Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.
Recommendation: Reimburse with Conditions

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

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

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that ibrutinib 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 one Phase III, double-blind, randomized controlled trial (iNNOVATE) demonstrated that treatment with ibrutinib plus rituximab (IR), when compared to rituximab-placebo, resulted in added clinical benefit in terms of progression-free survival (PFS) for patients with relapsed or refractory (RR) WM. In patients with RR WM, the median PFS was not reached (i.e., has not yet been determined) in the IR arm of the study, while it reached 14.8 months in the placebo-rituximab arm (95% CI 5.6 to 25.8). The rate of PFS among patients in the IR 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, while in patients treated with rituximab-placebo, the PFS rate started at 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 sub-study, with 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 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. The body of evidence on the effects of IR on overall survival (OS) was very uncertain due to study limitations and imprecision. One RCT (ASPEN) comparing ibrutinib to zanubrutinib, demonstrated that effect estimates between the two drugs were overall similar with no evidence of meaningful differences for OS, PFS, duration of CR/VGPR or DOR. More cases of atrial fibrillation were observed with ibrutinib, while neutropenia was reported more commonly with zanubrutinib.

pERC recognized the need for more treatment options for patients with RR WM; notably for treatments that are better tolerated with favourable toxicity profiles compared to current chemoimmunotherapy and BTKi 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 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 should be reimbursed in adults who have RR Waldenström's macroglobulinemia 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 and ASPEN 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. Patients with disease transformation	Clinical experts indicated that patients who are refractory to a BTKi should not receive ibrutinib. A biopsy-proven transformation to aggressive lymphoma would indicate that the patient does not have Waldenström's macroglobulinemia.	—
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 utilized 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.	—
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	—

Reimbursement condition	Reason	Implementation guidance
	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 Waldenström's macroglobulinemia.	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 Waldenström's macroglobulinemia.	—

Discussion Points

- pERC recommended the reimbursement of ibrutinib based on the results shown in the iNNOVATE trial which demonstrates better PFS and Hgb improvements of IR when compared to rituximab plus placebo that, according to clinical experts consulted by CADTH, will reflect on the overall health-related quality of life of patients with RR WM. pERC agreed that there is still uncertainty in other endpoints such as OS, DOR, and 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 IR as compared to rituximab-placebo.
- pERC noted, in agreement with clinical experts, that rituximab is not a widely relevant treatment for patients with RR WM in the current Canadian clinical practice, hence was not considered an appropriate comparator to ibrutinib.
- Zanubrutinib is a more appropriate comparator to ibrutinib as it is an available treatment for RR WM patients 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 two drugs for PFS and OS rates, while there was still uncertainty in any meaningful difference of effects on hematological values, duration of CR/VGPR, DOR, and TTNT between these two 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 IR vs ibrutinib monotherapy, IR vs rituximab monotherapy, and IR vs physician choice of treatments 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 (above ibrutinib) based on the ASPEN trial results demonstrating similar efficacy and fewer cases of atrial fibrillation with zanubrutinib.
- Ibrutinib was well tolerated with similar number of AEs when compared to rituximab-placebo, although with higher number of SAEs in combination with rituximab. Given the lack of direct evidence demonstrating improved outcomes with the combination of IR 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, as lower doses can maintain efficacy with a more favourable side effect profile. pERC also heard that failure of efficacy with ibrutinib in RR WM is typically noted through new progressive cytopenias (anemia most commonly) and increases in IgM monoclonal protein.
- pERC noted that ibrutinib fulfills some of the 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 (NHL) are a group of over 60 types of cancers originating from cells of the lymphatic system (i.e., B cells, T cells, and natural killer cells). Waldenström macroglobulinemia (WM) is a low grade slow growing cancer, also considered a subtype of lymphoplasmacytic lymphoma (LPL) developing from malignant B cells. Typical characteristics of WM include the overproduction of monoclonal immunoglobulin (IgM) antibody due to changes in the malignant to 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 about 1% of all hematologic malignancies. The incidence in Canada is estimated at 4 cases per 1,000,000 persons. About 150 new WM cases are reportedly diagnosed 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 has been approved by Health Canada (HC) on March 31, 2016, as follows: “Imbruvica (ibrutinib) for the treatment of adult patients with Waldenström macroglobulinemia (WM)”. Later, on February 11, 2019, Ibrutinib received HC approval for the indication: “in combination with rituximab for the treatment of adult patients with WM”. The requested listing criteria for ibrutinib are for a sub population of the Health Canada indication and the clinical trial populations. Specifically: Ibrutinib for the treatment of adult patients with previously treated, RR 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 one RCT comparing IR against rituximab-placebo, one RCT comparing ibrutinib to zanubrutinib, and two 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 Waldenström’s macroglobulinemia
- input from one 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 Waldenström’s Macroglobulinemia Foundation of Canada (WMFC) and Lymphoma Canada (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 WM Foundation of Canada 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 old and 57% identified as males. Most respondents reported that they had been diagnosed with WM for over 9 years. Forty-nine respondents had experience with ibrutinib, and 12 respondents had experience with ibrutinib plus rituximab (included 4 Canadians). Respondents describe 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 to treatment. A majority respondents (71%) of 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 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 that had received at least 1 therapy expressed they were satisfied or very satisfied with the treatment and 38% of respondents expressed satisfaction with treatments in relapsed/refractory.

Overall, 61 respondents indicated they had received ibrutinib in the relapsed/refractory 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 last 3 to 5 years and had accessed to ibrutinib via a compassionate access program or public/government program. Half of the respondents indicated that ibrutinib had controlled symptoms such as fatigue, 42% reported anemia, and 32% indicated night sweats. The WM Foundation of Canada 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 durable remissions, stopping progression, improving quality of life, and reduce symptoms burden while balancing with the less possible toxicity.

Until recently, BTK therapy in Canada for either relapsed/refractory or treatment-naïve patients was only available via access programs or private insurance. Zanubrutinib has been recently approved and funded in most provinces. While generally well-tolerated, there are patients who stop zanubrutinib due to side effects, and 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 (in particular 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 treatments 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 is 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 to 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 adverse events, —although dose-reduction could be considered, as 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 BTKi monotherapy vs BTKi + 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, although BTKi prescribing would generally be considered within the scope of Hematologist and Medical Oncologist training in Canada. Generally, WM and BTKi therapy is delivered as an outpatient. WM patients may, however, require hospitalization in tertiary care centres due to complication of disease or treatment.

Input from one clinician group, Ontario Health Cancer Care Ontario (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 WM patients: reducing paraprotein levels, reducing symptoms, improving blood counts, and improving quality of life. The group highlighted that zanubrutinib is available for WM patients in the relapse/refractory setting and is accessed via employee assistance programs (EAP). 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 WM patients; 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 WM patients in the second line setting or beyond and added that ibrutinib may be an appropriate alternative for patients that are intolerant to zanubrutinib. The group indicated that patients least suited for this treatment will be those for which BTK inhibitors are contraindicated and/or those with a history of severe reactions to rituximab. The group indicated that response to treatment will be assessed by evaluating IgM and paraprotein levels, blood counts, and symptom burden. Factors such as significant intolerance to treatment (bleeding, atrial fibrillation), disease progression, or lack of response will be considered when deciding treatment discontinuation according to the group. 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	Clinical expert response
Relevant comparators	
Zanubrutinib received a positive pERC recommendation for patients previously treated, relapsed or refractory (RR) WM and 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 re-initiated 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, RR WM if not used first-line.	This is a comment from the drug programs to inform pERC 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 is still uncertain to assert definitive conclusions on this question. More data is required to assess if rituximab adds any efficacy value to the ibrutinib monotherapy. Both experts agreed with using only ibrutinib.
Should patients who have been previously treated with a BTK inhibitor be eligible for ibrutinib?	Clinical experts agreed that patients can be eligible to ibrutinib, but only if they have not shown any progression of the disease

Drug program implementation questions	Clinical expert response
	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 included 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 don't 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 RR 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 disease-free interval of at least 6 months from the last rituximab exposure?*	There is uncertainty about generalizability in this case, according to the experts, 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), i.e., 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.
Should patients with CNS lymphoma be eligible?	Yes. There is some data for crossing blood brain barrier.
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 agent. According to experts, if patients had biopsy-proven transformation to aggressive lymphoma, then that would indicate it is not Waldenström's and would not belong to the indication being discussed.
Consider alignment with reimbursement criteria for zanubrutinib for RR WM.	This is a comment from the drug programs to inform pERC deliberations
Considerations for continuation or renewal of therapy	
None	Not applicable
Considerations for discontinuation of therapy	
Are the IWWM-7 (International Workshop on Waldenström macroglobulinemia) 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.
Should this criteria be used to determine progression of disease and when to discontinue ibrutinib +/- rituximab?	Mainly about progression, rather than response. The former is more clinically meaningful, according to the experts.
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.
For patients on the combination of ibrutinib and rituximab who experience disease relapse after completion of rituximab therapy, can ibrutinib be continued, and rituximab re-initiated at the time of relapse?	Experts mentioned that there was likely no clinical value in this strategy of re-starting rituximab if patients have started with rituximab-ibrutinib, stopped rituximab, and then progressed. .
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 considered that there was no sufficient data to make a strong recommendation but overall, 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.

Drug program implementation questions	Clinical expert response
Consider alignment with stopping criteria for zanubrutinib for RR WM	This is a comment from the drug programs to inform pERC deliberations
Considerations for prescribing of therapy	
In the iNNOVATE clinical trial combining ibrutinib with rituximab, the rituximab was administered IV on Day 1 of Week 1 weekly for four consecutive weeks, followed by a second four-weekly rituximab course after a three-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?*	Clinical experts considered this as a reasonable suggestion and, if reimbursed, it should be administered as it was in the study, but they cannot make this a strong recommendation due to the lack of direct comparison to no-rituximab (ibrutinib monotherapy).
Can subcutaneous rituximab be substituted for IV rituximab?	Yes.
Can ibrutinib be used with biosimilar rituximab?	Yes.
Consider alignment with prescribing criteria for zanubrutinib for RR WM	This is a comment from the drug programs to inform pERC deliberations
Generalizability	
Should patients currently receiving alternate therapy for previously treated RR WM (including zanubrutinib) be switched to ibrutinib monotherapy or ibrutinib in combination with rituximab?	Not in combination with rituximab. The best data available is for the comparison of ibrutinib monotherapy versus zanubrutinib, and the clinical experts would advocate more for the monotherapy with ibrutinib.
System and economic issues	
Zanubrutinib has successfully completed price negotiations through pCPA for previously treated RR WM. Biosimilar intravenous 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
The sponsor's BIA relied on an assumption that given ibrutinib is available to all Canadian patients through compassionate use, the formal listing of ibrutinib on provincial formularies would not impact the share of other publicly reimbursed regimens in the RR 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

Clinical Evidence

Pivotal studies

Description of Studies

Clinical evidence for this submission included one pivotal study identified in the sponsor's systematic review that included patients with RR WM treated with IR vs rituximab-placebo, the iNNOVATE study (N=150 for overall population, 82 for the RR population). This study incorporated a sub study with single-arm data of patients previously treated with rituximab that 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 endpoint in the iNNOVATE study, in which patients with RR WM the median PFS was not

reached in the IR arm of the study, while it reached 14.8 months in the placebo-rituximab arm (95% CI 5.6 to 25.8). The rate of PFS among patients in the IR 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, while in patients treated with placebo rituximab, the PFS rate started at 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 (95% CI) for this comparison in this RR WM population was 0.22 (95%CI 0.11 to 0.43; log rank test p <0.001). In the iNNOVATE sub study of 31 patients treated with ibrutinib monotherapy, the median PFS was 39 months (95% CI 25 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 RR population in the iNNOVATE study, the median OS was not reported across timepoints for any of the arms of the study. In the single arm sub study of those treated with ibrutinib monotherapy the OS rate reached 94% (95% CI 77 to 98) at 18 months and 73% (54 to 86) at 5 years.

DOR was defined as the duration from the date of initial documentation of response (i.e., partial response [PR] or better) to the date of first documented evidence of progressive disease or death for responders. In the RR WM population, 31 patients and 9 patients responded in the IR and placebo rituximab arms respectively. Events of PD or death occurred in 5 (16.1%) patients in the IR group and 5 (55.6%) in the placebo rituximab arm. The median DOR was not reached in the IR arm (95% CI: 55.8 months to NE) while it was 23.5 months (95% CI: 9.2 to NE) in the placebo rituximab arm. At 30 months, 96.6% of patients (95% CI: 77.9 to 99.5) in the IR 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 IR arm and no subject had DOR > 48 months observed, therefore DOR is NE, in the placebo-rituximab arm.

For the RR 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 IR arm and 21% in the placebo rituximab arm had not received subsequent therapy. The TTNT was reported also for the single arm sub study with 31 patients, but only 10 patients (32.3%) received subsequent treatment. In this group, the median for the 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 RR WM population baseline Hgb levels were 10.9 g/dL in the IR arm and 10.3 g/dL in the placebo rituximab arm. At follow up, 29 of 41 patients (70.7%) had sustained Hgb improvement in the IR arm, while in the placebo rituximab arm, 12 patients (29%) had sustained improvement. This represents an absolute difference of 41.5% (95% CI 19.3 to 60.5; p=0.003).

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

Harms Results

All 75 patients in each arm of the iNNOVATE study presented at least one adverse event (and 30 of the 31 in the ibrutinib monotherapy arm from the iNNOVATE sub study). The most common AEs of any grade in the IR and placebo-rituximab group were infusion-related reaction (43% and 59% respectively), anemia (24% and 28%) and diarrhea (31% and 15%). Some AEs more commonly reported in the IR arm when compared to placebo-rituximab 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%).

Serious AEs (SAEs) in the iNNOVATE study were more common in the IR arm as compared to 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 (sub study), 16 patients presented at least one SAE (52%). In the iNNOVATE study, 1 patient died due to an AE in the IR arm and three 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 sub study.

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

In this case, the proportion of patients with atrial fibrillation was larger in the IR arm (14 patients [19%]) when compared to the placebo-rituximab arm (2 patients [3%]) but none in the sub study of ibrutinib monotherapy arm. Similarly, serious respiratory

infections occurred in 4 patients (5%) in the IR arm, none in the placebo-rituximab arm, and 1 in the sub study population. Major hemorrhage occurred slightly more frequently in the IR arm (5 patients [7%]) than in the placebo arm (3 patients [4%]). Of the cytopenias evaluated, the IR arm presented more cases of neutropenia when compared to the placebo-rituximab arm (16% vs 9%), but not more cases of anemia (24% vs 28%) or thrombocytopenia (7% vs 11%).

Critical Appraisal

Overall, the iNNOVATE trial comparing IR to placebo-rituximab was deemed with low risk of bias. The iNNOVATE study presents no concerns in the randomization process with a properly generated randomization list and concealment 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 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 IR 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 prior to 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, one concern from the experts was the lack of a relatable direct comparison commonly used in practice (like ibrutinib monotherapy or zanubrutinib monotherapy). In terms of applicability, although the iNNOVATE trial is a well conducted study, their results would only be applicable to a relatively small proportion of patients in Canada, since 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 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 IR 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 1000 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 one level due to concerns on the sample size (N=82) in the study.

OS was very uncertain due to one 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 to the population in the summary of findings table (RR patients with or without previous rituximab use). There is another row with indirect evidence obtained from the overall population (RR and naïve treated patients) for the PICO question, hence was rated down one level for indirectness and 2 levels for imprecision.

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

In TTNT, low certainty evidence was included from the iNNOVATE study RR 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, but acknowledging from input from the clinical experts, that the results with such a large effect size are credible, well above a threshold of 100 per 1000 patients as the clinically important benefit – or harm if on either side. IgM were not deemed appropriate for evaluation with thresholds since 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 was 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 RR Waldenström's Macroglobulinemia

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			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 1000	795 per 1000 (632 to 892)	505 per 1000 more (from 311 more to 699 more)	Moderate [a]	IR likely results in large PFS rates when compared to rituximab placebo at 30 months
PFS rate Follow-up: 54 months	N=82 (1 RCT)	HR = 0.22 (0.11 to 0.43)	199 per 1000	675 per 1000 (496 to 802)	476 per 1000 more (from 273 more to 679 more)	Moderate [a]	IR likely results in large PFS rates when compared to rituximab placebo at 54 months
Overall Survival							
OS rate Follow-up: 18 to 60 months	N=31 (1 single arm sub study)	N.R.	In a single arm study (ibrutinib monotherapy), the OS rates were 94% (77 to 98) and 73% (54 to 86) at 18 months and 60 months respectively			Very low [b]	The evidence is uncertain about the effects of IR vs rituximab placebo for OS
OS rate [c] Follow-up: 54 months	N=150 (1 RCT)	HR= 0.80 (0.32 to 1.99)	842 per 1000	864 per 1000 (737 to 933)	23 more per 1000 (from 113 fewer to 158 more)	Very low [c]	The evidence is uncertain about the effects of IR vs rituximab placebo for OS in the overall population.
Duration of Response							
Duration of response event rate [d] Follow-up: 30 months	N=40 (1 RCT)	N.R.	PD or death occurred in 5 patients in the IR group and 5 in the placebo rituximab arm. The 30-month DOR rate (continued response) was 96.6% (77.9 to 99.5) in the IR arm and 37.5% (8.7 to 67.4) in the placebo-rituximab arm.			Low [e]	At 30 months, IR may result in a large increase in the DOR when compared to rituximab placebo.
Duration of response event rate* Follow-up: 54 months	N=40 (1 RCT)	N.R.	The 54-month DOR rate was 82.6% for the IR arm and no subject had DOR >48 months observed; therefore DOR is NE, in the placebo-rituximab arm.			Low [e]	At 54 months, IR may result in a large increase in the DOR when compared to rituximab placebo.
Time to Next Treatment							
TTNT rate Follow-up: 54 months	N=82 (1 RCT)	N.R.	Reported as subgroup; at 54 months, 84% of patients in the IR arm and 21% in the placebo rituximab arm had not received subsequent therapy.			Low [f]	At 54 months, IR may result in a large increase in the TTNT rates when compared to rituximab placebo.
TTNT rate – overall population Follow-up: 54 months	N=150 (1 RCT)	HR = 0.10 (0.05 to 0.21)	294 per 1000	874 per 1000 (772 to 933)	580 per 1000 more (from 438 more to 722 more)	Moderate [g]	At 54 months, IR likely results in a large increase in TTNT rates when compared to rituximab placebo in the overall population.
Hematological improvement							
Proportion of patients with sustained Hgb improvement Follow-up: 54 months	N=82 (1 RCT)	N.R.	293 per 1000	707 per 1000 (507 to 906)	415 per 1000 more (from 193 more to 605 more)	Moderate [h]	IR likely results in a large increase in the proportion of patients with sustained hemoglobin improvement when compared to rituximab-placebo
IgM improvement Follow-up: 30 to 54 months	N=31 (1 single arm sub study)	N.R.	Changes in IgM levels were reported only in the iNNOVATE sub study (31 patients with ibrutinib monotherapy). At baseline, IgM levels were 39.2 g/L. The maximum median decrease was 36.6 g/L less (95% CI 74.8 less to 4.5 less).			Very low [b]	The evidence is uncertain about the effects of IR vs rituximab placebo for IgM improvements
Harms							

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo-Rituximab	Ibrutinib-Rituximab	Difference		
Adverse events Follow-up: 60 months	N=150 (1 RCT)	N.R.	All patients in the IR and in the placebo-rituximab arm presented at least one AE.			High [i]	IR does not increase or reduce the number of patients with at least one AE when compared to rituximab-placebo.
Serious adverse events Follow-up: 60 months	N=150 (1 RCT)	N.R.	There were in total 40 (53%) patients in the IR and 25 (33%) in the placebo-rituximab arm with SAEs.			Moderate [j]	IR likely results in an increase in the proportion of patients with SAEs when compared to rituximab-placebo. The clinical significance of the difference is uncertain.
Atrial fibrillation Follow-up: 60 months	N=150 (1 RCT)	N.R.	There were in total 14 (19%) patients in the IR arm and 2 (3%) in the placebo-rituximab arm with atrial fibrillation events.			Moderate [j]	IR likely results in an increase in the proportion of patients with AF when compared to rituximab-placebo.
Respiratory infections Follow-up: 60 months	N=150 (1 RCT)	N.R.	In total, there were 4 (5%) patients in the IR arm and none (0%) in the placebo rituximab arm with serious respiratory infections.			Moderate [j]	IR 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)	N.R.	In total, there were 5 (7%) patients in the IR arm and 3 (4%) in the placebo rituximab arm with major bleeding (hemorrhage).			Moderate [j]	IR likely results in little to no difference in the proportion of patients with major bleeding.
Cytopenias Follow-up: 60 months	N=150 (1 RCT)	N.R.	In the IR vs placebo-rituximab arms, there were in total for Neutropenia 12 (16%) vs 7 (9%) patients; Anemia 18 (24%) vs 21 (28%); and Thrombocytopenia 5 (7%) vs 8 (11%).			Moderate [j]	IR likely results in a small increase in neutropenia, but little to no difference in the proportion of patients with anemia or thrombocytopenia.

Abbreviations: AE = adverse event; CI = confidence interval; DOR = duration of response; IgM = immunoglobulin M; IR = ibrutinib rituximab; N.R.= not reported; OS = overall survival; PD = progressive disease; PFS = progression free survival; RCT = randomized controlled trial; SAE = serious adverse events; TTNT = time to next treatment.

Explanations

a Rated down one level due to imprecision. The threshold for important benefit (or harm) was set at 10 patients per 1000 in consultation with clinical experts and stakeholders. Even though 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 one level for indirectness because the population is all previously treated with rituximab.

c Results from the RR and treatment-naïve population. Rated down for imprecision (-2 levels) and indirectness (-1). The data comes from the overall population (RR and naïve treated). The target of the certainty was for no important benefit or harm, and the threshold of clinical importance was also 10 per 1000, 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 IR and placebo rituximab arms respectively, hence only these 40 patients were included in the analysis.

e Rated down for imprecision two levels. 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 RR population. The null was used. Due to this and small sample size, the judgment on imprecision was to rate down by two levels.

g Effect estimates could be obtained and the threshold of 10 per 1000 patients was used, given this, we did not rate down for imprecision. However, we rated down one level for indirectness because the population comes from the full set of patients (RR and naïve treated) and not the RR WM population relevant to this CADTH submission.

h Rated down one level for imprecision due to the sample size 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 1000 patients considered by clinical experts and the CADTH team.

i No imprecision was deemed possible since all patients on 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 (1L or RR), a systematic review of the literature was conducted to identify if data were available to inform the ITCs section (date of the last search update 23 March 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 (MAIC), inverse probability of treatment weighting (IPTW) analyses, and adjusted Cox proportional hazard (PH) 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 (RWE) of patients with WM using PC regimens to be compared to IR or rituximab using data from the iNNOVATE study and single-arm sub-study, as well as to compare ibrutinib monotherapy to IR. Authors still were able to present assessments for these comparisons (by using MAIC, PSM, IPTW, and naïve assessments), although only the IR vs 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 one comparing PC vs IR, where authors used the iNNOVATE study arm with IR patients and compared to patients from the chart review. Despite trying to use PSM and IPTW, the small sample size and imbalances made it challenging to obtain effect estimates.

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

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 of 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 where 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 since one 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 vs zanubrutinib would provide more pertinent data to the Canadian practice since both are gaining more attention in the treatment of RR patients as compared to the combination of IR 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) evaluating ibrutinib monotherapy in 63 patients who had a clinicopathological diagnosis of WM, ECOG PS 0 to 2, and had received one or more prior treatments.

Second, the ASPEN study (N=201 for the total population), evaluating ibrutinib against zanubrutinib in patients were RR WM (N=164) after 1 prior line of therapy or treatment-naïve WM unsuitable for standard immunochemotherapy. ASPEN was a randomized, open-label, multi-centre, phase III trial comparing the efficacy and safety of ibrutinib and zanubrutinib in patients with WM who required treatment based on the 7th International Workshop on Waldenström Macroglobulinemia consensus criteria. Patients were assigned 1:1 to receive ibrutinib at an approved dose of 420 mg, once daily, or 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 (IRC). Secondary end points included IRC-assessed MRR, duration of response (DOR; time from initial qualifying response until progression or death), and PFS (time from randomization until progression or death), reductions in bone marrow and extramedullary tumor burden, and harms. Overall survival (OS) and changes in QoL 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 (Germany, Greece, Italy, Netherlands, Poland, Spain, Sweden, UK, and US).

Efficacy Results

In the PCYC-1118E, 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 cutoff. At the landmark of 18 months, the estimated survival rate was 92.7% (CI: 76.6% to 97.9%). The 5-year overall survival (OS) rate for all patients was 87% as shown 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 IRRC 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 patients (58.7%) in the All-Treated Population.

In the ASPEN study, when assessing progression-free survival, the median PFS was not reached in either treatment arm in all cohorts (i.e., RR or overall population). In the RR 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 patients (16%) in the ibrutinib and zanubrutinib arms respectively progressed or died. For Overall Survival, the median OS was not reached in either treatment arm of RR or overall population patients. There were 8 deaths reported in the ibrutinib arm (all in the RR population), and 6 deaths in the zanubrutinib arm (3 in the RR population). The event-free rates for patients in the ibrutinib versus zanubrutinib treatment arms were 93.9% (95% CI, 86.8 to 97.2) versus 97.0% (95% CI, 90.9% to 99.0%) at 12 months, and 92.8% (95% CI, 85.5% to 96.5%) versus 97.0% (95% CI, 90.9% to 99.0%) at 18 months. When assessing duration of response, the median duration of CR or VGPR and MRR had not been reached in the overall or for R/R patients in either treatment arm in patients 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 Time to Next Treatment 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 were 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 (23.5% each). In the zanubrutinib arm, the most common AEs were neutropenia (24.8%), upper respiratory tract infection (23.8%), and diarrhea (20.8%).

Serious adverse events 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 in the study. Deaths due to AEs occurred in 2 ibrutinib-treated patients and 1 zanubrutinib-treated patient.

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, non-randomized 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 CXCR4WHIM 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 adverse events 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 relapsed/refractory 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
Comparators	Rituximab monotherapy Physician's choice (PC, defined as a basket of chemotherapy treatments used in Canada) Zanubrutinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data source	iNNOVATE: direct head-to-head comparison of ibrutinib with rituximab (IR) versus rituximab monotherapy ASPEN: head-to-head comparison of ibrutinib monotherapy to zanubrutinib Adjusted analysis: Inverse probability treatment weighting for rituximab versus PC Naïve comparison for IR versus ibrutinib monotherapy
Key limitations	• While there is direct comparative data from the iNNOVATE and ASPEN trials (i.e., between IR 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 IR and comparators (excluding rituximab) or ibrutinib monotherapy and

Component	Description
	comparators (excluding zanubrutinib). Furthermore, due to study differences, the application of data from the direct, indirect, and naïve 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 IR was superior to ibrutinib monotherapy, however, the sponsor's assumption is based on a naïve 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 adverse events (AE) 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 IR and rituximab monotherapy when calculating drug costs; and, overestimated routine care frequencies for relapsed/refractory WM patients.
CADTH reanalysis results	• CADTH undertook the following changes to address some of the identified key limitations as part of its reanalysis: removed IR, 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 IR therapy and assuming equal efficacy for IR, ibrutinib monotherapy, and zanubrutinib in the absence of robust comparative clinical evidence, both IR 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; LY = life-year; PC = physician's choice; QALY= quality-adjusted life-year; vs. = versus; WM = Waldenström's macroglobulinemia.

Budget Impact

CADTH identified the following key limitations with the sponsor's BIA: incident WM patients 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, BR ± rituximab maintenance, CDR ± 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 three-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