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CADTH Reimbursement Recommendation

Ibrutinib (Imbruvica)

Indication: Ibrutinib, with or without rituximab, for the treatment of adult patients with previously treated refractory or relapsed Waldenström's macroglobulinemia

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Imbruvica?

CADTH recommends that Imbruvica, with or without rituximab, should be reimbursed by public drug plans for the treatment of adult patients with previously treated relapsed or refractory Waldenström's macroglobulinemia (WM) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Imbruvica should only be covered to treat adult patients who have WM and have received at least 1 prior line of therapy, have good performance status, and who meet at least 1 criterion for treating WM according to the latest International Workshop on WM criteria.

What Are the Conditions for Reimbursement?

Imbruvica should not be reimbursed for patients who have received prior treatment with a Bruton tyrosine kinase inhibitor and whose disease responded poorly or for patients with disease transformation. Imbruvica should only be prescribed by hematologists or oncologists with experience in treating patients with WM, and the cost of Imbruvica should be negotiated to provide cost savings for drug programs relative to zanubrutinib.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Imbruvica resulted in longer survival without disease progression compared with standard of care. Based on another published study, it had comparable benefit to other drugs currently available in Canada and indicated for patients with WM.
- Imbruvica may meet some of the needs identified by patients and caregivers, such as better toxicity profiles than current chemoimmunotherapies, and provide treatment options for patients with WM.
- Based on CADTH's assessment of the health economic evidence, Imbruvica does not represent good value to the health care system at the public list price. The committee determined that although Imbruvica is considered similarly effective as zanubrutinib, the available evidence suggests Imbruvica has a less favourable safety profile. As such, Imbruvica should result in cost savings in comparison with zanubrutinib.

Summary

- Based on public list prices, Imbruvica, used alone or in combination with rituximab, is estimated to cost the public drug plans approximately $754,000 over the next 3 years.

Additional Information

What Is Waldenström's Macroglobulinemia?

WM is a rare, slow-growing type of non-Hodgkin lymphoma that originates from malignant B cells. It leads to high levels of a circulating antibody, immunoglobulin M, which can cause symptoms such as fatigue, fever, weight loss, and vision problems. In Canada, the prevalence of this disease is approximately 4 cases per million persons per year.

Unmet Needs in Waldenström's Macroglobulinemia

Patients with WM whose disease relapses or does not respond to initial treatments are in need of more therapeutic options that are better tolerated with favourable toxicity profiles compared to current therapies. New treatments should provide better survival and survival without progression with improvement in hemoglobin levels, which are closely linked to improvements in quality of life.

How Much Does Imbruvica Cost?

Treatment with Imbruvica is expected to cost approximately $8,386 per patient per 28-day cycle.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that ibrutinib, with or without rituximab, be reimbursed for the treatment of adult patients with previously treated relapsed or refractory Waldenström's macroglobulinemia (WM), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, double-blind, randomized controlled trial (RCT) (iNNOVATE) demonstrated that treatment with ibrutinib-rituximab, when compared with placebo-rituximab, resulted in added clinical benefit in terms of progression-free survival (PFS) for patients with relapsed or refractory (r/r) WM. In patients with r/r WM, the median PFS was not reached (i.e., had not yet been determined) in the ibrutinib-rituximab arm of the study, whereas it was 14.8 months in the placebo-rituximab arm (95% CI, 5.6 to 25.8 months). The PFS rate for patients in the ibrutinib-rituximab arm ranged from 79.5% (95% CI, 63.2% to 89.2%) at 30 months to 67.5% (95% CI, 49.6% to 80.2%) at 54 months, whereas for patients treated with placebo-rituximab, the PFS rate ranged from 29.1% (95% CI, 15.5% to 44%) at 30 months to 19.9% (95% CI, 8.7% to 34.4%) at 54 months. The PFS hazard ratio (HR) was 0.22 (95% CI, 0.11 to 0.43; log rank test $P < 0.001$). In the single-arm iNNOVATE substudy, which had 31 patients who failed to achieve a response to rituximab and were treated with ibrutinib monotherapy, the median PFS was 39 months (95% CI, 25 months to not estimable [NE]) and the PFS rate ranged from 81% at 18 months (95% CI, 62% to 91%) to 40% (95% CI, 22% to 57%) at 5 years. The body of evidence on the effects of ibrutinib-rituximab on overall survival (OS) was very uncertain due to study limitations and imprecision. One RCT (ASPEN) that compared ibrutinib to zanubrutinib, demonstrated that effect estimates between the 2 drugs were similar with no evidence of meaningful differences for OS, PFS, duration of complete response (CR) or very good partial response (VGPR) as well as duration of response (DOR). More cases of atrial fibrillation were observed with ibrutinib, whereas neutropenia was reported more commonly with zanubrutinib.

pERC recognized the need for more treatment options for patients with r/r WM, notably for treatments that are better tolerated with favourable toxicity profiles compared with current chemoimmunotherapy and Bruton tyrosine kinase (BTK) inhibitor monotherapies. pERC concluded that ibrutinib met some of the needs identified by patients, including survival without progression and improvement in hemoglobin levels, which are closely linked to improvements in health-related quality of life among patients with WM.

At the sponsor-submitted price for ibrutinib and the publicly listed price for zanubrutinib, ibrutinib was more costly than zanubrutinib. Although ibrutinib is considered similarly effective in comparison with zanubrutinib, the available evidence suggests ibrutinib has a less favourable safety profile. As such, ibrutinib should result in cost savings to the CADTH-participating drug programs in comparison with zanubrutinib.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with ibrutinib, with or without rituximab, should be reimbursed in adults who have r/r WM and meet the following criteria: 1.1. received at least 1 prior line of therapy 1.2. patients should have good performance status 1.3. meet at least 1 criterion for treatment according to the IWWM consensus panel criteria.	The evidence from the iNNOVATE (comparing ibrutinib-rituximab to rituximab) and ASPEN (comparing ibrutinib to zanubrutinib) studies, showing clinical benefits in PFS and hematological values, applies directly to patients with these characteristics.	Monitoring for atrial fibrillation may be needed as deemed by the treating physician (e.g., patients with cardiovascular disease). Patients with an ECOG performance status ≤ 2 were included in the iNNOVATE and ASPEN trials. Patients with ECOG performance status greater than 2 may be treated at the discretion of their physician.
2. Patients are not eligible for reimbursement if they have either of the following: 2.1. have been previously treated and had a poor response with a BTK inhibitor 2.2. have disease transformation.	Clinical experts indicated that patients who are refractory to a BTK inhibitor should not receive ibrutinib. A biopsy-proven transformation to aggressive lymphoma would indicate that the patient does not have WM.	Patients who have been previously treated with a BTK inhibitor would be eligible for ibrutinib, if they have not shown any progression of the disease on another BTK inhibitor (i.e., as long as they are not refractory to a BTK).
Renewal		
3. Renewal of ibrutinib should be based on response to treatment using the following: 3.1. blood work, performed monthly at the beginning of treatment and then at the discretion of the treating physician 3.2. imaging studies at baseline and then at discretion of the treating physician.	These points are based on the assessments used in the iNNOVATE and ASPEN trials and aligns with assessments used to determine treatment response in clinical practice.	—
Discontinuation		
4. Ibrutinib must be discontinued upon occurrence of any of the following: 4.1. progression of disease according to the IWWM response assessment criteria 4.2. unacceptable toxicity.	The clinical experts noted that discontinuation of ibrutinib should be considered at time of disease progression or intolerable adverse events.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Ibrutinib should be prescribed by clinicians with expertise in managing patients with WM.	Clinical experts indicated that WM is a rare condition and should be managed by hematologists or oncologists with experience in treating lymphoproliferative disorders.	—
Pricing		
6. Ibrutinib should be negotiated to provide cost savings for drug programs relative to zanubrutinib for the treatment of WM.	Although ibrutinib is considered similarly effective in comparison with zanubrutinib, the available evidence suggests ibrutinib has a less favourable safety profile. As such, ibrutinib should result in cost savings in comparison with zanubrutinib for the treatment of WM.	—

BTK = Bruton tyrosine kinase; ECOG = Eastern Cooperative Oncology Group; IWWM = International Workshop on Waldenström's Macroglobulinemia; r/r = relapsed or remitting; WM = Waldenström's macroglobulinemia.

Discussion Points

- pERC recommended the reimbursement of ibrutinib based on the results shown in the iNNOVATE trial which demonstrated better PFS and hemoglobin level improvements with ibrutinib-rituximab compared with placebo-rituximab that, according to clinical experts consulted by CADTH, will reflect on the overall health-related quality of life of patients with r/r WM. pERC agreed that there is still uncertainty in other end points such as OS, DOR, and time to next treatment (TTNT).
- pERC acknowledged the uncertainty of the benefit of adding rituximab to ibrutinib from the body of evidence presented, highlighting that the uncertainty discussed is related to the use of ibrutinib-rituximab compared to placebo-rituximab.
- pERC noted, in agreement with clinical experts, that rituximab is not a widely relevant treatment for patients with r/r WM in current Canadian clinical practice, hence it was not considered an appropriate comparator to ibrutinib.
- Zanubrutinib is a more appropriate comparator to ibrutinib because it is an available treatment for patients with r/r WM in Canada. In this case, pERC addressed the ASPEN trial, a RCT directly comparing zanubrutinib to ibrutinib monotherapy that showed similar clinical benefits between the 2 drugs for PFS and OS rates. However, there was still uncertainty about any meaningful difference of effects on hematological values, duration of CR, VGPR, DOR, and TTNT between these 2 interventions.
- The available evidence to address additional comparisons available within the Canadian context was uncertain, posing challenges in deriving definite conclusions. pERC assessed different comparisons submitted by the sponsor, encompassing ibrutinib-rituximab versus ibrutinib monotherapy, ibrutinib-rituximab versus rituximab monotherapy, and ibrutinib-rituximab versus physician's choice of

treatment currently in use in Canada. Due to inherent limitations in the body of evidence for these specific comparisons, the conclusions drawn remained subject to uncertainty.

- pERC members agreed, in discussion with clinical experts, that zanubrutinib should be the preferred choice (before ibrutinib) based on the ASPEN trial results demonstrating similar efficacy and fewer cases of atrial fibrillation with zanubrutinib.
- Ibrutinib was well tolerated, with a similar number of AEs compared to rituximab-placebo, although there were a higher number of serious adverse events (SAEs) in combination with rituximab. Given the lack of direct evidence demonstrating improved outcomes with the ibrutinib-rituximab combination over current Canadian standards, pERC recognized that physicians will prefer ibrutinib monotherapy over the combination with rituximab.
- Clinical experts noted to pERC that although ibrutinib may be discontinued in the event of intolerable side effects, a dose reduction of ibrutinib could be considered as well because lower doses can maintain efficacy with a more favourable side effect profile. pERC also heard that failure of efficacy with ibrutinib in r/r WM is typically noted through new progressive cytopenias (anemia most commonly) and increases in immunoglobulin M (IgM) monoclonal protein.
- pERC noted that ibrutinib fulfills some patients' needs, especially among those who have intolerance to zanubrutinib, noting that more information is needed to know how often this will be the case.

Background

Non-Hodgkin lymphomas are a group of more than 60 types of cancers originating from cells of the lymphatic system (i.e., B cells, T cells, and natural killer cells). WM is a low-grade, slow-growing cancer, also considered a subtype of lymphoplasmacytic lymphoma that develops from malignant B cells. Typical characteristics of WM include the overproduction of monoclonal immunoglobulin (IgM) antibody due to changes in the B cells during maturation and the infiltration of lymphoplasmacytic cells bone marrow by malignant cells, leading to cytopenia. Clinical manifestations of the disease include hyperviscosity, cytopenias, lymphadenopathy, organomegaly, hemolytic anemia, peripheral neuropathy, and cryoglobulinemia.

WM comprises approximately 1% of all hematologic malignancies. The incidence in Canada is estimated at 4 cases per 1,000,000 persons. Approximately 150 new diagnoses of WM are reported yearly in Canada, with an overall prevalence estimated at 1,500 cases. The median age at diagnosis is 72 years.

Ibrutinib is an oral, first-in-class, BTK inhibitor that specifically targets PCI-45227. It was approved by Health Canada on March 31, 2016, as follows: "Imbruvica (ibrutinib) for the treatment of adult patients with Waldenström's macroglobulinemia (WM)." Later, on February 11, 2019, Ibrutinib received approval from Health Canada for the indication: "In combination with rituximab for the treatment of adult patients with WM." The requested listing criteria for ibrutinib are for a subpopulation of the Health Canada indication and the clinical trial populations. Specifically, ibrutinib for the treatment of adult patients with previously treated r/r WM.

Ibrutinib is available as oral capsules, and the dosage recommended in the product monograph is three 140 mg capsules once daily (420 mg) until disease progression or no longer tolerated. If applicable, rituximab is administered as an IV dose of 375 mg/m^2.

Sources of Information Used by the Committee

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

- a review of 1 RCT comparing ibrutinib-rituximab against placebo-rituximab, 1 RCT comparing ibrutinib to zanubrutinib, and 2 single-arm studies of ibrutinib monotherapy; the evidence from the indirect comparisons (adjusted analyses) had serious limitations that precluded the use of its effect estimates to draw conclusions
- patients' perspectives gathered by 2 patient groups, the Waldenström's Macroglobulinemia Foundation of Canada (WMFC) and Lymphoma Canada (LC)
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with WM
- input from 1 clinician group, Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups provided input for this submission: the WMFC and LC. Their activities include funding WM research and providing patient support services through education, support, advocacy, and research.

Input from the LC group was gathered from an anonymous online survey, The LC group collaborated with the WMFC to promote access to the survey for members within Canada. Of the 291 participants that contributed to the survey, 101 identified as Canadians. The majority of the respondents (43%) were between 65 and 74 years, and 57% identified as males. Most respondents reported that they had been diagnosed with WM for more than 9 years. Forty-nine respondents had experience with ibrutinib, and 12 respondents had experience with ibrutinib-rituximab (including 4 Canadians). Respondents described how WM had impacted their quality of life at diagnosis, expressing that fatigue, anemia, and night sweats were the most common symptoms, with stress and anxiety as common psychosocial impacts. Their current day-to-day quality of life was also affected. Some respondents expressed concerns about contracting infections, such as COVID-19, and treatment duration with current therapies.

The most important outcomes highlighted by respondents in surveys were the control of disease and symptoms, longer periods of remission, improvement in quality of life, longer survival, and fewer side effects.

Most respondents expressed the importance of having a choice in treatment. A majority of respondents (71%) indicated that they were willing to tolerate treatment side effects provided these were short term. Many respondents shared that treatment was initiated following diagnosis, and almost half (48%) reported going through a period of "watch and wait." In total, 34% (n = 82) of respondents reportedly received at least 1 line of therapy, 47% (n = 114) had received 2 or more lines, and 18% (n = 43) were currently not on any treatment. Most respondents (68%) expressed they were pleased with their current treatment options. Respondents expressed that the most difficult adverse events (AEs) to tolerate were fatigue, brain fog, neuropathy, and nausea. Ninety-six respondents from Canada provided input on WM treatments in the survey, of which 71% indicated they had little or no difficulty accessing their current or most recent treatment, 78% indicated they had local access to treatment, 25% indicated they needed to pay out-of-pocket for travel costs. Overall, 66% of respondents who had received at least 1 therapy expressed they were satisfied or very satisfied with the treatment and 38% of respondents expressed satisfaction with treatments for r/r WM.

Overall, 61 respondents indicated they had received ibrutinib in the r/r setting, of which 49 had received ibrutinib as monotherapy and 12 as a combination with rituximab. The majority of the respondents reported they had received a WM diagnosis within the past 3 to 5 years and had access to ibrutinib via a compassionate access program or public or government program. Of the respondents who indicated that ibrutinib had controlled symptoms, half reported fatigue, 42% reported anemia, and 32% indicated night sweats. The WMFC mentioned that zanubrutinib, another BTK inhibitor, is approved and currently funded across 4 jurisdictions in Canada. They noted that both therapies were considered equally effective for WM but have different toxicity profiles, which may be play a role in treatment selection.

Clinician Input

Two clinical specialists with expertise in the diagnosis and management of WM provided input to this submission. Both agreed that treatment goals of any therapy for patients with WM include lengthening remissions, stopping progression, improving quality of life, and reducing symptom burden while balancing least possible toxicity.

Until recently, BTK therapy in Canada for patients who are either r/r or treatment naive was only available via access programs or private insurance. Zanubrutinib has been recently approved and is funded in most provinces. Although generally well tolerated, there are patients who stop zanubrutinib due to side effects; in this situation, there is a need for an alternate BTK inhibitor for patients who fail an initial treatment for relapsed WM. Even if zanubrutinib is preferred due to its safety profile (particularly with respect to risk of atrial fibrillation and bleeding due to platelet inhibition), ibrutinib can have a role among patients who are intolerant to zanubrutinib and a place in therapy as another available option for patients with WM.

The clinical experts noted that it is unclear how much the addition of rituximab to BTK inhibitors would benefit current treatment paradigms. Experts also added that there are no specific patient criteria that would identify who would preferentially be best for ibrutinib. The clinical specialists acknowledged that there are very little data on the success of switching from zanubrutinib to ibrutinib for intolerance; hence, this may be an infrequent situation if both drugs are funded. Both experts would work under the assumption of using similar criteria as zanubrutinib in most cases.

According to clinical experts, response to treatment is assessed clinically based on blood counts and chemistry tests. Successful therapy for WM is expected to lead to improvements in cytopenias and reduction in IgM monoclonal protein. The clinical experts noted ibrutinib can be continued until evidence of disease progression or intolerable AEs, although dose reduction could be considered because lower doses can maintain efficacy with a more favourable side effect profile. Failure of efficacy is typically noted through new progressive cytopenias (anemia most commonly) and increases in IgM monoclonal protein. Clinicians felt that comparative data of BTK inhibitor monotherapy versus BTK inhibitor plus rituximab is needed to consider funding of rituximab in this combination in Canada.

Experts noted that WM is a rare condition and should generally be managed by hematologists or oncologists with experience in treating lymphoproliferative disorders. Prescribing of BTK inhibitors would generally be within the scope of hematologist and medical oncologist training in Canada. Typically, WM and BTK inhibitor therapy is delivered on an outpatient basis; however, patients with WM may require hospitalization in tertiary care centres due to complications of disease or treatment.

Input from 1 clinician group, OH-CCO Hematology Cancer Drug Advisory Committee, was summarized for this submission. The OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. Information from this group was gathered via videoconferencing.

The OH-CCO Hematology Cancer Drug Advisory Committee highlighted the following important goals for patients with WM: reducing paraprotein levels, reducing symptoms, improving blood counts, and improving quality of life. The group highlighted that zanubrutinib is available for patients with WM in the r/r setting and is accessed via employee assistance programs. Other treatments highlighted included chemotherapy (e.g., bendamustine or cyclophosphamide-vincristine-prednisone [CVP]) in combination with rituximab or bortezomib. The group expressed that current BTK inhibitors (e.g., zanubrutinib) do not address treatment gaps for patients with WM; thus, they were uncertain whether the addition of rituximab to a BTK inhibitor will be beneficial compared to a BTK inhibitor alone. The group highlighted that the addition of ibrutinib alone or ibrutinib with rituximab may be a beneficial alternative for patients with WM in the second-line setting or beyond and added that ibrutinib may be an appropriate alternative for patients who are intolerant to zanubrutinib. The group indicated that the patients least suited for this treatment will be those for whom BTK inhibitors are contraindicated and/or those with a history of severe reactions to rituximab. The group indicated that response to treatment is assessed by evaluating IgM and paraprotein levels, blood counts, and symptom burden. According to the group, factors such as significant intolerance to treatment (bleeding, atrial fibrillation), disease progression, or lack of response will be considered when deciding treatment discontinuation. The group noted that ibrutinib will be best administered in an outpatient setting.

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 body of evidence and input from the clinical experts

consulted by CADTH, which provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
Zanubrutinib received a positive pERC recommendation for patients previously treated who have r/r WM, and it is funded by most jurisdictions at the time of this input. In patients who have a long response to initial therapy, the same therapy may be reinitiated in some cases. Alternate chemoimmunotherapy (e.g., R-CHOP, R-CVP, R-fludarabine) may also be used in some patients depending on the timing of relapsed disease. A bortezomib-based regimen is also sometimes used in previously treated r/r WM, if not used first line.	This is a comment from the drug programs to inform pERC deliberations. pERC acknowledged the point during the deliberations.
Considerations for initiation of therapy	
Which patients should receive ibrutinib monotherapy vs. ibrutinib in combination with rituximab? Are there differences in the expected outcomes between ibrutinib monotherapy and ibrutinib in combination with rituximab?	The clinical experts mentioned that the data are still uncertain to assert definitive conclusions on this question. More data are required to assess if rituximab adds any efficacy value to ibrutinib monotherapy. Both experts agreed with using only ibrutinib. pERC recommended reimbursement of ibrutinib, with or without rituximab, and acknowledged the uncertainty of the benefit of adding rituximab to ibrutinib from the body of evidence presented, highlighting that the uncertainty discussed is related to the use of ibrutinib-rituximab compared to placebo-rituximab.
Should patients who have been previously treated with a BTK inhibitor be eligible for ibrutinib?	pERC agreed, only if patients have not shown any progression of the disease on another BTK inhibitor (i.e., as long as they are not refractory to a BTK). Clinical experts agreed that patients can be eligible for ibrutinib, but only if they have not shown any progression of the disease on another BTK inhibitor (i.e., as long as they are not refractory to a BTK).
The iNNOVATE clinical trial evaluating ibrutinib-rituximab vs. rituximab monotherapy excluded patients who experienced disease relapse < 12 months from the last rituximab exposure or who failed to achieve a minor response with a prior rituximab-containing regimen. Provinces typically do not fund rituximab re-treatment if disease relapse occurs less than 6 months (and some provinces may use 12 months) from completion of rituximab therapy. If both ibrutinib monotherapy and ibrutinib in combination with rituximab are recommended for previously treated r/r WM, provinces may only be able to implement ibrutinib monotherapy for patients who experience disease relapse less than 6 months (or 12 months in some provinces) from completion of rituximab therapy. Is the iNNOVATE trial data generalizable to patients who had a disease-free interval of at least 6 months from the last rituximab exposure?	pERC noted that the iNNOVATE clinical trial evaluating ibrutinib-rituximab vs. rituximab monotherapy excluded patients who received rituximab within the last 12 months before first study dose and who were refractory to last rituximab-based therapy. Clinical experts mentioned that there is uncertainty about generalizability in this case, mainly due to lack of data and the experience in Canada of treating patients within this scenario of using ibrutinib monotherapy for patients relapsing in a short period of time (whether 6 or 12 months). That is, there are no data to compare those who relapsed in less than 12 months to those who relapsed after 12 months to reach a judgment in the generalizability and applicability of results.

Drug program implementation questions	Response
Should patients with CNS lymphoma be eligible?	Yes. According to clinical experts, there are some data for crossing blood brain barrier. pERC agreed on this discussion point.
Should patients with evidence of disease transformation to a rapidly progressive, high-grade malignant lymphoma be eligible?	If there is a biopsy-confirmed transformation, the patient should not be treated with this drug. According to experts, if patients had biopsy-proven transformation to aggressive lymphoma, then that would indicate it is not WM and would not belong to the indication being discussed. pERC agreed on this point.
Consider alignment with reimbursement criteria for zanubrutinib for r/r WM.	This is a comment from the drug programs to inform pERC deliberations. pERC acknowledged the input from the drug plans.
Considerations for continuation or renewal of therapy	
None	Not applicable
Considerations for discontinuation of therapy	
Are the IWWM-7 response criteria used in Canada to determine response or loss of response to treatment?	In the clinical experts' opinion, it varies. As they perceive, it is used by some of clinicians treating patients with WM to determine progression. pERC agreed with this point. The latest IWWM criteria would be used when considering the prescription of ibrutinib.
Should this criteria be used to determine progression of disease and when to discontinue ibrutinib with or without rituximab?	Clinical experts agreed on this that these criteria can be used. Mainly about progression, rather than response. The former is more clinically meaningful, according to the experts. pERC agreed on this point.
What other criteria are used to determine disease progression or when to stop therapy?	Clinical measure in practice of progression and toxicity are usual among Canadian practitioners seeing patients with WM. pERC and clinical experts agreed on this point and allowing clinicians' judgment for determining progression of the disease.
For patients on the combination of ibrutinib and rituximab who experience disease relapse after completion of rituximab therapy, can ibrutinib be continued and rituximab reinitiated at the time of relapse?	Experts mentioned that there was likely no clinical value in this strategy of restarting rituximab if patients have started with ibrutinib-rituximab, stopped rituximab, and then progressed. pERC noted this point and agreed with the experts.
For patients on ibrutinib monotherapy who experience disease relapse, can rituximab be added to ibrutinib at the time of relapse?	Similar to the previous question, the clinical experts and pERC considered that there were no sufficient data to make a strong recommendation but the clinicians mentioned that they would not manage this situation with the addition of rituximab to ibrutinib.
In the PCYC-1118E study with ibrutinib monotherapy, treatment was continued for 40 months, with an option to continue with commercial therapy through an extension study thereafter. Should ibrutinib monotherapy end after 40 months?	The decision to stop should not be based on time but rather the disease progression and toxicity of the drug. pERC agreed that the decision will depend on the ongoing response monitoring and toxicity signs.
Consider alignment with stopping criteria for zanubrutinib for r/r WM	This is a comment from the drug programs to inform pERC deliberations. pERC acknowledged the input from the drug plans.

Drug program implementation questions	Response
Considerations for prescribing of therapy	
In the iNNOVATE clinical trial combining ibrutinib with rituximab, the rituximab was administered intravenously on day 1 of week 1, weekly for 4 consecutive weeks, followed by a second 4-weekly rituximab course after a 3-month interval (weeks 1, 2, 3, 4 and 17, 18, 19, 20). Should this schedule of rituximab be used in clinical practice when combined with ibrutinib?	pERC acknowledged the clinical experts' response that considered this a reasonable suggestion and, if reimbursed, it should be administered as it was in the study. However, they could not make this a strong recommendation due to the lack of direct comparison to without rituximab (ibrutinib monotherapy).
Can subcutaneous rituximab be substituted for IV rituximab?	Yes, clinical experts and pERC agreed.
Can ibrutinib be used with biosimilar rituximab?	Yes, clinical experts and pERC agreed.
Consider alignment with prescribing criteria for zanubrutinib for r/r WM	This is a comment from the drug programs to inform pERC deliberations. pERC acknowledged the input from the drug plans.
Generalizability	
Should patients currently receiving alternate therapy for previously treated r/r WM (including zanubrutinib) be switched to ibrutinib monotherapy or ibrutinib in combination with rituximab?	Not in combination with rituximab. The best data available are for the comparison of ibrutinib monotherapy vs. zanubrutinib, and the clinical experts would advocate more for the monotherapy with ibrutinib. pERC agreed and mentioned that switching to ibrutinib would usually occur in cases of a previously treated r/r WM with intolerance to zanubrutinib.
System and economic issues	
Zanubrutinib has successfully completed price negotiations through pCPA for previously treated r/r WM. Biosimilar IV rituximab and subcutaneous rituximab have also successfully completed price negotiations through pCPA. Generic bortezomib is also available.	This is a comment from the drug programs to inform pERC deliberations. pERC acknowledged the input from the drug plans.
The sponsor's BIA relied on an assumption that given ibrutinib is available to all patients in Canada through compassionate use, the formal listing of ibrutinib on provincial formularies would not impact the share of other publicly reimbursed regimens in the r/r WM space and that no additional demand would be generated due to the listing. However, the transition of patients from compassionate access to the public drug plans may affect that budget impact from funding ibrutinib.	This is a comment from the drug programs to inform pERC deliberations. pERC acknowledged the input from the drug plans.

BIA = budget impact analysis; BTK = Bruton tyrosine kinase; CNS = central nervous system; IWWM = International Workshop on Waldenström's Macroglobulinemia; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP = rituximab-cyclophosphamide, vincristine, and prednisone; R-fludarabine = rituximab and fludarabine; r/r = relapsed or remitting; WM = Waldenström's macroglobulinemia.

Clinical Evidence

Pivotal Studies

Description of Studies

Clinical evidence for this submission included 1 pivotal study identified in the sponsor's systematic review that included patients with r/r WM treated with ibrutinib-rituximab versus rituximab-placebo, the iNNOVATE

study (N = 150 for overall population, 82 for the r/r population). This study incorporated a substudy with single-arm data of patients previously treated with rituximab who received monotherapy with ibrutinib.

Efficacy Results

PFS is a critical outcome considered important by clinical experts, patient groups, and other stakeholders for decision-making and deliberations. It was also the primary end point in the iNNOVATE study, in which the median PFS was not reached for patients with r/r WM in the ibrutinib-rituximab arm of the study, while it reached 14.8 months in the placebo-rituximab arm (95% CI, 5.6 to 25.8 months). The PFS rate for patients in the ibrutinib-rituximab arm ranged from 79.5% (95% CI, 63.2% to 89.2%) at 30 months to 67.5% (95% CI, 49.6% to 80.2%) at 54 months; for patients treated with placebo-rituximab, the PFS rate ranged from 29.1% (95% CI, 15.5% to 44%) at 30 months to 19.9% (95% CI, 8.7% to 34.4%) at 54 months. The PFS HR for this comparison in this r/r WM population was 0.22 (95% CI, 0.11 to 0.43; log rank test P < 0.001). In the iNNOVATE substudy of 31 patients treated with ibrutinib monotherapy, the median PFS was 39 months (95% CI, 25 months to NE) and the PFS rate ranged from 81% at 18 months (95% CI, 62% to 91%) to 40% (95% CI, 22% to 57%) at 5 years.

OS was also of critical interest for clinical experts and from other stakeholders' perspective. For the r/r WM population in the iNNOVATE study, the median OS was not reported across time points for any of the arms of the study. In the single-arm substudy of those treated with ibrutinib monotherapy the OS rate reached 94% (95% CI, 77% to 98%) at 18 months and 73% (95% CI, 54% to 86%) at 5 years.

DOR was defined as the duration from the date of initial documentation of response (i.e., partial response or better) to the date of first documented evidence of progressive disease or death for responders. In the r/r WM population, 31 patients and 9 patients responded in the ibrutinib-rituximab and placebo-rituximab arms, respectively. Events of progressive disease or death occurred in 5 (16.1%) patients in the ibrutinib-rituximab group and 5 (55.6%) patients in the placebo-rituximab arm. The median DOR was not reached in the ibrutinib-rituximab arm (95% CI, 55.8 months to NE), whereas it was 23.5 months (95% CI, 9.2 months to NE) in the placebo-rituximab arm. At 30 months, 96.6% of patients (95% CI, 77.9% to 99.5%) in the ibrutinib-rituximab arm and 37.5% (95% CI, 8.7% to 67.4%) in the placebo-rituximab arm continued their response. At the 54-month landmark, the DOR rate was 82.6% for the ibrutinib-rituximab arm. No patient had a DOR greater than 48 months observed; therefore, DOR was NE in the placebo-rituximab arm.

For the r/r WM population, TTNT was reported in a Kaplan-Meier curve as subgroup analysis by prior treatment history with no specific data; at week 54, 84% of patients in the ibrutinib-rituximab arm and 21% in the placebo-rituximab arm had not received subsequent therapy. TTNT was also reported for the single-arm substudy with 31 patients, but only 10 patients (32.3%) received subsequent treatment. In this group, the median for TTNT was not reached. At the 60-month landmark estimate, 64.6% had not received subsequent treatment.

Improvements in hemoglobin levels was defined as the proportion of patients with sustained hemoglobin improvement for more than 56 days. In the r/r WM population, baseline hemoglobin levels were 10.9 g/dL in the ibrutinib-rituximab arm and 10.3 g/dL in the placebo-rituximab arm. At follow-up, 29 of 41 patients

(70.7%) had sustained hemoglobin improvement in the ibrutinib-rituximab arm, whereas 12 patients (29%) had sustained improvement in the placebo-rituximab arm. This represents an absolute difference of 41.5% (95% CI, 19.3% to 60.5%; P = 0.003).

For the r/r WM population, changes in IgM levels were reported only in the iNNOVATE substudy (31 patients with ibrutinib monotherapy). At baseline, mean IgM levels were 39.2 g/L. The maximum median decrease was 36.6 g/L (95% CI, 74.8 g/L to 4.5 less g/L) in this single-arm study.

Harms Results

All 75 patients in each arm of the iNNOVATE study presented at least 1 AE (including 30 of 31 in the ibrutinib monotherapy arm of the iNNOVATE substudy). The most common AEs of any grade in the ibrutinib-rituximab and placebo-rituximab arms were infusion-related reaction (43% and 59%), anemia (24% and 28%), and diarrhea (31% and 15%). Some AEs more commonly reported in the ibrutinib-rituximab arm compared with the placebo-rituximab arm included hypertension (25% vs. 5%), diarrhea (31% vs. 15%), nausea (23% vs. 12%), dyspepsia (17% vs. 1%), peripheral edema (23% vs. 12%), and arthralgia (27% vs. 12%).

SAEs in the iNNOVATE study were more common in the ibrutinib-rituximab arm compared with the placebo-rituximab arm (40 patients [53%] vs. 25 patients [33%]). These included pneumonia (11% vs. 3%) and atrial fibrillation (11% vs. 1%). In the ibrutinib monotherapy arm (substudy), 16 patients presented with at least 1 SAE (52%). In the iNNOVATE study, 1 patient died due to an AE in the ibrutinib-rituximab arm, and 3 patients died in the placebo-rituximab arm. Cause of patient deaths included pneumonia, Bing-Neel syndrome, and intracranial hemorrhage. No deaths were reported in the iNNOVATE substudy.

Among the significant concerns identified by the clinical experts consulted by CADTH and other stakeholders were issues such as atrial fibrillation, serious respiratory infections, major hemorrhage, and cytopenias. All these AEs were evaluated in the general population of the iNNOVATE study and substudy.

In this case, the proportion of patients with atrial fibrillation was higher in the ibrutinib-rituximab arm (14 patients [19%]) compared with the placebo-rituximab arm (2 patients [3%]) but none in the substudy of ibrutinib monotherapy arm. Similarly, serious respiratory infections occurred in 4 patients (5%) in the ibrutinib-rituximab arm, in no patients in the placebo-rituximab arm, and in 1 patient in the substudy population. Major hemorrhage occurred slightly more frequently in the ibrutinib-rituximab arm (5 patients [7%]) than in the placebo arm (3 patients [4%]). Of the cytopenias evaluated, the ibrutinib-rituximab arm had more cases of neutropenia compared with the placebo-rituximab arm (16% vs. 9%) but did not have more cases of anemia (24% vs. 28%) or thrombocytopenia (7% vs. 11%).

Critical Appraisal

Overall, the iNNOVATE trial comparing ibrutinib-rituximab to placebo-rituximab was deemed to have low risk of bias. The iNNOVATE study presents no concerns in the randomization process with a properly generated randomization list and concealment of allocation of patients to each arm of the study. No substantial baseline imbalances were detected to suggest an issue with the randomization process. The use of a placebo and blinding of patients and outcome assessors ameliorate concerns of risk of bias due to deviations from the intended interventions. An intention-to-treat analysis was performed to assess the

effects of assignment to the intervention. Although patients were allowed to cross over to receive ibrutinib after disease progression, patients were analyzed in the arm to which they were initially randomized. Data regarding primary outcomes were available for almost all randomly assigned participants, minimizing the potential for bias from incomplete outcome data. There were some discrepancies on the number of censored patients in the outcome of PFS, with more patients being censored in the ibrutinib-rituximab arm, maybe related to fewer patients available to analyze in the placebo-rituximab arm as the study advanced. Despite this difference, sensitivity analyses based on censoring at the last adequate response assessment before documented progression or death showed similar results to the base case of PFS.

In terms of external validity, according to clinical experts consulted by CADTH, the patients included in the iNNOVATE study had overall baseline characteristics and prognostic factors similar to those encountered in the Canadian clinical landscape. However, a concern from the experts was the lack of a relatable direct comparison commonly used in practice (e.g., ibrutinib monotherapy or zanubrutinib monotherapy). In terms of applicability, although the iNNOVATE trial is a well conducted study, the results would only be applicable to a relatively small proportion of patients in Canada because the direct comparison provided is only against rituximab, and currently other BTK inhibitors (zanubrutinib) are available and preferred over rituximab monotherapy. The generalizability of these findings is uncertain according to clinical experts, but unlikely to have differences in real-life practice.

GRADE Summary of Findings and Certainty of the Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessments included an evaluation of the main outcomes considered important by clinicians, patient groups, and stakeholders. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: PFS, OS, DOR, TTNT, hematological improvement, and harms. The comparison evaluated in the GRADE assessment was that of ibrutinib-rituximab against rituximab-placebo. Table 3 presents the GRADE summary of findings for this comparison.

Overall, there was moderate certainty for the outcome of PFS due to imprecision. The threshold of clinical importance for benefit or harm was set at 10 more (or fewer) patients per 1,000 on the event rate for PFS. This was obtained by iterative discussions with the clinical experts and the CADTH team. Despite observing an effect estimate beyond this threshold, the team decided to rate down 1 level due to concerns on the sample size (N = 82) in the study.

OS was very uncertain due to 1 single-arm study providing descriptive data for survival, which was rated down 3 levels for risk of bias, and 1 level due to indirectness because the population included in the study (previously treated with rituximab) was different than the population in the summary of findings table (patients with r/r WM with or without previous rituximab use). There is another row with indirect evidence obtained from the overall population (patients with r/r WM who have not been previously treated) for the PICO (population, intervention, comparison, outcome) question, hence it was rated down 1 level for indirectness and 2 levels for imprecision.

DOR was also imprecise due to the small number of observations available (i.e., only those patients who responded).

For TTNT, low certainty evidence was included from the iNNOVATE study r/r WM population (rated down 2 levels for imprecision and no thresholds to judge it, hence using only the null).

Sustained hemoglobin improvement was deemed as moderate certainty, rated down only for imprecision due to the sample size, while acknowledging input from the clinical experts that results with such a large effect size are credible, well above a threshold of 100 per 1,000 patients as the clinically important benefit — or harm if on either side. IgM were not deemed appropriate for evaluation with thresholds because no precise estimates could be obtained.

As with IgM levels, no precise estimates were obtained from AEs, SAEs, and other harms, hence the null and clinical assessment were used to judge the precision of the possible differences observed in a narrative way. Hence, except for AEs, all harms were deemed of moderate certainty.

Table 3: Summary of Findings for Ibrutinib–Rituximab for Patients With Relapsed or Remitting Waldenström's Macroglobulinemia

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo-rituximab	Ibrutinib-rituximab	Difference		
Progression-free survival							
PFS rate Follow-up: 30 months	N = 82 (1 RCT)	HR = 0.22 (0.11 to 0.43)	291 per 1,000	795 per 1,000 (95% CI, 632 to 892 per 1,000)	505 per 1,000 more (95% CI, 311 more to 699 more)	Moderate[a]	Ibrutinib-rituximab likely results in higher PFS rates compared with placebo-rituximab at 30 months.
PFS rate Follow-up: 54 months	N = 82 (1 RCT)	HR = 0.22 (0.11 to 0.43)	199 per 1,000	675 per 1,000 (95% CI, 496 to 802 per 1,000)	476 per 1,000 more (95% CI, 273 more to 679 more per 1,000)	Moderate[a]	Ibrutinib-rituximab likely results in higher PFS rates compared with placebo-rituximab at 54 months.
Overall survival							
OS rate Follow-up: 18 to 60 months	N = 31 (1 single-arm substudy)	NR	In the single-arm study (ibrutinib monotherapy), the OS rates were 94% (95% CI, 77% to 98%) and 73% (95% CI, 54% to 86%) at 18 months and 60 months, respectively.			Very low[b]	The evidence is uncertain about the effects of ibrutinib-rituximab vs. placebo-rituximab for OS.
OS rate[c] Follow-up: 54 months	N = 150 (1 RCT)	HR = 0.80 (0.32 to 1.99)	842 per 1,000	864 per 1,000 (95% CI, 737 to 933 per 1,000)	23 more per 1,000 (95% CI, −113 fewer to 158 more per 1,000)	Very low[c]	The evidence is uncertain about the effects of ibrutinib-rituximab vs. placebo-rituximab for OS in the overall population.
Duration of response							
Duration of response event rate[d] Follow-up: 30 months	N = 40 (1 RCT)	NR	PD or death occurred in 5 patients in the ibrutinib-rituximab arm and 5 in the placebo-rituximab arm. The 30-month DOR rate (continued response) was 96.6% (95% CI, 77.9% to 99.5%) in the ibrutinib-rituximab arm and 37.5% (95% CI, 8.7% to 67.4%) in the placebo-rituximab arm.			Low[e]	At 30 months, ibrutinib-rituximab may result in a large increase in DOR compared with placebo-rituximab.
Duration of response event rate Follow-up: 54 months	N = 40 (1 RCT)	NR	The 54-month DOR rate was 82.6% for the ibrutinib-rituximab arm. No patient had DOR > 48 months observed; therefore, DOR is NE in the placebo-rituximab arm.			Low[e]	At 54 months, ibrutinib-rituximab may result in a large increase in DOR compared with placebo-rituximab.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo-rituximab	Ibrutinib-rituximab	Difference		
Time to next treatment							
TTNT rate Follow-up: 54 months	N = 82 (1 RCT)	NR	Reported as subgroup: At 54 months, 84% of patients in the ibrutinib-rituximab arm and 21% in the placebo-rituximab arm had not received subsequent therapy.			Low[f]	At 54 months, ibrutinib-rituximab may result in a large increase in TTNT rate compared with placebo-rituximab.
TTNT rate: overall population Follow-up: 54 months	N = 150 (1 RCT)	HR = 0.10 (0.05 to 0.21)	294 per 1,000	874 per 1,000 (95% CI, 772 to 933 per 1,000)	580 per 1,000 more (95% CI, 438 more to 722 more per 1,000)	Moderate[g]	At 54 months, ibrutinib-rituximab likely results in a large increase in TTNT rate compared with placebo-rituximab in the overall population.
Hematological improvement							
Proportion of patients with sustained hemoglobin improvement Follow-up: 54 months	N = 82 (1 RCT)	NR	293 per 1,000	707 per 1,000 (95% CI, 507 to 906 per 1,000)	415 per 1,000 more (95% CI, 193 more to 605 more per 1,000)	Moderate[h]	Ibrutinib-rituximab likely results in a large increase in the proportion of patients with sustained hemoglobin improvement compared with placebo-rituximab.
IgM improvement Follow-up: 30 to 54 months	N = 31 (1 single-arm substudy)	NR	Changes in IgM levels were reported only in the iNNOVATE substudy (31 patients with ibrutinib monotherapy). At baseline, mean IgM levels were 39.2 g/L. The maximum median decrease was 36.6 g/L less (95% CI, 74.8 less g/L to 4.5 less).			Very low[b]	The evidence is uncertain about the effects of ibrutinib-rituximab vs. placebo-rituximab for IgM improvements.
Harms							
AEs Follow-up: 60 months	N = 150 (1 RCT)	NR	All patients in the ibrutinib-rituximab and placebo-rituximab arms presented at least 1 AE.			High[i]	Ibrutinib-rituximab does not increase or reduce the number of patients with at least 1 AE compared to placebo-rituximab.
SAEs Follow-up: 60 months	N = 150 (1 RCT)	NR	There were 40 (53%) patients in the ibrutinib-rituximab arm and 25 (33%) in the placebo-rituximab arm with SAEs.			Moderate[j]	Ibrutinib-rituximab likely results in an increase in the proportion of patients with SAEs compared with placebo-rituximab. The clinical significance of the difference is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo-rituximab	Ibrutinib-rituximab	Difference		
Atrial fibrillation Follow-up: 60 months	N = 150 (1 RCT)	NR	There were 14 (19%) patients in the ibrutinib-rituximab arm and 2 (3%) in the placebo-rituximab arm with atrial fibrillation events.			Moderate[j]	Ibrutinib-rituximab likely results in an increase in the proportion of patients with AF compared with placebo-rituximab.
Respiratory infections Follow-up: 60 months	N = 150 (1 RCT)	NR	In total, there were 4 (5%) patients in the ibrutinib-rituximab arm and none (0%) in the placebo-rituximab arm with serious respiratory infections.			Moderate[j]	Ibrutinib-rituximab likely results in little to no difference in the proportion of patients with serious respiratory infections.
Major bleeding Follow-up: 60 months	N = 150 (1 RCT)	NR	In total, there were 5 (7%) patients in the ibrutinib-rituximab arm and 3 (4%) in the placebo-rituximab arm with major bleeding (hemorrhage).			Moderate[j]	Ibrutinib-rituximab likely results in little to no difference in the proportion of patients with major bleeding.
Cytopenias Follow-up: 60 months	N = 150 (1 RCT)	NR	In the ibrutinib-rituximab vs. placebo-rituximab arms, there were the following: for neutropenia, 12 (16%) vs. 7 (9%) patients; for anemia, 18 (24%) vs. 21 (28%) patients; and for thrombocytopenia, 5 (7%) vs. 8 (11%) patients.			Moderate[j]	Ibrutinib-rituximab likely results in a small increase in neutropenia, but there is little to no difference in the proportion of patients with anemia or thrombocytopenia.

AE = adverse event; CI = confidence interval; DOR = duration of response; IgM = immunoglobulin M; NR = not reported; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; TTNT = time to next treatment; vs. versus.

[a]Rated down 1 level due to imprecision. The threshold for important benefit (or harm) was set at 10 patients per 1,000 in consultation with clinical experts and stakeholders. Although the effect estimate is beyond the threshold, the sample size did not reach the less restrictive optimal information size.

[b]Rated down by 3 levels for risk of bias because of the single-arm design with no comparator. Rated down 1 level for indirectness because the population was all previously treated with rituximab.

[c]Results from the relapsed or remitting (r/r) and treatment-naive population. Rated down for imprecision (−2 levels) and indirectness (−1). The data come from the overall population (r/r and naive treated). The target of the certainty was for no important benefit or harm, and the threshold of clinical importance was also 10 per 1,000, hence the CIs include plausible benefit and harms.

[d]DOR defined as the duration from the date of initial documentation of response to the date of first documented evidence of progressive disease or death for responders. Only 31 and 9 patients responded in the ibrutinib-rituximab and placebo-rituximab arms, respectively; hence, only these 40 patients were included in the analysis.

[e]Rated down 2 levels for imprecision. The target of the certainty aims at no important benefit or harm, but a threshold could not be obtained. Using the null and sample size, we judged there was very serious imprecision.

[f]No thresholds or effect estimates could be obtained for the r/r population. The null was used. Due to this and small sample size, the judgment on imprecision was to rate down by 2 levels.

[g]Effect estimates could be obtained and the threshold of 10 per 1,000 patients was used; given this, we did not rate down for imprecision. However, we rated down 1 level for indirectness because the population comes from the full set of patients (r/r and naive treated) and not the r/r WM population relevant to this CADTH submission.

[h]Rated down 1 level for imprecision due to the sample size being below a not restrictive optimal information size. The target of certainty was that of an important effect, and it was beyond a threshold of 100 per 1,000 patients considered by clinical experts and the CADTH team.

[i]No imprecision was deemed possible because all patients in each arm presented the event.

[j]Rated down for imprecision only. Even though there were no effect estimates obtained nor thresholds of clinical importance, it was deemed by the review team that the effects might still include important differences.

Indirect and Adjusted Comparisons

Description of Studies

To estimate the relative efficacy of the interventions for treatment of patients with WM (first line or r/r), a systematic review of the literature was conducted to identify if data were available to inform the indirect treatment comparison (ITC) section (date of the last search update: March 23, 2021). The identified evidence for treatments of WM was limited by the availability of only a few RCTs and by methodological flaws within the included studies, including small sample sizes and lack of blinding. Specific methods of ITC and adjusted comparisons depended on the type of data available, and included propensity score matching (PSM), matching adjusted indirect comparison, inverse probability of treatment weighting (IPTW) analyses, and an adjusted Cox proportional hazard model.

Despite attempts to compare ibrutinib to other interventions relevant to this submission, there were no direct feasible comparisons using these bodies of evidence. The network of evidence was not appropriate to create loops to use in a network meta-analysis. The only feasible way was using the bodies of evidence from databases and chart reviews (real-world evidence) of patients with WM using physician's choice (PC) regimens compared to ibrutinib-rituximab or rituximab using data from the iNNOVATE study and single-arm substudy or to compare ibrutinib monotherapy to ibrutinib-rituximab. Authors still were able to present assessments for these comparisons (by using matching adjusted indirect comparison, PSM, IPTW, and naive assessments), although only the ibrutinib-rituximab versus PC was a comparison applicable to this review report, albeit with important limitations to obtain credible effect estimates.

Efficacy Results

The only possible adjusted comparison was the 1 comparing PC versus ibrutinib-rituximab, in which the authors used data from the iNNOVATE study arm with patients treated with ibrutinib-rituximab and compared it to data from patients in the chart review. Despite trying to use PSM and IPTW, the small sample size and imbalances made it challenging to obtain effect estimates.

Ibrutinib-rituximab versus ibrutinib monotherapy was a relevant comparison for this CADTH submission; however, no comparison was possible other than a naive comparison of the iNNOVATE ibrutinib-rituximab arm versus the single-arm PCYC-118E study with ibrutinib monotherapy. The HR obtained was 1.25 (95% CI, 0.63 to 2.48). The comparisons of PC versus rituximab and PC versus ibrutinib-rituximab are described but the former is not relevant for the submission and the latter was not possible to analyze.

Harms Results

No harms were assessed in the ITCs or adjusted analyses submitted by the sponsor.

Critical Appraisal

All effect estimates from comparisons assessed in the ITCs or adjusted analyses remain very uncertain due to the limitations of the data. These include imbalances in patients' characteristics and the nature of the observational data, generating the possibility of confounding and risk of bias due to selection of patients, or deviations from the intended interventions. All these limitations are connected to the unfeasibility of

conducting any direct or indirect comparisons. Furthermore, the low number of patients and events produced very imprecise effect estimates in those situations in which HRs could be obtained.

The results of these ITCs or adjusted analyses also have limited applicability and generalizability in the current clinical practice in Canada because 1 of the main comparators currently used (zanubrutinib) was not included in the ITCs or adjusted analyses. Furthermore, according to clinical experts consulted by CADTH, the comparison of ibrutinib monotherapy versus zanubrutinib would provide more pertinent data to the Canadian practice because both are gaining more attention in the treatment of patients with r/r WM compared with the combination of ibrutinib-rituximab or rituximab monotherapy.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

Two studies are included in this section. The single-arm PCYC-118E study (with a long-term assessment update) evaluated ibrutinib monotherapy in 63 patients who had a clinicopathological diagnosis of WM, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and had received 1 or more prior treatments.

The ASPEN study (N = 201 for the total population) evaluated ibrutinib against zanubrutinib in patients with r/r WM (N = 164) after 1 prior line of therapy or treatment-naive WM unsuitable for standard immunochemotherapy. ASPEN was a randomized, open-label, multicentre, phase III trial that compared the efficacy and safety of ibrutinib and zanubrutinib in patients with WM who required treatment based on the consensus criteria from IWWM-7. Patients were assigned 1:1 to receive ibrutinib at an approved dose of 420 mg, once daily or to receive zanubrutinib, 160 mg, twice daily. The primary rationale was to demonstrate the superiority of zanubrutinib versus ibrutinib, measured by the proportion of patients achieving a CR or VGPR, assessed by an independent review committee. Secondary end points included major response rate (MRR) assessed by independent review committee, DOR (time from initial qualifying response until progression or death), PFS (time from randomization until progression or death), reductions in bone marrow and extramedullary tumour burden, and harms. OS and changes in quality of life were exploratory end points. The study consisted of an initial screening phase, a treatment phase, and a follow-up phase. The study was conducted across 60 centres in 12 countries.

Efficacy Results

In the PCYC-1118E study at a median follow-up of 14.8 months, the median OS was not reached at the data cut-off (February 28, 2014). In total, 95.2% of patients were alive at the study cut-off. At the landmark of 18 months, the estimated survival rate was 92.7% (95% CI, 76.6% to 97.9%). The 5-year OS rate for all patients was 87% in the long-term evaluation. The median PFS was also not reached at the median follow-up (i.e., time on study) of 14.8 months. The 18-month landmark estimate of PFS per the independent review committee evaluation was 79.5% (95% CI, 65.8% to 88.2%). The 5-year PFS rate reported for all patients was 54% (95% CI, 39% to 67%). Sustained improvement in hemoglobin was observed in 37 of 63 (58.7%) patients in the all-treated population.

In the ASPEN study, when assessing PFS, the median PFS was not reached in either treatment arm in all cohorts (i.e., r/r or overall population). In the r/r WM population, the event-free rates at 18 months were 81.7% (95% CI, 71.1% to 88.8%) versus 85.9% (95% CI, 73.7% to 92.7%) in the ibrutinib and zanubrutinib arms, respectively. In the overall population, after a median follow-up of 18 and 18.5 months, 15 (15%) patients and 16 (16%) patients in the ibrutinib and zanubrutinib arms respectively progressed or died. For OS, the median OS was not reached in either treatment arm of r/r or the overall population. There were 8 deaths reported in the ibrutinib arm (all in the r/r population) and 6 deaths in the zanubrutinib arm (3 in the r/r population). The event-free rates for patients in the ibrutinib and zanubrutinib treatment arms at 12 months were 93.9% (95% CI, 86.8% to 97.2%) and 97.0% (95% CI, 90.9% to 99.0%), respectively. At 18 months, event-free rates were 92.8% (95% CI, 85.5% to 96.5%) and 97.0% (95% CI, 90.9% to 99.0%), in the ibrutinib and zanubrutinib arms, respectively. When assessing DOR, the median duration of CR or VGPR and MRR was not reached in the overall population or in patients with r/r WM in either treatment arm who had achieved a response to study treatment. Four events occurred in patients with VGPR or CR in the ibrutinib arm, and 1 event occurred in patients with VGPR or CR in the zanubrutinib arm. Among patients who achieved a major response, 9 events occurred in the ibrutinib arm, and 6 events occurred in the zanubrutinib arm. The event-free rates at 12 months and 18 months for patients in the ibrutinib arm who achieved a major response were 87.9% (95% CI, 77.0% to 93.8%) and 87.9% (95% CI, 77.0% to 93.8%), respectively. Median TTNT was not reached. Data showed that 9 patients in the ibrutinib arm and 6 patients in the zanubrutinib arm had begun non-protocol anticancer therapy. The median time to initiation of non-protocol anticancer therapy was 6.44 months in the ibrutinib treatment arm and 6.83 months in the zanubrutinib treatment arm.

Harms Results

From the ASPEN study, the most common AEs in the ibrutinib arm (overall population) were diarrhea (31.6%), upper respiratory tract infection (28.6%), and contusion and muscle spasms (both 23.5%). In the zanubrutinib arm, the most common AEs were neutropenia (24.8%), upper respiratory tract infection (23.8%), and diarrhea (20.8%).

SAEs were reported in 40 patients (40.8%) in the ibrutinib treatment arm and in 40 patients (39.6%) in the zanubrutinib treatment arms. The most common SAE in the ibrutinib treatment arm was pneumonia (9 patients [9.2%]) followed by pyrexia and sepsis (each reported by 3 patients [3.1%]). The most common SAEs in the zanubrutinib treatment arm were febrile neutropenia, influenza, and neutropenia (each reported by 3 patients [3.0%]). In total, 7 patients (7.1%) in the ibrutinib treatment arm and 6 patients (5.9%) in the zanubrutinib treatment arm died during the study. Deaths due to AEs occurred in 2 patients treated with ibrutinib and 1 patient treated with zanubrutinib.

When assessing harms of special interest, neutropenia was reported in 12 patients (13%) in the ibrutinib arm and 25 patients (29%) in the zanubrutinib arm. Hemorrhage (including minor and major bleeding) was reported in 58 patients (59.2%) in the ibrutinib arm and 49 patients (48.5%) in the zanubrutinib arm. Cardiovascular events included atrial fibrillation or flutter and were reported in 14 patients (14.3%) in the ibrutinib arm and 2 patients (2.0%) in the zanubrutinib treatment arm.

Critical Appraisal

The open-label, nonrandomized design with no concurrent comparator is a key limitation of the PCYC-1118E study; hence, any treatment effects observed will be very uncertain for estimating causal effects and should be interpreted with caution.

The ASPEN trial was a randomized, phase III, open-label design. Randomization was stratified based on relevant prognostic factors, which included *CXCR4*(*WHIM)* mutational status and prior lines of therapy. Appropriate methods of randomization and treatment allocation were implemented, which reduced the potential for selection bias. The study was generally well balanced with respect to patient baseline demographics and disease characteristics, suggesting that randomization was successful. The open-label design may have introduced bias for subjective outcomes, such as the reporting of AEs and health-related quality of life outcomes, although these were not of concern according to clinical experts consulted by CADTH.

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. There were no methods or techniques outlined to account for missing data, and no methods were described for imputing data. The absence of appropriate methods to account for missing data may have introduced bias in the assessment of efficacy outcomes. The direction of bias is unclear. Sensitivity analyses were conducted for the primary outcome, although it was unclear whether there were major differences between the primary and the sensitivity analyses. There were no credible subgroup effects observed. Subgroup analyses were predefined, and the results presented were consistent with the primary analyses.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with r/r WM
Treatments	Ibrutinib monotherapy Ibrutinib with rituximab
Dose regimen	420 mg once daily until disease progression or until it is no longer tolerated by the patient
Submitted price	$99.84 per 420 mg capsule
Treatment cost	$8,386 per 28-day cycle

Component	Description
Comparators	Rituximab monotherapy Physician's choice (defined as a basket of chemotherapy treatments used in Canada) Zanubrutinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (30 years)
Key data source	iNNOVATE: direct head-to-head comparison of ibrutinib-rituximab vs. rituximab monotherapy ASPEN: head-to-head comparison of ibrutinib monotherapy to zanubrutinib Adjusted analysis: Inverse probability treatment weighting for rituximab vs. PC Naive comparison for ibrutinib-rituximab vs. ibrutinib monotherapy
Key limitations	• While there is direct comparative data from the iNNOVATE and ASPEN trials (i.e., between ibrutinib-rituximab to rituximab and ibrutinib monotherapy to zanubrutinib), only indirect evidence was available for other comparators. Overall, no conclusion could be drawn regarding the comparative clinical effectiveness between ibrutinib-rituximab and comparators (excluding rituximab) or ibrutinib monotherapy and comparators (excluding zanubrutinib). Furthermore, due to study differences, the application of data from the direct, indirect, and naive analyses in a single sequential analysis introduced uncertainty and pairwise analysis of comparators for which there is direct evidence may be more reflective of the available evidence. • The sponsor assumed ibrutinib-rituximab was superior to ibrutinib monotherapy; however, the sponsor's assumption is based on a naive comparison and there is no robust evidence to support an additional clinical benefit from the addition of rituximab to ibrutinib. • With the availability and reimbursement of zanubrutinib, PC and rituximab monotherapy are not relevant comparators in Canadian clinical practice based on clinical expert feedback. • In the sponsor's base case, rates of AEs for ibrutinib monotherapy were informed by the PCYC-118e study and clinical expert feedback noted that some rates such as atrial fibrillation, were lower than the rates expected to be seen in Canadian clinical practice. • CADTH also identified other limitations including: the distribution of immunotherapy regimens informing PC costs not being reflective of Canadian clinical practice; the use of RDI informed by the iNNOVATE trial for ibrutinib-rituximab and rituximab monotherapy when calculating drug costs; and, overestimated routine care frequencies for patients with r/r WM.
CADTH reanalysis results	• CADTH undertook the following changes to address some of the identified key limitations as part of its reanalysis: removed ibrutinib-rituximab, PC, and rituximab as comparators; based AE rates for ibrutinib monotherapy on the APSEN trial; and adjusted routine care frequency to be more aligned with Canadian clinical practice. • Based on the CADTH reanalysis, ibrutinib monotherapy was associated with equal QALYs but greater costs (incremental costs = $65,303) when compared with zanubrutinib. • In an exploratory analysis considering ibrutinib-rituximab therapy and assuming equal efficacy for ibrutinib-rituximab, ibrutinib monotherapy, and zanubrutinib in the absence of robust comparative clinical evidence, both ibrutinib-rituximab and ibrutinib monotherapy were dominated by zanubrutinib due to greater incremental costs. • There was insufficient comparative clinical evidence to justify a price premium for ibrutinib with or without rituximab in comparison with zanubrutinib.

ICER = incremental cost-effectiveness ratio; IR = ibrutinib with rituximab; PC = physician's choice; QALY = quality-adjusted life-year; r/r = relapsed or refractory; vs. = versus; WM = Waldenström's macroglobulinemia.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: incident patients with WM were not incorporated into the patient population and market share estimates were not reflective of Canadian clinical practice. The CADTH reanalysis updated the market share for ibrutinib monotherapy to reflect an uptake of 20%, 15%, and 10% in year 1, year 2, and year 3, respectively, along with the market shares of zanubrutinib, bendamustine-rituximab with or without rituximab maintenance, dexamethasone-rituximab-cyclophosphamide with or without rituximab maintenance, and "other" therapies. In the CADTH base case, the budget impact of reimbursing ibrutinib is expected to be $150,012 in year 1, $263,921 in year 2, and $340,806 in year 3. Therefore, the 3-year total budget impact is $754,739.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: November 8, 2023

Regrets: Two members did not attend.

Conflicts of interest: None

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