

CADTH Reimbursement Recommendation

Zanubrutinib (Brukinsa)

Indication: For the treatment of patients with Waldenström macroglobulinemia

Sponsor: BeiGene Canada ULC

Final recommendation: Reimburse with conditions

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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 relapsed or refractory Waldenström macroglobulinemia (WM), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Brukinsa should only be covered to treat patients with relapsed or refractory WM who have received at least 1 prior line of therapy, meet at least 1 criterion for treatment according to International Workshop on WM (IWWM) consensus panel criteria, and have good performance status. Patients eligible for reimbursement of Brukinsa should not have disease transformation, which is WM that has transformed into another type of cancer, or received prior treatment with a drug of the same class (i.e., a Bruton tyrosine kinase [BTK] inhibitor) unless such therapy was stopped because the drug was not tolerated and the disease had not progressed.

What Are the Conditions for Reimbursement?

Brukinsa should only be reimbursed if prescribed by a clinician with expertise and experience in the treatment of WM and monitoring of therapy and if it does not cost more than other treatments for WM.

Why Did CADTH Make This Recommendation?

- Clinical evidence demonstrated that Brukinsa was similar to ibrutinib with respect to complete response or very good partial response and had a manageable toxicity profile.
- Brukinsa met patient needs for an additional treatment option for oral administration with fewer side effects, and no apparent deterioration in quality of life.
- There was not enough evidence to suggest Brukinsa is any better than other therapies used to treat relapsed/refractory WM that are reimbursed by public drug plans. Economic evidence suggests that a price reduction of at least 93% is needed to ensure Brukinsa is no more costly to the health system than therapies that are currently reimbursed by public drug plans.
- Based on public list prices, Brukinsa is expected to cost the public drug plans \$12,979,175 in the second-line setting over 3 years.

Additional Information

What Is WM?

WM is a cancer which grows mainly in the bone marrow, causing low levels of red blood cells leading to weakness and fatigue, and low numbers of white blood cells making it hard for the body to fight infection. WM is a rare disease with 1 in 200,000 people diagnosed each year in Canada.

Unmet Needs in WM

All patients with WM eventually relapse and need additional treatment. There are few treatment options for patients who relapse after initial treatment, such as chemotherapy.

How Much Does Brukinsa Cost?

Treatment with Brukinsa is expected to cost approximately \$99,324 per patient per year.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that zanubrutinib be reimbursed for the treatment of patients with relapsed or refractory (R/R) Waldenström macroglobulinemia (WM) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

pERC reviewed evidence from a randomized cohort of the ASPEN trial (164 patients with R/R WM) that evaluated zanubrutinib against ibrutinib, a treatment comparator that is currently used in Canadian practice accessed through compassionate programs or private insurance, but is not publicly funded in any jurisdiction. The ASPEN trial was originally designed and powered as a noninferiority trial; however, a protocol amendment revised the design to a superiority trial and noninferiority of zanubrutinib was evaluated in a post hoc analysis. At the primary analysis, the ASPEN trial demonstrated no statistically significant difference ($P = 0.116$) in complete response (CR) or very good partial response (VGPR) rate by International Workshop on WM (IWWM-6) response criteria between the zanubrutinib (28.9%; 95% CI, 19.5% to 39.9%) and ibrutinib (19.8%; 95% CI, 11.7% to 30.1%) treatment arms in patients with R/R WM. The post hoc analysis indicated zanubrutinib was noninferior to ibrutinib for VGPR/CR. Although the post hoc data are supportive of the primary analysis results, they are limited by the exploratory nature of the analysis. Data on longer-term outcomes including duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were assessed in the trial but were considered immature at the time of the primary analysis. The trial data suggested no difference between zanubrutinib and ibrutinib in measures of health-related quality of life (HRQoL) and a similar incidence of adverse events (AEs) albeit different safety profiles were observed. Compared to ibrutinib, zanubrutinib was associated with a lower incidence of atrial fibrillation (2.0% versus 14.3%) and major bleeding (5.9% versus 9.2%). The sponsor submitted an indirect treatment comparison (ITC) of zanubrutinib to relevant comparators in Canada but there were significant limitations of the analysis, and no conclusions could be drawn on comparative efficacy with respect to PFS and OS, and HRQoL and safety outcomes were not assessed.

Given the rarity of WM, pERC acknowledged there should be greater allowance for uncertainty in the evidence. pERC considered there is a significant unmet need for more treatment options in WM, most notably for patients with R/R WM for whom there is presently no clear standard of care regimen and retreatment with chemoimmunotherapy is of limited efficacy. Within this context, ibrutinib (obtained through compassionate access) has become a de facto standard of treatment in Canada for patients in the R/R setting, 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 that patients need additional treatment options that provide longer remission and survival and improved quality of life with fewer side effects. Given the totality of the evidence, pERC concluded that zanubrutinib met some of the needs identified by patients as it provides an additional treatment option for oral administration with the potential for fewer side effects and no apparent deterioration in quality of life.

Using the sponsor-submitted price for zanubrutinib and publicly listed prices for all other drug costs, zanubrutinib was more costly compared with funded comparators. There was

no reliable evidence to quantify any additional benefit provided by zanubrutinib in R/R and treatment-naive patients with WM relative to funded comparators. As such, zanubrutinib should be no more costly than the least costly alternative that is funded for patients in this setting. Given that zanubrutinib is given until disease progression rather than for a fixed period, this would require price reductions of more than 93% to ensure cost parity over the patient's lifetime.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Treatment with zanubrutinib should only be initiated in adult patients who have R/R WM and meet all of the following criteria: <ul style="list-style-type: none"> 1.1. Received at least 1 prior line of therapy 1.2. Meet at least 1 criterion for treatment according to IWWM consensus panel criteria 	Evidence from the ASPEN trial showed that zanubrutinib had similar efficacy for CR/VGPR when compared to ibrutinib (i.e., lack of demonstrated superiority or noninferiority) among adult patients with R/R WM who had received at least 1 prior line of therapy and met at least 1 of the established criteria for requiring treatment.
2. Patients must have an ECOG PS ≤ 2.	The CADTH review identified no evidence to demonstrate a benefit of zanubrutinib in patients with ECOG PS > 2 at baseline as these patients were not enrolled in the ASPEN trial.
3. Patients must not have any of the following: <ul style="list-style-type: none"> 3.1. Prior exposure to a BTK inhibitor 3.2. Disease transformation 	The CADTH review identified no evidence to demonstrate a benefit of zanubrutinib in patients with prior exposure to a BTK inhibitor or disease transformation, as these patients were not enrolled in the ASPEN trial.
Renewal	
4. Renewal of zanubrutinib should be based on the following assessments: <ul style="list-style-type: none"> 4.1. Blood work should be performed monthly at the beginning of treatment and then can be performed less frequently at the discretion of the treating physician 4.2. Imaging at baseline; and for patients with extramedullary disease, imaging should be at the discretion of the treating physician 	<p>This condition reflects the type of assessments that were performed in the ASPEN trial to assess patients' response to zanubrutinib.</p> <p>In the ASPEN trial, blood work was performed every 28 days until cycle 12, and every 3 cycles thereafter. This bloodwork schedule was considered more frequent compared to that used for other BTK inhibitors. Blood work should be performed monthly at the beginning of treatment and then can be performed less frequently at the discretion of the treating physician.</p> <p>Imaging should be performed at baseline for all patients as per the ASPEN trial; however, for patients with extramedullary disease, the frequency of imaging used in the trial (i.e., every 3 cycles until cycle 12; thereafter every 6 cycles) was considered unnecessary based on Canadian clinical practice, and therefore imaging should be performed at the discretion of the treating physician.</p>
Discontinuation	
5. Treatment with zanubrutinib should be discontinued upon the occurrence of any of the following: <ul style="list-style-type: none"> 5.1. Progression of disease according to IWWM response assessment criteria 5.2. Unacceptable toxicity 	The CADTH review identified no evidence that continuing treatment with zanubrutinib in patients whose disease has progressed is effective.

Reimbursement condition	Reason
Prescribing	
6. Zanubrutinib should only be prescribed by a clinician with expertise and experience in the treatment of WM and monitoring of therapy. As an oral therapy, zanubrutinib would likely be provided in an outpatient clinic.	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 be negotiated so that it does not exceed the drug program cost of treatment with the least costly comparator reimbursed for the treatment of R/R WM.	There is insufficient evidence to justify a cost premium for zanubrutinib over the least expensive comparator reimbursed for R/R WM. This is due to the absence of direct head-to-head evidence and methodological limitations associated with the indirect comparison. Given that zanubrutinib is given until disease progression rather than for a fixed period, this would require price reductions of more than 93% to ensure lifetime drug costs were equal.
Feasibility of adoption	
8. The feasibility of adoption of zanubrutinib must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.

BTK = Bruton tyrosine kinase; CNS = central nervous system; CR = complete response; ECOG = Eastern Cooperative Oncology Group; IWWM = International Workshop on Waldenström macroglobulinemia; PS = performance status; VGPR = very good partial response; R/R = relapsed/refractory; WM = Waldenström macroglobulinemia.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance From pERC

Condition number in Table 1	Implementation Considerations and Guidance
3.0	Patients with evidence of active CNS lymphoma were excluded from the ASPEN trial. pERC agreed with the clinical experts that CNS lymphoma should not be a reason to exclude a patient from receiving zanubrutinib. Patients with active CNS lymphoma from WM (Bing Neel syndrome) would benefit from early treatment with zanubrutinib, similar to how ibrutinib is used in these patients.
3.1	Patients with prior exposure to a BTK inhibitor were excluded from the ASPEN trial. pERC agreed with the clinical experts consulted by CADTH 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. If a patient did not respond to ibrutinib, they should be ineligible for zanubrutinib. Treatment with zanubrutinib should only be considered for patients who discontinued ibrutinib for intolerance and not disease progression.

BTK = Bruton tyrosine kinase; R/R = relapsed/refractory; WM = Waldenström macroglobulinemia.

Discussion Points

- WM is a rare lymphoplasmacytic lymphoma malignancy with an incidence in Canada of 1 in 200,000 people per year. Given its indolent nature and associated symptoms, WM can become a serious and life-threatening condition causing significant morbidity in the elderly. pERC discussed that the standard first-line treatment for WM in Canada is chemoimmunotherapy, most commonly with bendamustine and rituximab (BR) followed by rituximab maintenance. BR is associated with remissions beyond 5 years; however, the regimen is not curative. All patients with WM will eventually relapse and require additional treatment. According to the clinical experts consulted by CADTH, there is no standard of care therapy for R/R WM as few patients are eligible for retreatment with chemoimmunotherapy and even fewer are eligible for stem cell transplant. Among those who are treated with further chemoimmunotherapy, patient outcomes are suboptimal, and remissions tend to be shorter with each subsequent round of chemoimmunotherapy. Presently, there is no BTK inhibitor publicly funded for this indication in Canada. CADTH reviewed ibrutinib for the same indication in 2016 and did not recommend reimbursement citing limitations of the non-comparative evidence that was available for review at that time. Patients currently have access to BTK inhibitors through temporary compassionate access programs or private insurance plans and based on input from the clinical experts and patients, ibrutinib and zanubrutinib are the most frequently used treatments in the R/R setting after failure of chemoimmunotherapy. pERC agreed there remains a significant need for additional effective treatment options in WM, particularly for patients with R/R WM.
- pERC discussed the results of the ASPEN trial, a phase III superiority trial that demonstrated no statistically significant difference in CR/VGPR rates between zanubrutinib and ibrutinib in patients with R/R WM. The similar efficacy between the treatments in terms of response was supported by the post hoc analysis. The results indicated zanubrutinib was noninferior to ibrutinib, suggesting that had the design of the trial not been amended, noninferiority of zanubrutinib compared to ibrutinib would have been met. However, pERC discussed these results are limited by the exploratory nature of the analysis. pERC noted the data on long-term outcomes, DOR, PFS and OS, were immature at the primary analysis. The ASPEN trial is ongoing, so further data on these end points will be forthcoming; however, pERC considered that the interpretation of eventual results will be limited since the trial was not powered to assess between-group differences, and their assessment (PFS and OS) was exploratory.
- A major limitation of the submission for zanubrutinib was the lack of direct evidence comparing it to publicly funded chemoimmunotherapy regimens (i.e., rituximab-based chemotherapy) for patients with WM. pERC discussed that limitations identified in the sponsor's ITC of zanubrutinib to standard of care chemoimmunotherapy regimens precluded pERC's ability to draw conclusions on comparative efficacy, safety and HRQoL. pERC acknowledged, however, that given the rarity of WM and the high unmet need for patients with R/R WM, there should be greater allowance for uncertainty in the evidence. In addition, pERC recognized the current widespread use of ibrutinib in Canadian clinical practice through temporary compassionate access programs and agreed the frequency of its use deemed it a relevant treatment comparator.
- pERC discussed that the ASPEN trial included a small subgroup (n = 37) of patients who were considered unsuitable for standard chemoimmunotherapy in the first-line setting (unfit treatment naive). pERC noted that the trial did not use explicit criteria to define this patient population and patients' suitability to receive standard front-line

chemoimmunotherapy was decided by treating investigators based on age and comorbidities. pERC agreed with the clinical experts consulted by CADTH that the data from the trial are insufficient for determining the specific patients with WM who are truly unsuitable for standard first-line chemoimmunotherapy and that true ineligibility to front-line chemoimmunotherapy is rare, as dose intensity can be adjusted to address frailty and comorbidity concerns. Further, because the trial evaluated zanubrutinib in a small unfit treatment-naive patient population, pERC agreed it was highly uncertain whether the trial results were generalizable to WM patients typically considered for front-line therapy. pERC also noted that the sponsor's ITC did not include an analysis in treatment-naive patients comparing zanubrutinib to BR, the most used standard of care regimen. Given these limitations and considering the efficacy of current standard of care in this setting, pERC concluded zanubrutinib should not be reimbursed as first-line treatment in patients with WM who are treatment naive.

- No differences in HRQoL (as measured using the EORTC QLQ-C30 and EQ-5D-5L) were observed in the ASPEN trial between the zanubrutinib and ibrutinib treatment arms. Overall, pERC agreed that zanubrutinib did not result in deterioration of patients' quality of life. However, pERC noted that the patient-reported outcomes in trial were exploratory in nature for which only descriptive results were presented. Therefore, only limited interpretations could be made on the available quality of life data.
- 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 adverse events (SAEs) was comparable in the 2 treatment arms with a few exceptions. Zanubrutinib was associated with a higher incidence of neutropenia, although pERC noted this increase did not translate into a higher incidence of infections. In patients treated with ibrutinib, there was a higher incidence of atrial fibrillation and major bleeding, key side effects of BTK inhibitors. pERC discussed that the comparative safety of zanubrutinib to standard chemoimmunotherapy regimens was not assessed in the ITC but considered that based on the experience of the clinical experts consulted by CADTH, zanubrutinib may be more tolerable than the chemoimmunotherapy treatments currently used to treat patients with R/R WM. Based on the available evidence, pERC concluded that zanubrutinib has the potential for less side effects than comparator treatments.
- Input from patient groups indicated that patients value additional treatment options that provide longer remission and survival and improved quality of life with fewer side effects. Based on the evidence from the ASPEN trial, pERC concluded that zanubrutinib met some of the needs identified by patients as 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 noted that ibrutinib is used for some patients with WM however is not funded across any provinces. Therefore, from a health care payer perspective, the cost-effectiveness of zanubrutinib versus ibrutinib is less relevant than publicly reimbursed options which will be displaced if zanubrutinib is funded.

Background

Zanubrutinib (Brukinsa) is a second-generation small molecule inhibitor of BTK and has a Health Canada indication for the treatment of adult patients with WM. Zanubrutinib is supplied in 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 their recommendation, pERC considered the following information:

- A review of 1 randomized phase III trial in patients with WM.
- Patients' perspectives gathered by 4 patient groups, The CanCertainty Coalition, Lymphoma Canada (LC) in collaboration with the Canadian Organization for Rare Disorders (CORD), and the WM Foundation of Canada (WMFC).
- 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 WM.
- Input from 1 clinician group, the 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 the input provided by the patient and clinician groups who responded to CADTH's call for input, and from clinical experts consulted by CADTH for the purpose of this review. As well, issues identified by the provincial drug plans that may impact their ability to implement a recommendation are summarized.

Patient Input

Four patient groups provided input for the review of zanubrutinib in WM: The CanCertainty Coalition, LC in collaboration with the CORD, and the WMFC. The CanCertainty Coalition data collection were sourced through literature, Canadian prescription drug insurance coverage, population demographics, and previously conducted surveys. The CanCertainty data collection and submission were completed exclusively using CanCertainty resources and personnel and contract personnel. LC, CORD, and WMFC conducted an anonymous online survey for patients with WM between February 28, 2021, and May 10, 2021, in patients registered through their respective databases and through social media outlets.

Symptoms of WM that most impacted patients' HRQoL at diagnosis included fatigue (66%), night sweats (28%), neuropathy (24%), weight loss and loss of appetite (20%), and easy bruising and bleeding (20%). A total of 81% of respondents experienced at least 1 psychological and social impact of a WM diagnosis including stress and anxiety (66%), difficulty sleeping (30%), impact on daily activities (28%), memory loss and concentration problems (19%), and depression (19%). In terms of treatment, 17% of patient respondents were receiving front-line treatment, 41% were in remission following a previous line of treatment, and 6% relapsed following previous treatment and were waiting to begin treatment.

The most common treatments patients had received included chemotherapy monotherapy (55%), monoclonal antibodies (63%), and BTK inhibitors (36%). The most common side effects experienced by patients during treatment for WM included fatigue (72%), neutropenia (47%), nausea (39%), anemia (37%), peripheral neuropathy (37%), thrombocytopenia (30%), rash and itch (26%), back and joint pain (23%), mouth sores (22%), diarrhea (20%), headache (19%), and hair loss (17%). Patients noted that fatigue was particularly difficult to handle. Having a choice of treatment and having enough treatment options were considered particularly important to patients. Access to an effective oral therapy was also considered important to address access issues for patients who are unable to access treatment locally. Further, the inequity of funded access to oral therapies across Canada was also emphasized. In terms of outcomes, patients rated longer survival (75%), longer remission (76%), better HRQoL (70%), and fewer side effects (57%) as the most important outcomes of treatment.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH indicated that zanubrutinib would be used in the R/R setting after failure of standard chemoimmunotherapy as they expect it to be more efficacious, leading to more prolonged remission, and less toxic than a repeated round of chemoimmunotherapy. The clinical experts indicated that they would generally not consider zanubrutinib in the front-line treatment setting. All patients should be offered chemoimmunotherapy first line unless truly unfit for anything other than rituximab therapy or even oral chlorambucil. These patients have a defined treatment interval and can enjoy a prolonged remission after chemoimmunotherapy (with or without rituximab), and as such, reserving zanubrutinib in later lines does not result in reduced survival. Zanubrutinib should only be offered to patients who have failed at least 1 line of therapy. The clinical experts consulted by CADTH also indicated that patients with asymptomatic disease should not be treated with zanubrutinib unless there is concern about impending hyperviscosity syndrome. Patients who are at high risk for bleeding complications (e.g., those who cannot tolerate antiplatelet or anticoagulation equivalent) would also be least suitable for treatment with zanubrutinib.

One clinical expert commented that WM is truly an orphan disease, a rare group of patients with unique clinical manifestations that do not respond as well to chemoimmunotherapy as other indolent lymphomas (e.g., follicular lymphoma), with few and generally ineffective treatment options at relapse and little or no availability of new therapies through clinical trials. Consequently, having access to BTK inhibitors is imperative for this group of patients.

Clinician Group Input

A joint clinician input was received from 2 registered clinicians on behalf of the Ontario Health-Cancer Care Ontario Hematology Cancer Drug Advisory Committee for the review of zanubrutinib for the treatment of WM.

The clinicians stated that most patients demonstrate a good response to front-line BR and remain free of relapse for a few years. Contrary to the clinical experts consulted by CADTH, the clinician group advised that zanubrutinib may be used in the first-line setting or after relapse of the disease given there is currently no evidence to suggest the specific sequencing of treatment with zanubrutinib. However, it is patients with relapsed disease that have a significant unmet need for additional treatment options, including BTK

inhibitors. The clinicians indicated that patients best suited to this treatment are those with symptomatic R/R WM.

Drug Program Input

Input from the drug plans identified factors pertaining to relevant comparators, considerations for initiation and discontinuation of therapy, generalizability, care provision issues, and system and economic considerations. pERC weighed evidence from the ASPEN trial and other clinical considerations, including input from clinical experts consulted by CADTH, to provide responses which are presented in Table 3.

Table 3: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
<p>How does zanubrutinib compare to rituximab-based chemotherapy regimens for treatment-naive patients as well as those with R/R disease?</p>	<p>pERC agreed with the clinical experts consulted by CADTH that rituximab-based regimens are commonly used in front-line settings, whereas zanubrutinib would be considered only as second- or later line treatment of patients with R/R WM. There are no clinical trial data comparing rituximab-based regimens with zanubrutinib for R/R WM. The CADTH review team's appraisal of the sponsor's indirect comparison of zanubrutinib to relevant rituximab-containing treatment comparators indicated no conclusions could be drawn on comparative efficacy given limitations of the analysis.</p>
<p>The drug plans noted that in the ASPEN trial, zanubrutinib was compared to ibrutinib which is not publicly funded in any jurisdiction in Canada. Ibrutinib, for the treatment of patients with WM who have received at least 1 prior therapy, was previously reviewed by pERC and not recommended for reimbursement. Ibrutinib may be available for some patients (at no charge) through the manufacturer sponsored patient support program.</p> <p>Relevant comparators for WM in Canadian jurisdictions include rituximab-based chemotherapy for treatment-naive patients and relapsed disease. Retreatment with rituximab is funded for patients with a relapse-free interval (6 to 12 months, depending on the jurisdiction) following the last dose of rituximab.</p> <p>Rituximab-based chemotherapy regimens include: BR, DRC, and occasionally rituximab/cyclophosphamide/dexamethasone.</p>	<p>pERC acknowledged the lack of direct evidence comparing zanubrutinib to funded standard of care treatments in Canada. However, pERC also recognized the current widespread use of ibrutinib in Canada through compassionate access programs and therefore considered it a relevant treatment comparator.</p>

Implementation issues	Response
Considerations for initiation of therapy	
<p>In the ASPEN trial, participants with no prior therapy must have been considered unsuitable candidates for treatment with standard chemoimmunotherapy due to comorbidities and risk factors. In the trial, the definition of “unsuitable” was physician-determined based on comorbidities and risk factors. Patient preference was not considered a factor in determining whether a patient is considered unsuitable.</p> <p>Should zanubrutinib for treatment-naive WM be limited to patients with a contraindication to, or who are unsuitable for, chemoimmunotherapy? If so, what determines or defines being unsuitable for standard chemoimmunotherapy?</p>	<p>pERC did not recommend reimbursement of zanubrutinib in patients with WM who are considered unsuitable for treatment with standard chemoimmunotherapy in the first-line setting (treatment naive).</p>
<p>Patients with prior BTK inhibitor exposure were excluded from ASPEN. Should patients who have progressed on a prior BTK inhibitor be eligible for zanubrutinib?</p>	<p>pERC agreed with the clinical experts that there is no evidence from clinical trials to suggest that patients who progress on prior BTK inhibitors would benefit from treatment with a different covalent BTK inhibitor. If a patient did not respond to ibrutinib, they should be ineligible for zanubrutinib. Treatment with zanubrutinib should only be considered for patients who discontinued ibrutinib for intolerance and not disease progression.</p>
<p>Patients with evidence of disease transformation and patients with active CNS lymphoma were excluded from ASPEN. Should these patients be eligible for treatment with zanubrutinib?</p>	<p>pERC agreed with the clinical experts that BTK inhibitors are not used for disease transformation and therefore patients with evidence of disease transformation should not be eligible for treatment with zanubrutinib.</p> <p>pERC agreed with the clinical experts that CNS lymphoma should not be a reason to exclude a patient from receiving zanubrutinib. Patients with active CNS lymphoma from WM (Bing Neel syndrome) would benefit from early treatment with zanubrutinib, similar to how ibrutinib is used in these patients.</p>
Considerations for continuation or renewal of therapy	
<p>Per the product monograph, zanubrutinib is dosed at 320 mg po daily or 160 mg po BID until disease progression or unacceptable toxicity.</p> <p>Is there a preferred dosing schedule that should be used for zanubrutinib?</p>	<p>pERC agreed with the clinical experts that a once per day regimen is preferable.</p>
<p>Zanubrutinib has potential for drug-drug interactions, increasing potential for pharmacy resource use.</p>	<p>pERC acknowledged the potential for increased pharmacy resource use with zanubrutinib.</p>
Generalizability	
<p>Should patients receiving alternate treatment, who have not progressed, be switched to zanubrutinib if they otherwise meet criteria? If so, what is the appropriate time frame for switching?</p>	<p>pERC agreed with the clinical experts that if current treatment is effective and well tolerated, no switching would be required.</p>
<p>Under what clinical circumstances would zanubrutinib be used over currently available treatments (e.g., BR, rituximab-chemotherapy, privately funded ibrutinib)?</p>	<p>pERC agreed with the clinical experts that zanubrutinib would be considered in patients with R/R WM as a second or later line of therapy who have not received BTK inhibitor therapy previously (unless it was received then discontinued due to intolerance).</p>

Implementation issues	Response
Funding algorithm	
Zanubrutinib may change place in therapy for currently available treatment options. If first-line zanubrutinib is recommended for treatment-naive patients unsuitable for chemoimmunotherapy, would rituximab-bendamustine and/or rituximab-chemotherapy be available in second- and subsequent lines of therapy?	pERC did not recommend reimbursement of zanubrutinib in patients with WM who are considered unsuitable for treatment with standard chemoimmunotherapy in the first-line setting (treatment naive).
Care provision issues	
Capsule strength of 80 mg (in bottles of 120 capsules) facilitates dispensing and dose adjustments without wastage.	pERC acknowledged the available capsule strength of zanubrutinib facilitates dispensing and dose adjustment without wastage.
System and economic issues	
The drug plans noted the following: <ul style="list-style-type: none"> Confidential negotiated price exists for biosimilar rituximab and rituximab SC. Bendamustine and bortezomib are available in a generic format. 	The presence of confidential negotiated prices will need to be considered if price negotiations for zanubrutinib are conducted.

BIA = budget impact analysis; BID = twice daily; BTK = Bruton tyrosine kinase; BR = bendamustine-rituximab; CNS = central nervous system; DRC = dexamethasone-rituximab, cyclophosphamide; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pCODR Expert Review Committee; R/R = relapsed/refractory; SC = subcutaneously; WM = Waldenström macroglobulinemia.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The ASPEN study is an ongoing phase III, randomized, open-label, multicenter study, designed to compare the efficacy and safety of zanubrutinib and ibrutinib in patients with WM who required therapy. Between January 2017 and July 2018, 164 R/R and 37 unfit treatment-naive patients with WM were recruited into cohort 1 (patients with MYD88 mutation) who were randomized 1:1 to receive either ibrutinib (420 mg once a day) or zanubrutinib (160 mg twice a day) in 28-day cycles. Cohort 2 was a non-randomized, no-comparator arm which included 28 patients (wild-type or unknown MYD88 mutation status) including 23 R/R and 5 unfit treatment-naive patients who all received zanubrutinib (160 mg twice a day). The primary efficacy end point was the proportion of patients in each arm of cohort 1 achieving either CR or VGPR, as determined by an Independent Review Committee (IRC) using an adaptation of the response criteria updated at the IWWM-6. Other end points included DOR, PFS, improvement in cancer-related symptoms, OS, HRQoL, and medical resource utilization.

The most common indications (> 20%) for therapy initiation in cohort 1 were fatigue (57.2%), anemia (43.8%), B symptoms (30.3%), hyperviscosity (26.9%), and peripheral neuropathy (22.4%). The median age of all patients was 70.0 years. The majority of patients were male (66.7%), and white (91.0%). In cohort 2, the median age was 72 years; 50% of patients were male and 96.4% were white. The most common indications for therapy initiation were fatigue (60.7%), B symptoms (35.7%), anemia (32.1%), hyperviscosity (21.4%), and peripheral neuropathy (10.7%).

Efficacy Results

Cohort 1 - MYD88^{L265P}

The median follow-up time in cohort 1 was 19.4 months. The IRC-assessed CR/VGPR rate in the ibrutinib and zanubrutinib arms was 19.2% (95% CI, 12.0%, 28.3%) and 28.4% (95% CI, 19.9%, 38.2%), respectively. In R/R patients, the IRC-assessed CR/VGPR rate was 19.8% (95% CI, 11.7%, 30.1%) in the ibrutinib arm and 28.9% (95% CI, 19.5%, 39.9%) in the zanubrutinib arm (P = 0.116). In unfit treatment-naive patients, the IRC-assessed CR/VGPR rate was 16.7% (95% CI, 3.6%, 41.4%) in the ibrutinib arm and 26.3% (95% CI, 9.1%, 51.2%) in the zanubrutinib arm.

Nine patients in the ibrutinib arm and 6 patients in the zanubrutinib arm started non-protocol anti-cancer therapy. The median time to initiation of non-protocol anti-cancer therapy were 6.44 months in the ibrutinib treatment arm and 6.83 months in the zanubrutinib treatment arm. The median PFS had not been reached in either treatment arm. The event-free rates at 12 months for patients in the ibrutinib and zanubrutinib treatment arms were 87.2% (95% CI, 78.6%, 92.5%) versus 89.7% (95% CI, 81.7%, 94.3%), respectively, and 83.8% (95% CI, 74.5%, 89.9%) versus 85.0% (95% CI, 75.2%, 91.2%) at 18 months. The median OS was not reached in either treatment arm. At the data cut-off date (August 31, 2019), 8 deaths occurred in the ibrutinib arm, and 6 deaths occurred in the zanubrutinib arm. The event-free rates for patients in the ibrutinib versus zanubrutinib treatment arms were 93.9% (95% CI, 86.8%, 97.2%) versus 97.0% (95% CI, 90.9%, 99.0%) at 12 months.

HRQoL which was an exploratory end point and on average increased numerically during the trial observation period in both treatment arms. The least square (LS) mean (standard error [SE]) for EORC QLQ-C30 change in global health status/QoL score was 69.0 (2.3) in the ibrutinib arm and 68.3 (2.2) in the zanubrutinib arm (difference [95% CI], -0.69 [-4.95 to 3.57]). The mean (SD) change in EQ-5D-5L score from baseline was 9.0 (17.90) in the ibrutinib arm and 13.7 (14.66) in the zanubrutinib arm (at cycle 13 day 1).

Cohort 2 - MYD88^{WT}

The median follow-up time in cohort 2 was 17.8 months. The IRC-assessed CR/VGPR rate was 26.9% (95% CI, 11.6%, 47.8%). In cohort 2, no patients achieved CR. Three patients (1 unfit treatment-native and 2 R/R) started non-protocol anti-cancer therapy with a median time to initiation of 3.61 months.

Harms Results

In cohort 1, nearly all patients (97 [99.0%] of ibrutinib-treated, and 98 [97.0%] of zanubrutinib-treated patients) had at least 1 AE; grade of at least or greater than 3 AEs were reported in 62 (63.3%) and 59 (58.4%) of patients in the ibrutinib and zanubrutinib treatment arms, respectively. SAEs were reported in 40 (40.8%) and 40 (39.6%) patients in the ibrutinib and zanubrutinib treatment arms, respectively. The most common SAE in the ibrutinib treatment arm was pneumonia (9 [9.2%] patients), followed by pyrexia and sepsis (each 3 [3.1%] patients). The most common SAEs in the zanubrutinib treatment arm were febrile neutropenia, influenza, and neutropenia (each 3 [3.0%] patients). Nine (9.2%) patients in the ibrutinib arm, and 4 (4.0%) patients in the zanubrutinib treatment arm had AEs leading to study treatment discontinuation. A total of 7 (7.1%) patients in the ibrutinib treatment arm and 6 (5.9%) patients in the zanubrutinib treatment arm had died at the time of the data cut-off date; 5 (5.1%) patients in the ibrutinib arm and 1 (1.0%) patient in the zanubrutinib arm died within 30 days of the last dose of study drug.

Notable AEs included neutropenia, hemorrhage (minor and major bleeding), cardiovascular events, and second primary malignancy. In cohort 1, neutropenia was reported in 12 (12.2%) patients in the ibrutinib and 25 (24.8%) patients in the zanubrutinib arm. However, the higher incidence of neutropenia among zanubrutinib-treated patients did not translate to an increased occurrence of infections in the zanubrutinib arm. Fifty-eight (59.2%) patients in the ibrutinib arm and 49 (48.5%) in the zanubrutinib arm had hemorrhage (including minor bleeds involving mucous membranes and skin). Major hemorrhage was observed in 9 (9.2%) patients in the ibrutinib arm and 6 (5.9%) patients in the zanubrutinib arm. Atrial fibrillation and flutter was reported in 14 (14.3%) of patients in the ibrutinib arm and 2 (2.0%) patients in the zanubrutinib treatment arm. Second primary malignancy was reported in 11 (11.2%) patients in ibrutinib arm and 12 (11.9%) patients in the zanubrutinib arm.

Critical Appraisal

The ASPEN trial was an open-label study. Therefore, important sources of bias from lack of blinding of patients and investigators to study treatments exist; patient's knowledge of their treatment may have affected some safety end points, and different supportive care may have been offered to patients in the 2 treatment arms. The primary end point and key secondary end points were appropriate and adequately described. Data were immature for time to event outcomes and median PFS and OS were not reached in either treatment arm. Given that the ASPEN trial is ongoing, future analyses may be more informative with respect to time to event outcomes. In addition to PFS and OS, time to next treatment was identified in the systematic review protocol as an important efficacy outcome, but this was an exploratory outcome which limits interpretation of results. Some other important outcomes including OS and HRQoL were also exploratory outcomes in the trial. Of note, the only outcome defined in the statistical testing hierarchy, CR/VGPR rate in the R/R patient population of cohort 1, did not reach statistical significance.

Ibrutinib is not the most relevant comparator for zanubrutinib in Canadian clinical practice. The most relevant public-funded comparators for WM in Canadian jurisdictions include rituximab-based chemotherapy for treatment-naive patients and relapsed disease. Therefore, relevance to the current clinical setting is limited and the question of comparative efficacy and safety of zanubrutinib to current standard of care in Canada cannot be answered. The inclusion criteria for the ASPEN study were generally reasonable based on the intended patient population. However, the exclusion of patients with central nervous system (CNS) involvement in the ASPEN trial, although justified at the time the trial was designed due to a lack of disease management guidelines, was not considered appropriate as these patients (i.e., patients with Bing Neel disease) may benefit from early BTK inhibitor treatment. The definition of treatment naive used in the trial was patients who were unsuitable for chemoimmunotherapy based on age or comorbidities. This definition does not align with the standard definition of treatment-naive in oncology practice, which is a patient with no prior anti-cancer therapy. Therefore, the trial evidence regarding the efficacy and safety of zanubrutinib compared to ibrutinib in truly treatment-naive patients is insufficient to guide treatment decisions in this patient population in clinical practice.

Indirect Comparisons

Description of Studies

The sponsor-submitted ITC that was used to inform the pharmacoeconomic model, was appraised and summarized. A matching-adjusted indirect comparison (MAIC) was conducted based on a systematic literature review that compared the individual patient data

of zanubrutinib arm of the ASPEN trial to match the populations of relevant trial reports for chemotherapy regimens in adult patients with treatment-naive, or R/R WM. The analysis was informed by a systematic literature review that identified 33 trials, mainly retrospective that were subsequently excluded from the ITC. In total, 3 trials were included in the MAIC that included mixed, R/R, and treatment-naive WM patients, respectively. The interventions included zanubrutinib, BR, and DRC; however, DRC was used in the treatment-naive population, and BR in the R/R population. Three sets of pairwise MAICs were conducted; 2 pairwise comparisons matched the overall zanubrutinib population (N = 102) to the BR (N = 71) and DRC (N = 72) populations separately. A subgroup analysis was conducted matching zanubrutinib patients with R/R disease to the BR population. No MAIC was conducted specifically comparing the unfit treatment-naive subpopulation in ASPEN given the small sample size of unfit treatment-naive patient population in the zanubrutinib arm of the ASPEN trial (n = 19). Several of the preidentified variables including ECOG performance status, Beta2-microglobulin concentration, and MYD88/CXCR4 mutation status, were not accounted for during weighting due to the limitations of available data. In the MAIC comparing zanubrutinib to BR, the variables included in the weighting process included age, prior lines of therapy, IgM concentration, IPSS WM score, and presence of extramedullary disease. In the MAIC comparing zanubrutinib to DRC, the variables included in weighting were age, platelet count, hemoglobin count, and presence of extramedullary disease.

Efficacy Results

Results of the MAIC comparing zanubrutinib to BR after weighting suggest that zanubrutinib is favoured over BR, as well as in the R/R subgroup for PFS and OS, however the results lacked precision, showing wide 95% CIs. Zanubrutinib was associated with significantly longer PFS (HR: 0.37 [95% CI, 0.15 to 0.91]) after weighting compared to BR. Compared to DRC, zanubrutinib was associated with significantly longer PFS 0.35 [95% CI, 0.14 to 0.86]) after weighting. The hazard ratio for OS comparing zanubrutinib to BR indicated a statistically significantly longer OS in the overall population after weighting (HR: 0.29 [95% CI, 0.10 to 0.85]).



Harms Results

No indirect evidence was available for comparative safety or impact on HRQoL of zanubrutinib to relevant chemotherapy regimens.

Critical Appraisal

The ITC was informed by an appropriately conducted systematic review of the literature, highlighting the relevant population, and outcomes of interest for this review. Screening was conducted based on standard methods, with studies selected independently in duplicate, according to pre-specific criteria. No formal quality assessment of the included studies was conducted which is an important limitation. The sponsor's submitted MAIC, assumes that all effect modifiers and prognostic factors are accounted for in the model. A comprehensive list of prognostic factors and treatment-effect modifiers identified through appropriate channels was included in the report and based on discussions with the clinical experts consulted by CADTH, were considered relevant; however, some of these factors; including ECOG performance status, B2 microglobulin, and MYD88/CXCR4 mutation status were not accounted for in the calculation of weight. This may result in bias as not all prognostic factors and effect modifiers that were originally identified were accounted for in the weights.

Additionally, there were discrepancies between the cutoffs of identified variables, and those available for weighting, potentially further biasing the results. In terms of external validity, the studies selected for indirect comparison included treatment with DRC in the treatment-naive population, and BR in the R/R population. In discussion with the clinical experts consulted by CADTH, the comparison to DRC in the treatment-naive, first-line population was considered irrelevant as it does not reflect clinical practice in Canada. No studies were identified in the SLR reporting results for BR in the treatment-naive population, which is the standard of care in Canada, and were thus not included in the analysis for treatment-naive patients. Moreover, no studies were included in the treatment-naive population for patients whom chemoimmunotherapy was considered unsuitable.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target populations	Relapsed/refractory (R/R) and treatment-naive (TN) patients with Waldenström macroglobulinemia (WM)
Treatment	Zanubrutinib
Submitted price	\$67.9833 per 80 mg oral capsule
Treatment cost	First year: \$99,324 Subsequent years: \$99,324
Comparators	In R/R patients: bendamustine plus rituximab (BR) In TN patients: DRC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data source	<ul style="list-style-type: none"> An open-label, phase III trial (ASPEN), which included both R/R and TN patients with WM, was used to determine the OS and PFS for zanubrutinib MAICs were conducted to assess the comparative effectiveness of zanubrutinib to BR and DRC in 2 single-arm studies

Component	Description
Key limitations	<ul style="list-style-type: none"> • The sponsor used the comparator DRC in TN patients, rather than BR which was noted as the preferred first-line therapy by clinical experts. The comparator used in the R/R setting was BR, while clinicians noted that bortezomib-based regimens were preferred. No information was presented in the submission that compared zanubrutinib to BR in a first-line/TN setting or to bortezomib in an R/R setting. • The MAICs conducted by the sponsor were limited by the clinical heterogeneity between included studies, imprecise results for PFS and OS, and their inherent methodological deficiencies. Thus, no conclusions could be drawn from the MAICs regarding the efficacy of zanubrutinib compared with standard chemotherapy regimens and there is no evidence to support an incremental benefit of zanubrutinib over treatments used in current Canadian practice. • The sponsor overestimated the OS of patients with WM as a result of their extrapolation, particularly in patients receiving zanubrutinib. Clinical experts assisted in determining more appropriate estimates of survival in patients with WM. • The sponsor's assumptions surrounding subsequent treatment use were associated with substantial uncertainty.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH was unable to determine a base case due to a paucity of clinical evidence and a high degree of uncertainty involving the appropriate comparators. • As zanubrutinib is given until progression rather than a fixed period, as per BR and Bor-DR, CADTH performed a cost analysis comparing the lifetime costs of zanubrutinib if given until progression/toxicity (discounted at 1.5% per annum) with the relevant comparators Bor-DR and BR in the R/R and TN settings, respectively. • In the R/R setting, lifetime zanubrutinib drug costs were estimated to be \$514,116 per patient while Bor-DR had drug costs of \$32,463 per patient, if taken for the maximum number of treatment cycles. • In the TN setting, lifetime zanubrutinib drug costs were estimated to be \$805,190 per patient while BR had drug costs of \$37,135 per patient if taken for the maximum number of treatment cycles. • Although there is substantial uncertainty regarding whether zanubrutinib provides clinical benefit over currently funded treatments, it is evident that zanubrutinib will be associated with substantial costs. Price reductions of over 93% and 95% for zanubrutinib would be necessary to ensure cost parity with Bor-DR and BR in the R/R and TN settings, respectively.

Bor-DR = bortezomib, dexamethasone, and rituximab; BR = bendamustine plus rituximab; DRC = dexamethasone, rituximab, cyclophosphamide; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Budget Impact

Based on the CADTH base case, the budget impact of the reimbursement of zanubrutinib for the treatment of WM is expected to be \$3,075,366 in year 1, \$5,673,159 in year 2, \$8,665,803 in year 3, with a 3-year budget impact of \$17,414,328. CADTH estimated the budget impact in the first-line setting to be \$4,435,153 and \$12,979,175 in the second-line setting over 3 years. This was more than twice as large as the sponsor's estimated 3-year budget impact of \$5,125,851 (\$1,510,557 in the first-line setting and \$3,615,293 in the second-line setting).

pCODR Expert Review Committee Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan, Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: October 13, 2021

Regrets: Two expert committee members did not attend.

Conflicts of interest: None.