life. The limitations associated with current treatments for patients with CLL include tumour cell resistance and patients stop responding or relapse on therapy.

Zanubrutinib (Brukinsa) is a second-generation small molecule inhibitor of BTK and has a Health Canada indication for the treatment of adult patients with CLL. Zanubrutinib is supplied as 80 mg oral capsules and the recommended total daily oral dose is 320 mg that may be taken as either 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily. Treatment with zanubrutinib should continue until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

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

- a review of 2 ongoing international, phase III, open-label, randomized clinical studies (SEQUOIA and ALPINE), 2 indirect treatment comparisons, and 1 ongoing phase II, multicentre, single-arm study (Study 215) in adult patients with CLL
- patients' perspectives gathered by 1 patient group: Lymphoma Canada with the assistance of CLL Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process

- input from 1 clinical specialist with expertise diagnosing and treating patients with CLL
- input from 2 clinician groups, including Lymphoma Canada organized Canadian hematologists and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Patient input was provided from Lymphoma Canada, which is a national charity with a mission to advocate and improve access to health care for Canadians affected by CLL and small lymphocytic lymphoma (SLL). Lymphoma Canada submitted input based on information collected from an anonymous online survey that had been distributed throughout Canada and international locations via email and social media from November 2022 to February 2023. A total of 173 people (64 from Canada, 9 from the US, 1 from Costa Rica, and 99 from unknown locations) responded to the survey. Of the total respondents, 149 respondents had confirmed CLL, 23 respondents were diagnosed with SLL, and 1 respondent was newly diagnosed with unknown lymphoma. CLL Canada assisted Lymphoma Canada in distributing the survey and preparing the submission.

According to the survey, most patients with CLL and SLL are diagnosed through routine bloodwork and experienced no or minor symptoms at the time of diagnosis. For 122 respondents who rated high on negative impact (score 3 to 5 out of 5) at the time of diagnosis, fatigue (40%), night sweats (27%), and body aches and pains (20%) were the most frequent symptoms. In terms of psychosocial impact of CLL and SLL at the time of diagnosis, 109 respondents reported anxiety and worry (61%) and stress of diagnosis (41%) as the most common factors. In 109 respondents who reported the highly negative impact (score 3 to 5 out of 5) being currently experienced, fatigue (44%), body aches and pains (25%), and night sweats (16%) were the most frequently reported symptoms. Up to 75% of 109 respondents with CLL experienced a negative impact on quality of life, such as anxiety and worry (61%), stress of diagnosis (40%), or difficulty sleeping (37%). Of 109 respondents who indicated that CLL had a negative impact on daily activities, travel (35%), volunteering (25%), and spending time with family and friends (24%) were the most frequently affected activities.

Approximately 76 patients responded that the following factors were extremely important when considering a novel therapy over their current treatment option(s): longer survival (85%), control of disease and symptoms (79%), longer remission (75%), and better quality of life (66%). Approximately 77 patients who responded to a question about importance of choice and options when deciding CLL treatment course, 60% of patients answered it is extremely important to have choice and 65% answered it is extremely important to

have a higher number of CLL and SLL treatment options available. When asked about the preference of a pill versus IV administration, 63 of 77 patients (82%) confirmed that they would prefer oral administration.

Eleven patients (10 patients had been previously treated) had experience with zanubrutinib for CLL treatment. Two patients said they are in remission after 6 months and 1 to 2 years of zanubrutinib treatment and 5 patients indicated that zanubrutinib controlled CLL and SLL symptoms better than their previous treatments. Seven respondents are still on zanubrutinib treatment, and 1 patient stopped. Four of 11 patients reported that they did not experience any side effects, and 8 patients reported that side effects of zanubrutinib were lower in severity than they had previously experienced with other therapies. Symptoms reported were fatigue, easy bruising and bleeding, confusion or memory loss, diarrhea, muscle or joint pain, peripheral edema, hypertension, and localized infections. Two patients said that zanubrutinib negatively impacted their quality of life compared with other treatments.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH indicated that the most important goals of treatment for patients with CLL is to reverse symptoms and control the disease for as long as possible with treatments that have minimal toxicity and do not have a significant negative impact on quality of life. The clinical expert stated that the biggest limitation to current treatments for patients with CLL is that tumour cell resistance usually occurs, and patients stop responding or relapse on therapy. Other limitations include toxicity and drug interactions, the requirement for continuous ongoing treatment, and there are no curative treatments for patients with CLL. The clinical expert believed that the value of zanubrutinib would be incremental rather than transformative because there are already 2 BTK inhibitors (i.e., ibrutinib and acalabrutinib) commonly used in clinical practice. The clinical expert speculated that zanubrutinib would be a welcome option for first-line treatment of patients with CLL and would not be efficacious in patients who progress on other BTK inhibitors. According to the clinical expert, the patient population for zanubrutinib includes untreated patients aged 65 years or older with a good performance status with or without high-risk mutations (i.e., *TP53* mutations, 17p deletion, or unmutated *IGHV* genes) or patients younger than 65 who were not candidates for fludarabine-cyclophosphamide-rituximab, and patients with r/r CLL without transformation or central nervous system involvement. Although patients who had previous treatment with a BTK inhibitor or had a bleeding disorder were not ideal for the treatment with zanubrutinib, the clinical expert consulted by CADTH indicated that zanubrutinib may be better tolerated in those patients who need to stop other BTK inhibitors because of toxicity.

The clinical expert indicated that response to treatment is assessed by changes in peripheral blood counts. Disease progression as measured by increasing lymphocyte count or worsening cytopenias is a major reason for discontinuing treatment with zanubrutinib as per expert opinion. Toxicities that cannot be managed with dose reductions or the drug being held could also be a reason for stopping treatment. Zanubrutinib must be held before various surgical procedures due to the risk of bleeding. The clinical expert stated that zanubrutinib treatment should be managed by a specialist (i.e., hematologist or medical oncologist) who is familiar with this class of drugs to manage toxicities and optimally dose the medication.

Clinician Group Input

Lymphoma Canada, represented by 1 hematologist, and Ontario Health-Cancer Care Ontario Hematology Cancer Drug Advisory Committee with 4 hematologists, submitted 2 clinician group inputs. In alignment with clinician group input, the clinical expert consulted by CADTH stated that patients who had previous treatment with a BTK inhibitor is not an ideal patient for zanubrutinib treatment, and patients with high-risk mutations (i.e., *TP53* mutations, 17p deletion, or unmutated *IGHV* genes) 65 years and older and patients younger than 65 who were not candidates for fludarabine-cyclophosphamide-rituximab are eligible for zanubrutinib treatment. Also, the clinical expert put more emphasis on duration of response or response to next treatment as important end points. Otherwise, the clinical expert and 2 clinician groups generally agreed on the following:

- zanubrutinib is a viable first-line option for patients with CLL who are treatment-naive and in patients with r/r disease
- important outcomes include reduced symptom burden and improved quality of life with minimal toxicity from treatment
- routine blood counts and clinical exam are done for measuring response to therapy
- in case of progressive disease and/or intolerable toxicity despite dose reduction should be considered to discontinue zanubrutinib treatment
- a specialist, such as a hematologist, a medical oncologist, or any other staff specialized in managing malignant hematological conditions and/or familiar with this class of drug, should be involved in the management of CLL with zanubrutinib.

Drug Program Input

The clinical expert 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	
In treatment-naive CLL, relevant funded comparators include acalabrutinib, ibrutinib, obinutuzumab plus venetoclax, obinutuzumab-chlorambucil, and other rituximab-based chemoimmunotherapy combinations (e.g., bendamustine-rituximab [comparator in SEQUOIA trial], chlorambucil-rituximab). In relapsed or refractory CLL, relevant funded comparators depend upon prior therapies used in earlier treatment lines; however, notable comparators would be other BTK inhibitors (ibrutinib [comparator in ALPINE trial], acalabrutinib), or venetoclax with or without rituximab. 1. As zanubrutinib has not been directly compared to all potential comparators, what is the relative efficacy and safety of zanubrutinib to funded comparators in both	The clinical expert consulted by CADTH stated that obinutuzumab-chlorambucil has been historically used as a control treatment in many trials for the first-line treatment in patients with CLL (particularly in older patients). However most randomized trials using this control arm have shown that new treatments, such as ibrutinib, acalabrutinib, or venetoclax combinations, demonstrated superiority. When bendamustine and rituximab have been used as a control, superiority has been seen with newer treatments, such as venetoclax and obinutuzumab or BTK inhibitors. There is no evidence regarding how zanubrutinib will compare to ibrutinib, acalabrutinib, or venetoclax and obinutuzumab in the first-line setting. The clinical expert indicated that chlorambucil is not used for the treatment of older patients with CLL unless they are much older with a poor cumulative illness rating scale score. The clinical

Implementation issues	Response
treatment-naive and relapsed/refractory CLL? 2. With multiple BTK inhibitor options in the same clinical settings, how is 1 BTK inhibitor selected over another?	expert stated that cross-trial comparisons are relevant and should be explored for the efficacy and safety of ibrutinib, acalabrutinib, or venetoclax-obinutuzumab in the first-line setting and to acalabrutinib-venetoclax-rituximab for patients with relapsed or refractory CLL. The clinical expert indicated that ibrutinib is a very relevant comparator in the relapsed or refractory setting. pERC agreed with the clinical expert consulted by CADTH that selection of a BTK inhibitor as a treatment option will be influenced by differences in patient populations and preferences such as dosing schedule and duration of therapy, side effect profile, and concomitant drug interactions. pERC also noted the lack of definitive clinical evidence and rationale that favours 1 BTK inhibitor option over another, and thus selection of the BTK inhibitor would be for the treating clinician to determine in agreement with the patient.
Considerations for initiation of therapy	
For patients who are treatment-naive, other BTK inhibitors are reimbursed for first-line treatment when CLL or SLL expresses high-risk features (e.g., 17p deletion, *TP53* mutation, unmutated *IGHV*). 1. Should first-line use of zanubrutinib be limited to CLL or SLL with high-risk features? 2. Should patients who are unsuitable for IV therapy (e.g., age, proximity to treatment centre) be eligible for first-line zanubrutinib?	Zanubrutinib has received approval from Health Canada for the treatment of adult patients with CLL. The indication did not include patients with SLL. The clinical expert consulted by CADTH stated that zanubrutinib should not be limited to those patients with high-risk features because patients with or without *TP53* mutations (or 17p deletion) or patients with mutated or unmutated *IGHV* genes could also benefit from the treatment. pERC agreed with the clinical expert consulted by CADTH that patients who have high-risk features or could not receive IV therapy should be able to obtain a BTK inhibitor.
Should the reimbursement criteria align with that of ibrutinib and acalabrutinib?	Although the clinical expert consulted by CADTH noted there should not be too many restrictions on the use of zanubrutinib because the drug may have certain benefits over the earlier BTK inhibitors, pERC recommended that reimbursement criteria for zanubrutinib be aligned with the eligibility criteria outlined under Initiation in Table 1.
Other BTK inhibitors approved in Canada (ibrutinib and acalabrutinib) are currently reimbursed for both CLL and SLL, although none have been approved by Health Canada for use in SLL. Would it be appropriate extend reimbursement of zanubrutinib to patients with SLL?	Zanubrutinib has received approval from Health Canada for the treatment of adult patients with CLL. The indication did not include patients with SLL. Acknowledging that usage would be off-label in Canada, pERC noted that jurisdiction could consider extending reimbursement of zanubrutinib to patients with SLL for the following reasons: 1. Clinical experts consulted by CADTH noted that CLL and SLL are treated the same in Canadian clinical practice. 2. SLL is rare condition and there are no BTK inhibitors treatments specifically approved for use in these patients in Canada. 3. Zanubrutinib is like other BTK inhibitors that are currently reimbursed by the participating plans.

Implementation issues	Response
Considerations for prescribing of therapy	
Both the SEQUOIA and the ALPINE trials dosed zanubrutinib at 160 mg orally twice daily. Zanubrutinib has been evaluated in dosing schedules of 320 mg orally once daily and 160 mg orally twice daily. Is there a preferred dosing schedule for zanubrutinib in clinical practice?	The clinical expert consulted by CADTH would like to follow the guidelines from the SEQUOIA and ALPINE trials (i.e., 160 mg orally twice daily) and indicated that there may be tighter serum levels with the 160 mg orally twice daily administration. pERC suggested that the choice of a preferred dosing schedule should be a decision between patient and physician.
Generalizability	
Should patients who are currently receiving ibrutinib or acalabrutinib and have not experienced disease progression be eligible on a time-limited basis?	The clinical expert noted that patients who are doing well on current treatment should not be switched.
Funding algorithm	
Drug may change place in therapy of comparator drugs	This was a comment from the drug programs to inform pERC deliberations.
Care provision issues	
Zanubrutinib is supplied as an 80 mg capsule in a bottle of 120 capsules. The product monograph indicates to "Store BRUKINSA at room temperature, between 15°C-30°C, in the original bottle." In the event of dose adjustments, these storage restrictions (e.g., original bottle) may introduce dispensing issues.	This was a comment from the drug programs to inform pERC deliberations.
Zanubrutinib has potential for drug-drug, drug-food, and drug-herb interactions, requiring assessment and/or intervention.	This was a comment from the drug programs to inform pERC deliberations.

CLL = chronic lymphocytic leukemia; BTK = Bruton tyrosine kinase; SLL = small lymphocytic lymphoma.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

Both the SEQUOIA and ALPINE trials were ongoing phase III, open-label RCTs. The SEQUOIA cohort 1 compared efficacy and safety of zanubrutinib to bendamustine-rituximab in patients with CLL or SLL who were treatment naive and were negative for 17p deletion. These patients were either 65 years or older or younger than 65 years with comorbid illnesses and at least 1 indication to treat. The SEQUOIA trial also included a cohort 2, which included patients with CLL or SLL who were treatment naive and who were positive for 17p deletion. Cohort 2 was a single-arm study. The ALPINE trial compared efficacy and safety of zanubrutinib to ibrutinib in patients with r/r CLL or SLL. Patients were randomized to receive zanubrutinib or bendamustine-rituximab in the SEQUOIA trial and ibrutinib in the ALPINE trial using an Interactive Response Technology system. The stratification factors were age, geographic region, genetic mutations, refractory to last therapy (ALPINE trial), and disease stage (SEQUOIA trial). A total of 479 patients in cohort 1 of the SEQUOIA trial were randomized at a 1:1 ratio to receive zanubrutinib (n = 241) or bendamustine-rituximab

(n = 238); 652 patients in the ALPINE trial were randomized at a 1:1 ratio to receive zanubrutinib (n = 327) or ibrutinib (n = 325). No Canadian sites were included in both trials.

The primary end point in the SEQUOIA trial was PFS per IRC according to the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines and ORR per investigator assessment in the ALPINE trial. Other outcomes of interest included PFS per investigator assessment, ORR per IRC, overall survival (OS), duration of response (DOR) (per IRC and investigator assessment), time to treatment failure, incidence of atrial fibrillation or flutter, and HRQoL.

For the SEQUOIA trial, the demographic and baseline characteristics were similar in the zanubrutinib and bendamustine-rituximab arms in cohort 1. However, slightly more patients in the zanubrutinib arm were white (91.7% and 86.6% in the zanubrutinib and bendamustine-rituximab arms, respectively). Most patients in the zanubrutinib and bendamustine-rituximab arms in cohort 1 were enrolled at sites in Europe (72.2% and 72.3%, respectively) and had an ECOG performance status of 0 or 1 (93.8% and 91.6%, respectively). The demographic and baseline characteristics were similar between the zanubrutinib arms in cohort 1 (without 17p deletion) and cohort 2 (with 17p deletion), except there were more patients from the Asia-Pacific region enrolled in cohort 2 (13.7% in cohort 1; 42.3% in cohort 2).

For the ALPINE trial, the demographic and baseline patient characteristics were similar across the zanubrutinib and ibrutinib arms in the ITT analysis set (final ORR analysis). The median age of patients was 67.0 years (range, 35 to 90 years) in the zanubrutinib arm and 68.0 years (range, 35 to 89 years) in the ibrutinib arm. Most patients in the zanubrutinib and ibrutinib arms were enrolled at sites in Europe (60.6% and 58.8%, respectively), were white (79.8% and 83.1%, respectively), and had an ECOG performance status between 0 and 1 (97.9% and 96%, respectively). Demographic and baseline patient characteristics in the final PFS analysis ITT analysis set were similar to the ALPINE final ITT ORR analysis set.

Efficacy Results

Progression-Free Survival

PFS per IRC: SEQUOIA Trial

As of the May 7, 2021, data cut-off, median PFS per IRC had not yet been reached in the zanubrutinib arm; in the bendamustine-rituximab arm, the median PFS per IRC was 33.7 months (95% CI, 28.1 months to NE). Median follow-up time was 25.1 months (95% CI, 24.9 to 25.4 months) in the zanubrutinib arm and 24.6 months (95% CI, 22.8 to 25.2 months) in the bendamustine-rituximab arm. The HR for PFS per IRC comparing zanubrutinib with bendamustine-rituximab was 0.42 (95% CI, 0.28 to 0.63; P value < 0.0001) in favour of zanubrutinib. Higher event-free rates were observed in the zanubrutinib arm (94.5%) versus the bendamustine-rituximab arm (90.2%) at 12 months, 24 months (85.5% for the zanubrutinib arm vs. 69.5% for the bendamustine-rituximab arm), and 36 months (81.5% for the zanubrutinib arm vs. 40.8% for the bendamustine-rituximab arm). Subgroup analyses of PFS per IRC by age (< 65 versus ≥ 65 years), sex, and ECOG performance status (0 versus ≥ 1) were generally consistent with the primary analysis across all strata. However, inconsistent findings were reported in the subgroup analyses of high-risk genetic factors (*IGHV* mutation status [unmutated vs. mutated], and *TP53* mutation status [unmutated vs. mutated]),

cancer type (CLL vs. SLL), disease stage (Binet stage of A/B vs. Binet stage) and complex karyotype (< 3 abnormalities vs. ≥ 3 abnormalities). In addition, several prespecified sensitivity analyses based on the IRC assessment of PFS were included in the statistical analysis plan, including unstratified analysis, using the per-protocol analysis set, and changes to definitions of PFS and censoring events. The results were generally consistent with the results of the primary analysis (HR = 0.42; 95% CI, 0.28 to 0.63; P < 0.0001) and showed HR values ranging from 0.45 (95% CI, 0.31 to 0.67) to 0.34 (95% CI, 0.22 to 0.53).

In cohort 2, the median PFS by IRC was not reached for the zanubrutinib arm. The event-free rates were 93.6% at 12 months, 88.9% at 24 months, and 84.9% at 36 months. A higher rate of progression was observed in patients with concurrent *TP53* mutation (21.3% for patients with *TP53* mutation vs. 8.1% for patients without *TP53* mutation). Consistent results were observed for investigator-assessed PFS, with event-free rates of 94.5% at 12 months, 87.0% at 24 months, and 82.6% at 36 months.

PFS per Investigator Assessment: SEQUOIA Trial

The analysis of PFS per investigator assessment was the secondary outcome in SEQUOIA cohort 1. High concordance for PFS was also observed comparing the IRC and investigator assessments (concordance rate for disease progression: 91.4.%), and the HRs for IRC-assessed and investigator-assessed PFS were also similar (HR = 0.42 [95% CI, 0.28 to 0.63] for PFS per IRC; HR = 0.42 [95% CI, 0.27 to 0.66] for PFS per investigator assessment).

In cohort 2, the median PFS by investigator assessment was not reached for the zanubrutinib arm. The event-free rates were 94.5% at 12 months, 87.0% at 24 months, and 82.6% at 36 months.

PFS per IRC: ALPINE Trial

Analysis of PFS per IRC was a secondary outcome in the ALPINE trial. This analysis was not part of the statistical hierarchy and not adjusted for multiplicity. At the final PFS analysis cut-off date of August 8, 2022, IRC-assessed PFS events had occurred in 88 patients (26.9%) in the zanubrutinib arm and 120 patients (36.9%) in the ibrutinib arm (HR = 0.65; 95% CI, 0.49 to 0.86; nominal P = 0.0024). Median follow-up time was 32.9 months (95% CI, 27.8 to 33.1 months) in the zanubrutinib arm and 28.1 months (95% CI, 27.6 to 33.0 months) in the ibrutinib arm. The median PFS was not reached in the zanubrutinib arm, with the lower bound of the 95% CI of 34.3 months and the median PFS was 35.0 months (95% CI, 33.2 to 44.3 months) in the ibrutinib arm.

Generally, similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

PFS per Investigator Assessment: ALPINE Trial

Analysis of PFS per investigator assessment in the ALPINE trial was the key secondary outcome and was adjusted for multiplicity in the final PFS analysis. At the final PFS analysis cut-off date of August 8, 2022, the investigators assessed that PFS events had occurred in 87 patients (26.6%) in the zanubrutinib arm and 118 patients (36.3%) in the ibrutinib arm. Patients in the zanubrutinib arm had a lower risk of PFS events based on investigator assessment (HR = 0.65; 95% CI, 0.49 to 0.86), which was both noninferior (P < 0. 0001 vs. prespecified 1-sided significance level of 0.02498) and superior (P = 0.0024 vs. prespecified 1-sided

significance level of 0.02498). Median follow-up time was 31.4 months (95% CI, 27.7 to 33.1 months) in the zanubrutinib arm and 27.8 months (95% CI, 27.6 to 33.1 months) in the ibrutinib arm. The median PFS was not reached in the zanubrutinib arm, with the lower bound of the 95% CI of 34.3 months; the median PFS was 34.2 months (95% CI, 33.3 to NE) in the ibrutinib arm.

Similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

Overall Survival

SEQUOIA Trial

As of the final data cut-off of May 7, 2021, OS events had occurred in 16 (6.6%) patients in the zanubrutinib arm and 14 (5.9%) patients in the bendamustine-rituximab arm. The HR for OS comparing zanubrutinib with bendamustine-rituximab was 1.07 (95% CI, 0.51 to 2.22; P = 0.5672). Median OS was not reached in the zanubrutinib arm, with a median follow-up time of 26.5 months, whereas in the bendamustine-rituximab arm, the median OS was 37.8 months (95% CI, 37.8 months to NE), with a median follow-up time of 25.1 months. The event-free rates for the zanubrutinib and bendamustine-rituximab arms were 98.3% and 96.4% at 12 months, 94.3% and 94.6% at 24 months, and 92.3% and 93.6% at 36 months, respectively.

In cohort 2, at the data cut-off date of May 7, 2021, there were 8 deaths (7.3%) reported in the zanubrutinib arm. Median OS was not reached in the zanubrutinib arm with a median follow-up time of 30.4 months. The event-free rates were 96.4% at 12 months, 93.6% at 24 months, and 90.7% at 36 months.

ALPINE Trial

Analysis of OS in the ALPINE trial was a secondary outcome. This analysis was not part of the statistical hierarchy and not adjusted for multiplicity.

At the final PFS analysis cut-off in the ITT analysis set (August 8, 2022), there were 48 deaths (14.7%) reported in the zanubrutinib arm and 60 deaths (18.5%) reported in the ibrutinib arm (HR = 0.76; 95% CI, 0.51 to 1.11; nominal P = 0.1533). Median OS was not reached in either arm at median follow-up times of 32.9 months in the zanubrutinib arm and 32.7 months in the ibrutinib arm. Most patients were alive and in the study at the data cut-off date (79.5% and 73.8% in the zanubrutinib and ibrutinib arms, respectively).

Similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

Overall Response Rate

ORR per IRC and per Investigator Assessment: SEQUOIA Trial

The analysis of the ORR per IRC and per investigator assessment (data cut-off: May 7, 2021) was the secondary outcome in the SEQUOIA study cohorts 1 and 2. This analysis was not part of the statistical hierarchy and not adjusted for multiplicity. The ORR per IRC was 94.6% (95% CI, 91.0% to 97.1%) in the zanubrutinib arm and 85.3% (95% CI, 80.1% to 89.5%) in the bendamustine-rituximab arm. The majority of patients in the zanubrutinib and bendamustine-rituximab arms had partial response (PR) (85.5% and 64.3%, respectively), followed by complete response (CR) (6.6% and 15.1%, respectively), nodular PR (1.2% and

5.9%, respectively), and partial response with lymphocytosis (1.2% and 0, respectively). Generally, ORR per investigator assessment was consistent with ORR per IRC. In cohort 2, the ORR per IRC was 90.0% (95% CI, 82.8% to 94.9%); ORR per investigator assessment was slightly higher (96.4%, 95% CI, 91.0% to 99.0%).

ORR per IRC: ALPINE Trial

In the ITT analysis set at the final PFS analysis cut-off of August 8, 2022, when ORR was assessed by the IRC, a higher response rate was observed in the zanubrutinib arm than in the ibrutinib arm (86.2% vs. 75.7%, respectively). The majority of patients in the zanubrutinib and ibrutinib groups arms had PR (78.6% and 69.8%, respectively), followed by CR (6.7% and 5.5% for zanubrutinib, respectively), nodular PR (0.9% and 0 for zanubrutinib, respectively), and complete response with incomplete bone marrow recovery (0 and 0.3%, respectively). The analysis of the ORR per IRC was the secondary outcome in the ALPINE study.

Similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

ORR per Investigator Assessment: ALPINE Trial

In the final ORR analysis ITT analysis set (data cut-off: December 1, 2021), ORR per investigator assessment was higher in the zanubrutinib arm than in the ibrutinib arm (79.5% vs. 71.1%, respectively). Most patients in the zanubrutinib and ibrutinib arms had PR (73.7% and 68.3%, respectively), followed by CR (33.7% and 22.5%, respectively), CRi (1.2% and 0.3%, respectively), and nodular PR (0.9% and 0, respectively). In this analysis, the response ratio for zanubrutinib to ibrutinib was 1.12 (95% CI, 1.02 to 1.22; superiority 2-sided nominal P = 0.0013).

Similar findings were observed in the interim analysis set ITT analysis set (data cut-off: December 31, 2020) and the final PFS analysis set ITT analysis set (data cut-off: August 8, 2022).

EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 1 Global Health Status scale, 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), and 6 single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties). Each raw scale score is converted to a standardized score that ranges from 0 to 100, with a higher score reflecting better function on the function scales, worse state on the symptom and single-item symptom scales, and better quality of life on global quality of life scale.

[redacted]

EQ-5D-5L

SEQUOIA Trial

[redacted]

ALPINE Trial

[redacted]

Harms Results

Incidence of Atrial Fibrillation or Flutter

SEQUOIA Trial

In cohort 1, the proportion of patients who had atrial fibrillation or flutter was 3.3% in the zanubrutinib arm versus 2.6% in the bendamustine-rituximab arm. [redacted]

ALPINE Trial

Atrial fibrillation or flutter was tested as a key secondary end point, separate from the fixed-sequence hierarchical testing for the primary end point (ORR per investigator assessment) because zanubrutinib was found to be noninferior to ibrutinib in investigator-assessed ORR at the interim analysis. Multiplicity was controlled at the interim and final ORR analyses.

In the safety analysis set (data cut-off: December 31, 2020), atrial fibrillation and flutter was analyzed in the first 415 randomized patients from the safety analysis set and according to actual treatment received. In that analysis, the zanubrutinib arm had a significantly lower frequency of atrial fibrillation or flutter versus the ibrutinib arm (2.5% versus 10.1%), which corresponded to a rate difference of −7.7% (95% CI, −12.3% to −3.1%; P = 0.0014).

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), atrial fibrillation and flutter was less common in the zanubrutinib arm (4.6%) than in the ibrutinib arm (12.0%), which corresponded to a rate difference of −7.4% (95% CI, −11.6% to −3.2%; P = 0.0006).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), atrial fibrillation and flutter was less common in the zanubrutinib arm (5.2%) than in the ibrutinib arm (13.3%), which corresponded to a rate difference of −8.0% (95% CI, −12.4% to −3.6%; nominal P = 0.0004).

Adverse Events, Serious Adverse Events, Withdrawals Due to Adverse Events, Mortality, and Notable Harms

The percentage of patients with any reported treatment-emergent AEs (TEAEs) was 93.3% in the zanubrutinib arm and 96.0% in the bendamustine-rituximab arm in SEQUOIA cohort 1, and it was 98.1% in the zanubrutinib arm and 99.1% in the ibrutinib arm in the ALPINE trial (final PFS analysis data cut-off: August 8, 2022). In SEQUOIA cohort 1, the most commonly reported AEs (occurring in ≥ 15% of patients) with a higher percentage of greater than 5% in the zanubrutinib arm were contusion (19.2% vs. 3.5% for zanubrutinib vs. bendamustine-rituximab) and upper respiratory tract infection (17.1% vs. 11.9% for zanubrutinib vs. bendamustine-rituximab). In cohort 2, 109 (98.2%) patients had at least 1 AE. The most commonly reported AEs in this arm were upper respiratory tract infection (20.7%), arthralgia and contusion (19.8% each), diarrhea (18.0%), nausea (16.2%), and constipation (15.3%).

In the ALPINE trial, COVID-19 (23.1% vs. 17.9% for zanubrutinib vs. ibrutinib) and upper respiratory infection (17.9% vs. 12.7% for zanubrutinib vs. ibrutinib) were reported more commonly in the zanubrutinib arm than the ibrutinib arm. SAEs were reported in 36.7% of patients in the zanubrutinib arm and 49.8% of patients in the bendamustine-rituximab arm in the SEQUOIA trial, and 42.0% of patients in the zanubrutinib arm and 50.0% for in the ibrutinib arm in the ALPINE trial (final PFS analysis data cut-off: August 8, 2022).

In the safety analysis set of cohort 1, TEAEs leading to treatment discontinuation were less common in the zanubrutinib arm (8.3%) than in the bendamustine-rituximab arm (13.7%). In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), the incidence of TEAEs leading to treatment discontinuation was lower in the zanubrutinib arm (15.4%) than in the ibrutinib arm (22.2%). In SEQUOIA cohort 1, death was recorded for 15 patients (6.6%) in the bendamustine-rituximab arm and 16 patients (6.7%) in the zanubrutinib arm. The most common cause of death was AEs in the bendamustine-rituximab arm (11 patients; 4.8%) and in the zanubrutinib arm (11 patients; 4.6%). In cohort 2, death was recorded for 8 patients (7.2%) in the zanubrutinib arm, which was most commonly related to disease progression (4 patients; 3.6%) or AEs (3 patients; 2.7%).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), a total of 108 deaths were reported. A lower proportion of patients died in the zanubrutinib arm than the ibrutinib arm (14.8% vs. 18.5%, respectively). The most common causes of death in the zanubrutinib and ibrutinib arms were TEAEs (9.0% and 11.4%, respectively) and CLL and SLL (4.6% and 5.6%, respectively, with no detailed breakdown data reported). Regarding AEs of special interest, in SEQUOIA cohort 1, the zanubrutinib and bendamustine-rituximab arms had similar overall rates of AEs of special interest (82.9% and 89.0%, respectively). Hemorrhage (45.0% vs. 11.0% for zanubrutinib vs. bendamustine-rituximab arms) and infection (62.1% vs. 55.99% for zanubrutinib vs. bendamustine-rituximab arms) were reported more commonly in the zanubrutinib arm compared to the bendamustine-rituximab arm. In cohort 2, the most commonly reported AEs of special interest were infections (79 patients; 71.2%), hemorrhage (57 patients; 51.4%), and second primary malignancies (24 patients; 21.6%). In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), the zanubrutinib and ibrutinib arms had similar overall rates of AEs of special interest (90.7% and 92.6%, respectively), except for atrial fibrillation and flutter (5.2% versus 13.3% for

zanubrutinib versus ibrutinib), which was reported lower in the zanubrutinib arm compared to the ibrutinib arm. Neutropenia (29.3% versus 24.4% for zanubrutinib versus ibrutinib) was reported more commonly in the zanubrutinib arm compared to the ibrutinib arm. The most common AEs of special interest in the zanubrutinib arm were infections (71.3% vs. 73.1% for zanubrutinib vs. ibrutinib arms) and hemorrhage (42.3% vs. 41.4% for zanubrutinib vs. ibrutinib arms). Similar findings were observed in the interim safety set (data cut-off: December 31, 2020) and final ORR analysis safety set (data cut-off: December 1, 2021).

Critical Appraisal

Both the SEQUOIA and ALPINE trials were ongoing phase III, open-label RCTs. There was no particular concern with the methods of randomization and stratification. For the SEQUOIA trial, the CADTH review team considered the open-label design to be reasonable given the distinct dosing regimens and administration routes between zanubrutinib and bendamustine-rituximab which could likely allow investigators and patients to make inferences on treatment assignment regardless of blinding. In addition, cohort 2 in the SEQUOIA trial was designed as a single-arm study based on ethical considerations because it is unethical to assign high-risk patients with 17p deletion to receive bendamustine-rituximab, which is associated with poor clinical outcomes and poor response in this patient population. The open-label design of the SEQUOIA and ALPINE trials had the potential to introduce reporting bias in the assessment of subjective outcomes reported by patients, such as HRQoL and AEs. Disease response outcomes (PFS, ORR, DOR) were assessed by investigator assessments and an IRC to help mitigate the biases associated with the open-label study design for both trials. Many of the outcomes used in the SEQUOIA and ALPINE trials (PFS, OS, ORR, DOR) are standard in oncology trials. Because the SEQUOIA and ALPINE trials are ongoing, the early reporting of the studies resulted in data immaturity at the primary efficacy analysis for the SEQUOIA, and at the interim and subsequent final ORR and PFS analyses for the ALPINE trial, the median of OS was not being reached in the zanubrutinib group in the SEQUOIA trial and both treatment groups in the ALPINE trial. There were several critical protocol amendments impacting the conduct of the trial after patients had first been randomized that may have biased the results and increased uncertainty through increased heterogeneity in the patient population. The type I error rate was controlled for the primary and selected secondary outcomes in both studies. Several outcomes of interest to this review were tested, and nominal P values reported (e.g., PFS per IRC in SEQUOIA, ORR per IRC, DOR per IRC and per investigator assessment), but any results with a P value less than the prespecified significance level should be interpreted with caution considering the potentially inflated type I error rate. Although the subgroup analyses were prespecified, there is no evidence that the studies were powered to detect subgroups differences. In addition, there were imbalances in dose reduction, missing doses, and treatment exposure between treatment arms in the SEQUOIA trial, which bias the study results.

In terms of generalizability of the pivotal SEQUOIA and ALPINE studies, the clinical expert commented that the eligibility criteria for the SEQUOIA study was restricted and excluded the population of younger patients (younger than 65 years) who are healthy with no comorbid illnesses, who are often seen in patients with CLL in Canadian clinical practice. Thus, the study results may not be generalizable to younger patients with CLL who have no comorbid illnesses. In addition, the SEQUOIA cohort 1 excluded patients without 17p deletion, which may compromise the generalizability of the study findings regarding the comparative efficacy of

zanubrutinib to the general population of patients with CLL; however, a separate nonrandomized cohort was included to assess patients with *TP53* deletions or mutations. In the SEQUOIA trial, the comparator was bendamustine-rituximab, although it was considered as the standard of care at the time of study design and study initiation (2017), bendamustine-rituximab was not a clinically relevant comparator according to the clinical expert consulted by CADTH because it is not commonly used in clinical practice currently. The majority of older patients have either nonmutated immunoglobulin variable regions or *TP53* mutations that make them eligible for treatment with BTK inhibitors, such as ibrutinib or acalabrutinib or venetoclax and obinutuzumab, which are preferred treatments by most physicians over bendamustine-rituximab. Regarding the choice of ibrutinib as the comparator in the ALPINE study, the clinical expert commented that ibrutinib is a clinically relevant comparator in the r/r setting if the patients received first-line chemoimmunotherapy. Overall, there was no direct evidence available regarding the comparative efficacy and safety of zanubrutinib to ibrutinib, acalabrutinib, or venetoclax-obinutuzumab in the first-line setting, and to venetoclax and rituximab in the r/r setting, thus these results may not address the question of the most optimal treatment for these patients. At the time this report was prepared, the duration of follow-up was inadequate for assessment of OS. Symptom data from the SEQUOIA and ALPINE studies could not be generalized to a broader context due to limited data available.

Indirect Comparisons

Description of Studies

The sponsor submitted an NMA and MAIC comparing zanubrutinib to relevant comparators in both the treatment-naive and r/r CLL settings. The sponsor-submitted NMA was informed by a systematic literature review to identify existing RCTs conducted in adults with treatment-naive or r/r CLL. Following completion of the NMA, the sponsor considered there to be notable uncertainty in the results due to the distance between nodes and heterogeneity in patient populations, and therefore conducted MAICs comparing zanubrutinib versus both acalabrutinib and ibrutinib in the treatment-naive and r/r settings. The primary objective of the sponsor-submitted NMA and MAIC was to compare the efficacy (PFS, OS) and safety (AEs, SAEs, discontinuations due to AEs, and AEs by preferred term) of zanubrutinib in patients with treatment-naive or r/r CLL.

Efficacy Results

Network Meta-Analysis

In the treatment-naive CLL network, a total of 5 interventions, including zanubrutinib (SEQUOIA trial), ibrutinib (ALLIANCE trial), bendamustine-rituximab (SEQUOIA, ALLIANCE, and MABLE trials), rituximab-chlorambucil (MABLE and CLL11 trials), and obinutuzumab (Gazyvaro)-chlorambucil (Study CLL11) were evaluated, and the only evaluable outcome was PFS. In the fixed-effect model of PFS, zanubrutinib was favoured over obinutuzumab-chlorambucil (HR = 0.45; 95% credible interval [CrI], 0.23 to 0.86), bendamustine-rituximab (HR = 0.42; 95% CrI, 0.27 to 0.66) and rituximab-chlorambucil (HR = 0.22; 95% CrI, 0.12 to 0.41); however, there was no difference between zanubrutinib and ibrutinib (HR = 1.07; 95% CrI, 0.59 to 1.98) in terms of PFS.

In the r/r CLL network, a total of 5 interventions were evaluated including zanubrutinib (ALPINE trial), ibrutinib (ALPINE and ELEVATE-RR trials), acalabrutinib (ELEVATE-RR and ASCEND trials), bendamustine-rituximab (ASCEND and MURANO trials), and venetoclax-rituximab (MURANO trial). Both PFS and OS were available for inclusion in the r/r CLL NMA. In the fixed-effect model of PFS, zanubrutinib was favoured over bendamustine-rituximab (HR = 0.13; 95% CrI, 0.06 to 0.26), and acalabrutinib (HR = 0.52; 95% CrI, 0.30 to 0.89); however, there was no difference between zanubrutinib and venetoclax-rituximab (HR = 0.69; 95% CrI, 0.32 to 1.46). In the fixed-effect model of OS, there was no difference between zanubrutinib and any of the other treatments.

Matching-Adjusted Indirect Comparison

[redacted].

Harms Results

Network Meta-Analysis

Harms were not evaluated in the sponsor-submitted NMA.

Matching-Adjusted Indirect Comparison

[redacted].

Critical Appraisal

Network Meta-Analysis

The sponsor-submitted NMA was informed by a targeted literature review and systematic literature review which included planned searches of multiple databases; however, clinical trial databases were not searched, and given the methodology of conducting a targeted literature review followed by a systematic literature review, it remains unclear if any relevant studies were missing. A quality assessment of the included studies was conducted; however, the results were not included. As part of the feasibility assessment for the NMA, a list of potential treatment effect modifiers was developed from subgroups of the included trials, though these were not powered to detect differences, and no formal search of potential effect modifiers was conducted.

Based on the results of the feasibility assessment, PFS was the only outcome evaluated in the treatment-naive CLL NMA as OS was deemed too immature for comparison by NMA. For the treatment-naive CLL NMA, 3 of the trials included in the systematic literature review (RESONATE-2, ELEVATE-TN, and CLL14 trials) were excluded from the NMA due to substantial differences in effect modifiers across trials, which may have increased transitivity but reduced the robustness of network. However, no sensitivity analysis was performed on the impact of excluding these trials.

Baseline characteristics between studies were generally similar apart from the included populations; the SEQUOIA and ALPINE studies included both CLL and SLL patients, whereas all other studies included only CLL patients. The proportion of SLL patients from SEQUOIA and ALPINE likely had little impact on the results, though this was not explored. No adjustments for differences in baseline characteristics were conducted.

For both PFS and OS (when reported) in the treatment-naive and r/r CLL NMAs, results were mostly associated with wide 95% CrIs, suggesting notable imprecision. Although results for both NMAs suggested that zanubrutinib is favoured over most treatments, particularly for PFS, it should be noted that the results were produced using a fixed-effect model. It is uncertain if the fixed-effect model was the appropriate model to use in these comparisons due to lack of reporting of model statistics. As a result, superiority of zanubrutinib from the NMA cannot be concluded.

Matching-Adjusted Indirect Comparison

The choice to conduct a MAIC was justified considering the lack of comparison included in the sponsors' NMA for the relevant comparators acalabrutinib and venetoclax-obinutuzumab in the treatment-naive setting. As with the NMA, a major difference in populations was the inclusion of both CLL and SLL patients in the zanubrutinib studies (SEQUOIA and ALPINE trials), whereas all comparator studies only included CLL patients. Additionally, in the r/r MAIC, the population for the ELEVATE-RR study only included high-risk patients (patients with 17p and 11q deletions); therefore, the population in the ALPINE trial was also restricted to a subset of high-risk patients, which resulted in reduced sample sizes for the zanubrutinib and ibrutinib arms. The removal of patients who were not high-risk from the zanubrutinib studies may render the results for the r/r CLL MAIC as not generalizable to the r/r CLL population in Canada. [redacted].

[redacted].

Overall, there were multiple limitations of the sponsor-submitted MAIC, such as the reduction in sample sizes in both treatment-naive and r/r populations, as well as the heterogeneity in baseline characteristics across studies leading to uncertainty about the overall generalizability of the results to the Canadian population, and wide 95% CIs leading to imprecision and uncertainty in the results.

Studies Addressing Gaps in the Pivotal and RCT Evidence

A lack of evidence for zanubrutinib's safety and effectiveness in previously treated patients with CLL who could not tolerate existing BTK inhibitors (ibrutinib and acalabrutinib) was identified as a gap in evidence.

Description of Studies

One ongoing phase II, multicentre, single-arm study evaluating the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies, including CLL, who are intolerant to ibrutinib and/or acalabrutinib was submitted by the sponsor to address a gap in evidence. Of the estimated 90 participants, 67 patients had been enrolled as of the data cut-off date, September 8, 2021. Cohort 1 (57 patients) had prior experience with ibrutinib, and cohort 2 (10 patients) had prior experience with acalabrutinib alone or in addition to ibrutinib. Of the total 67 patients enrolled, 43 (64.2%) patients were diagnosed with CLL.

Efficacy Results

Based on outcomes measured in 64 patients with a study duration of more than 90 days, disease was under control (i.e., stable disease or better) in 60 (93.8%) patients. In 64.1% of patients, their condition improved while taking zanubrutinib. Two (3.1%) patients, 1 patient from each cohort, experienced progression on zanubrutinib as of the data cut-off date.

Harms Results

Overall, 34 of 57 (59.6%) patients on prior ibrutinib and 7 of 10 (70%) patients on prior acalabrutinib did not experience recurrence of the intolerance event while taking zanubrutinib. One patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerance event (myalgia while taking acalabrutinib). For severity, 25 of 38 grade 3 events (65.8%) that had occurred on ibrutinib and for 3 of 4 grade 3 events (75.0%) that occurred on acalabrutinib did not recur on zanubrutinib. None of the grade 4 intolerance events (2 cases of neutropenia, 1 case of alanine aminotransferase increase, and 1 case of aspartate aminotransferase increase) recurred. Among the intolerance events that did recur on zanubrutinib, the recurrent events were mainly of lower severity (26 of 34 events [76.5%] for ibrutinib intolerance and 1 of 3 events [33.3%] for acalabrutinib intolerance); none of the events recurred at a higher severity.

Critical Appraisal

Because 2 pivotal trials, SEQUOIA and ALPINE, had exclusion criteria for patients with CLL who have been treated with a BTK inhibitor, Study 215 addresses a gap in evidence by including such patients. However, there are a few limitations. As a single-arm trial, Study 215 does not address the comparative effectiveness of zanubrutinib. Second, because Study 215 is still ongoing, the interim data may overestimate the safety profile of zanubrutinib. In addition, a small sample size (N = 67) with a subgroup of patients with CLL (n = 43; 64.2%) introduces uncertainty in the results and issues with generalizability. Finally, none of the study sites are in Canada, which may raise another issue with external validity of study results.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with CLL for whom a fludarabine-based regimen is inappropriate
Treatment	Zanubrutinib
Dose regimen	320 mg once daily or 160 mg twice daily until disease progression or unacceptable toxicity
Submitted price	Zanubrutinib, 80 mg capsule: $67.98 per capsule
Treatment cost	Annual cost: $99,256
Comparators	Ibrutinib Acalabrutinib
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data source	In the treatment-naive subgroup, an NMA was used to estimate the comparative clinical efficacy of zanubrutinib and ibrutinib and an MAIC was used to estimate the comparative clinical efficacy of zanubrutinib and acalabrutinib. In the relapsed or refractory subgroup, the pivotal ALPINE trial was used to estimate comparative efficacy of zanubrutinib and ibrutinib. An NMA and MAIC were used to estimate the comparative clinical efficacy of zanubrutinib and acalabrutinib.
Costs considered	Drug acquisition costs
Key limitations	• Feedback from clinical experts consulted by CADTH noted that although most adult patients with CLL for whom a fludarabine-based regimen is inappropriate may receive either ibrutinib or acalabrutinib, a significant proportion of patients in the treatment-naive subgroup could be eligible for venetoclax in combination with obinutuzumab. Therefore, exclusion of venetoclax in combination with obinutuzumab as a relevant comparator was not appropriate. • The comparative clinical effectiveness of zanubrutinib is uncertain because of the limitations in the sponsor-submitted MAIC and NMA. This included the reduction in sample sizes in both subgroups during the weighting process, the heterogeneity in baseline characteristics, and wide confidence intervals. Additionally, the results of the NMA and MAIC were not supportive of each other regarding the comparative efficacy and safety of zanubrutinib.
CADTH reanalysis results	• CADTH did not undertake a reanalysis of the sponsor's base case because the results of the CADTH clinical review and clinical expert opinion were generally in alignment. • As the drug acquisition costs for zanubrutinib are lower than ibrutinib and acalabrutinib, a price reduction was not completed. The analysis was conducted based on the public list prices of ibrutinib and acalabrutinib because the confidentially negotiated prices for ibrutinib and acalabrutinib are unknown.

CLL = chronic lymphocytic leukemia; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis.

Budget Impact

CADTH identified the following key limitations from the sponsor's analysis: exclusion of venetoclax in combination with obinutuzumab as a relevant comparator, and the market uptake of zanubrutinib and the proportion of patients eligible for BTK treatment are uncertain.

CADTH did not conduct a base-case reanalysis because the sponsor's submission provided adequate presentation of the budget impact for zanubrutinib. The budget impact analysis suggested the reimbursement of zanubrutinib is associated with a 3-year budgetary cost savings of **$4,023,729.** CADTH presented 2 scenario analyses to test the impact of alternative assumptions on the estimated budget impact.

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. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: July 12, 2023

Regrets: One expert committee member did not attend.

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

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