

Reimbursement Recommendation

Acalabrutinib (Calquence)

Indication: Acalabrutinib in combination with bendamustine and rituximab for the treatment of adult patients with previously untreated mantle cell lymphoma who are ineligible for autologous stem cell transplant

Sponsor: AstraZeneca Canada Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Calquence?

Canada's Drug Agency (CDA-AMC) recommends that Calquence should be reimbursed by public drug plans for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous stem cell transplant (ASCT) in combination with bendamustine and rituximab (BR), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Calquence plus BR should only be covered to treat patients aged 65 years or older with previously untreated MCL, with a good performance status. Calquence plus BR should not be covered in patients who have a history of central nervous system lymphoma or leptomeningeal disease, or if the goal of therapy is tumour debulking before stem cell transplant.

What Are the Conditions for Reimbursement?

Calquence plus BR should only be reimbursed if prescribed by clinicians with expertise in managing MCL and monitoring therapy, and if the cost of Calquence is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial (ECHO) in patients with previously untreated MCL who are not eligible for ASCT demonstrated that treatment with Calquence plus BR likely delays disease progression compared with placebo plus BR. However, there was not enough certainty that the treatment could prolong survival.
- Based on the CDA-AMC assessment of the health economic evidence, Calquence does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Calquence plus BR met some important patient needs by delaying progression, prolonging life with no significant detriment to health-related quality of life (HRQoL), although it is associated with a higher risk of toxicities such as infection, atrial fibrillation and/or flutter, and hemorrhage.
- Based on public list prices, Calquence is estimated to cost the public drug plans approximately \$25.6 million over the next 3 years.

Summary

Additional Information

What Is MCL?

MCL is a rare and aggressive type of non-Hodgkin lymphoma (NHL) that starts in B cells in the lymph nodes and is linked to poorer survival compared to other NHL types. The overall 10-year prevalence of NHL in Canada is 141.0 cases per 100,000 people, with MCL making up about 7.1 to 9.9 cases per 100,000 people.

Unmet Needs in MCL

Many patients with MCL who are not eligible for stem cell transplant need treatments that can delay the spread of cancer without adding serious side effects, especially given their older age and risk of complications.

How Much Does Calquence Cost?

Treatment with Calquence is expected to cost approximately \$7,995 per patient per 28-day cycle. Treatment with Calquence plus BR is expected to cost \$13,574 per patient per 28-day cycle, and Calquence plus maintenance rituximab is expected to cost \$9,035 per patient per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that acalabrutinib in combination with BR be reimbursed for the treatment of adult patients with previously untreated MCL who are ineligible for ASCT only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

Evidence from 1 ongoing, phase III, randomized controlled trial (RCT) (ECHO, N = 598) demonstrated that treatment with acalabrutinib in combination with BR likely results in an added clinical benefit for adult patients with previously untreated MCL who are ineligible for ASCT, when compared with placebo plus BR. At a planned interim analysis with data cut-off date of February 15, 2024, the median progression-free survival (PFS) per independent review committee (IRC) assessment was 66.4 months (95% confidence interval [CI], 55.1 months to not estimable) in the acalabrutinib plus BR group and 49.6 months (95% CI, 36.0 to 64.1 months) in the placebo plus BR group (hazard ratio [HR] = 0.73, 95% CI, 0.57 to 0.94). The difference in the probability of being progression-free at 48 months between the acalabrutinib plus BR group and the placebo plus BR group was █████ (95% CI, █████ to █████). The median overall survival (OS) was not estimable at the time of the interim analysis for both treatment groups, and there was no difference in the risk of death between acalabrutinib plus BR and placebo plus BR (HR = 0.86; 95% CI, 0.65 to 1.13). The addition of acalabrutinib to BR resulted in more adverse events (AEs) but likely did not elevate the risk of infections, infestations, ventricular arrhythmia, or atrial fibrillation and/or flutter in a meaningful way.

Patients identified a need for new effective treatment options that can provide longer disease remission, prolong life, control disease symptoms, improve quality of life, and have fewer side effects. pERC concluded that acalabrutinib in combination with BR met some very important unmet needs identified by patients in that it offers an additional oral treatment option that delays disease progression with no significant detriment to HRQoL, compared to placebo plus BR. pERC noted that the OS data do not provide enough certainty on the treatment effect of acalabrutinib plus BR on prolonging survival. The committee agreed that no unexpected toxicities for acalabrutinib plus BR were identified and noted that, given the potential for improved efficacy (PFS), some patients may opt for acalabrutinib plus BR despite the higher risk of toxicities associated with the treatment.

Using the sponsor-submitted price for acalabrutinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for acalabrutinib plus BR was \$533,458 per quality-adjusted life-year (QALY) gained compared with BR alone. At this ICER, acalabrutinib plus BR is not cost-effective at a \$50,000 per QALY gained willingness-to-pay (WTP) threshold for the submitted indication. A price reduction is required for acalabrutinib to be considered cost-effective at a \$50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with acalabrutinib plus BR should be initiated in patients who meet all the following criteria: 1.1. with pathologically confirmed MCL 1.2. aged 65 years or older 1.3. ineligible for ASCT 1.4. have not received previous systemic anticancer therapies for MCL 1.5. have good performance status.	Evidence from the ECHO trial suggested that treatment with acalabrutinib plus BR resulted in a clinical benefit in patients with these characteristics. Patients with an ECOG PS score of 0 to 2 were included in the ECHO trial.	pERC agreed with the clinical experts that patients younger than 65 years who are ineligible for transplant may be considered for acalabrutinib plus BR treatment at the discretion of the treating physician, although this scenario is relatively uncommon.
2. Treatment with acalabrutinib plus BR should not be initiated in the following situations: 2.1. patient has a history of CNS lymphoma or leptomeningeal disease 2.2. goal of therapy is tumour debulking before stem cell transplant.	There is no evidence to support the benefit of acalabrutinib plus BR in patients with these characteristics because they were excluded from the ECHO trial.	—
Discontinuation		
3. Treatment should be discontinued upon occurrence of any of the following: 3.1. disease progression 3.2. unacceptable toxicity.	This condition reflects the treatment discontinuation criteria used in the ECHO trial.	If 1 component of acalabrutinib plus BR is discontinued permanently because of tolerability concerns, the patient may continue to receive the other component at the discretion of the treating physician until the discontinuation criteria in condition 3 are met.
Prescribing		
4. Acalabrutinib plus BR should be prescribed by clinicians with expertise in managing MCL and monitoring therapy.	This condition is meant to ensure that acalabrutinib plus BR is prescribed only for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
5. A reduction in price.	The ICER for acalabrutinib plus BR is \$533,458 per QALY gained when compared with BR alone. A price reduction greater than 70% would be required for acalabrutinib to achieve an ICER of \$50,000 per QALY gained compared to BR alone. Price reductions for different thresholds are available from Appendix 4 in the Pharmacoeconomic Review report.	—

ASCT = autologous stem cell transplant; BR = bendamustine + rituximab; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; ICER = incremental cost-effectiveness ratio; MCL = mantle cell lymphoma; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet need:** pERC noted that MCL presents a significant unmet need, particularly among patients who are ineligible for ASCT, who represent more than half of the MCL population. These patients are typically older, have frailty, and have multiple comorbidities, limiting their treatment options. pERC agreed with the clinical experts that current therapies are not curative, and relapse is inevitable, underscoring the need for strategies that prolong PFS without adding substantial toxicity. The clinical experts also noted that the standard regimen — BR — offers limited durability in controlling disease, especially in high-risk subgroups such as those with TP53 mutations, high Ki-67, or blastoid morphology. Patients and clinicians emphasized the importance of longer remission, improved quality of life, and manageable side effects. They added that treatment-related toxicities and the lack of fixed-duration options remain challenges.
- **PFS surrogacy:** pERC noted that acalabrutinib plus BR likely results in a clinically important difference in the probability of being progression-free at 48 months, compared to placebo plus BR (moderate certainty). pERC discussed that although some studies have demonstrated that PFS can serve as a surrogate end point positively correlated with OS in NHL, this association has primarily been established in the context of chemoimmunotherapy trials. Its applicability to targeted therapies, such as acalabrutinib, remains uncertain. pERC noted that the extent to which these benefits may translate into an OS advantage in MCL was unclear because the median OS was not reached in either treatment group and the data remain immature in the ECHO trial.
- **Uncertainty with OS:** pERC noted that the ECHO trial showed no clinically meaningful difference in OS between acalabrutinib plus BR and placebo plus BR in patients with untreated MCL ineligible for transplant. Data maturity was only 34%, and the interim nature of the analysis raises concerns about overestimating treatment effects. Median OS was not reached in either group at the interim analysis, and the reported HR of 0.86 (95% CI, 0.65 to 1.13) was not statistically significant. The trial was not powered to detect OS differences, and the analysis lacked adjustment for multiple comparisons, limiting interpretability. pERC additionally discussed that substantial crossover from the placebo group to acalabrutinib upon progression could have confounded OS results. The committee noted that, although OS is a clinically important outcome, the trial design and early reporting hinder conclusions. Thus, OS findings are considered supportive but uncertain, pending final analysis with longer follow-up and more events.
- **Sequencing:** pERC agreed that treatment sequencing in MCL is nuanced and patient-centred. pERC agreed with the clinical experts consulted for this review that, although acalabrutinib plus BR shows promise in improving PFS, it does not demonstrate an OS benefit, which may lead clinicians to favour traditional sequencing — starting with chemoimmunotherapy and reserving Bruton tyrosine kinase inhibitor (BTKi)-based therapy for second-line use. This approach is especially relevant in an incurable disease context in which OS remains unchanged. However, for patients with high-risk features (e.g., TP53 mutation, blastoid morphology, high Ki-67, or high MCL International Prognostic Biological Index scores), upfront use of acalabrutinib plus BR may be preferred due to concerns about the limited efficacy of chemoimmunotherapy alone. The committee also discussed the

importance of personalizing treatment based on patient fitness, comorbidities, and values, especially given the continuous nature of acalabrutinib therapy. There was agreement that CAR T-cell therapy eligibility and funding criteria may need to be reassessed if this regimen becomes standard in frontline settings.

- **Uncertainty in cost-effectiveness:** pERC discussed the outstanding uncertainty in the cost-effectiveness results. First, the incremental QALYs associated with treatment with acalabrutinib plus BR may be overestimated because the benefit is contingent upon an improvement in OS, for which the clinical evidence remains uncertain. Additionally, in the cost-utility analysis, the cost of acalabrutinib was offset by cost savings in subsequent therapy due to both the proportion of patients requiring subsequent therapy and the distribution of subsequent therapies used, both of which are uncertain. As a result, further price reductions than those presented may be required to achieve a given WTP threshold.

Background

MCL is an aggressive but rare form of NHL that originates from a malignant transformation of B cells in the mantle zone of the lymph node. In 2024, there were an estimated 11,700 new cases of NHL diagnosed in Canada, of which 585 to 820 cases would be attributed to new MCL diagnoses. The overall 10-year prevalence of NHL is 141.0 cases per 100,000 persons, of which 7.1 to 9.9 cases per 100,000 would be attributed to MCL. MCL occurs 3 times more often in males than females, with a median age at diagnosis of 67.5 years. Patients with MCL have poor survival, with a 5-year survival of 65.9% compared with 73.3% in patients with any NHL.

Approximately 90% of patients with MCL are classified as having aggressive disease, which requires upfront treatment. Patients with MCL often present with disseminated lymphadenopathy, splenomegaly, and bone marrow infiltration. Other common symptoms of MCL include weight loss, unexplained fever, night sweats, loss of appetite, nausea and/or vomiting, indigestion, abdominal pain, and bloating. According to clinical experts and inputs from clinician groups, the current standard of care for patients with MCL who are ineligible for ASCT is BR, followed by rituximab maintenance therapy every 3 months for up to 2 years. However, patients' disease inevitably relapses with current treatment strategies. As a result, there is a significant unmet need for strategies that can improve PFS in patients with MCL who are ineligible for ASCT.

Acalabrutinib has been approved by Health Canada for use in combination with BR for the treatment of adult patients with previously untreated MCL who are ineligible for ASCT. Acalabrutinib is a second-generation, selective, covalent BTKi. It is available as 100 mg oral tablets, and the dosage recommended in the product monograph is 100 mg twice daily.

Sources of Information Used by the Committee

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

- a review of 1 ongoing phase III, double-blind, placebo-controlled RCT (ECHO) in adult patients with previously untreated MCL who are ineligible for ASCT
- patients' perspectives gathered by 1 patient group, Lymphoma Canada
- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise in diagnosing and treating patients with MCL
- input from 3 clinician groups, the Lymphoma Canada Scientific Advisory Board (Lymphoma Canada), the Leukemia & Lymphoma Society of Canada (LLSC) Pharmacist Network, and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH [CCO] Hem DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received 1 patient group input from Lymphoma Canada, which conducted an anonymous patient survey between January 31, 2025, and April 6, 2025, which was shared via email and social media by Lymphoma Canada (102 responses from patients with MCL). The review team notes that the eligibility of these patients' disease for ASCT and the advancement of their disease (newly diagnosed versus recurrent) are unknown, and thus their alignment to the current target population is unclear.

At the diagnosis of MCL, respondents of the survey noted that they often experience significant physical symptoms like fatigue and/or lack of energy, abdominal issues, and enlarged lymph nodes, and face psychosocial impacts such as anxiety, stress, and fear of disease progression, which also affect patients and their families' emotional well-being.

The results of the survey also highlighted that patients with MCL often require immediate treatment (i.e., ASCT) and multiple lines of therapy. Common side effects with these treatments include fatigue, nausea, and hair loss, which had negative impacts on the patient's quality of life and were considered a significant issue by the survey respondents. Also, access to treatment can be challenging due to the location of treatment centres and the related financial implications, impacting survey respondents' overall satisfaction and quality of life.

Surveyed patients indicated that, when making MCL treatment decisions, they prioritize longer disease remission, survival, improved quality of life, symptom control, and normalized blood counts. They were willing to tolerate manageable side effects and emphasized the need for more therapy options to enhance their treatment outcomes and quality of life. Most surveyed patients believe it is very important to have choices in their treatment decision and a variety of treatment options to choose from.

From the survey responses, 8 patients indicated they were treated with acalabrutinib in combination with BR with no prior treatment. These patients resided in Canada (5) and the US (3). Patients reported side effects with treatment with acalabrutinib plus BR such as fatigue, diarrhea, and neutropenia. Despite these issues, most patients rated their experience with treatment with acalabrutinib plus BR positively and would recommend the drug to other patients with MCL.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts indicated that there is a significant unmet need for improved strategies for treating patients with MCL who are ineligible for ASCT that can improve PFS without the addition of significant toxicity to a population of older adults who are already at risk of complications. However, the clinical experts also highlighted the high toxicity with acalabrutinib plus BR (associated with, for example, diarrhea, infections, and arrhythmias) and noted that the OS was similar between treatment groups in the ECHO trial. The clinical experts identified patients who are most likely to respond to treatment with acalabrutinib would be aligned with the ECHO trial inclusion criteria. The clinical experts suggested that other meaningful treatment responses include complete response or partial response — assessed through blood work, physical exams, and end-of-treatment scans like CT or PET-CT — and improved quality of life. The clinical experts indicated that the most important considerations when deciding to discontinue treatment with acalabrutinib include disease progression or unacceptable toxicity from acalabrutinib. The clinical experts indicated that acalabrutinib should be prescribed and monitored by a specialist in hematology and/or oncology. The appropriate setting for treatment with acalabrutinib plus BR would typically be the outpatient setting.

Clinician Group Input

Clinician group input for this review was received from 3 clinician groups: the Lymphoma Canada Scientific Advisory Board (Lymphoma Canada), the LLSC Pharmacist Network, and OH (CCO) Hem DAC. A total of 7 clinicians (4 from Lymphoma Canada, 1 from LLSC Pharmacist Network, and 2 from OH [CCO] Hem DAC) provided input for this submission.

Input from the clinician groups aligned with that of the clinical experts consulted for this review with regard to treatment goals, the unmet needs of this patient population, assessing treatment response, the drug's place in therapy, deciding when to discontinue treatment, which specialists should manage these patients, and where patients should be treated with acalabrutinib. Clinicians from OH (CCO) Hem DAC and the LLSC Pharmacist Network noted that BTKi therapy may be less suitable for patients at a higher risk of bleeding disorders (e.g., cardiovascular bleeding) because BTKis can interfere with platelet function, increasing the risk of bleeding complications. Additionally, clinicians from the LLSC Pharmacist Network indicated that patients with uncontrolled infections or those on medications that may interact with acalabrutinib would be least suitable for treatment with acalabrutinib. Clinicians from the LLSC Pharmacist Network highlighted that when prescribing acalabrutinib, it is crucial to consider polypharmacy and thoroughly review the patient's current medications to manage potential interactions and minimize the risk of bleeding complications, ensuring safe and effective treatment. Input from the LLSC Pharmacist Network suggested that treatment response is typically assessed every 2 to 3 months, and clinicians from Lymphoma Canada suggested

that serial imaging to assess treatment response could be performed at infrequent intervals (i.e., every 6 months). Input from the LLSC Pharmacist Network noted that when considering treatment sequencing, it is crucial to recognize that combining therapies with different mechanisms of action may exhaust multiple lines of treatment at once, especially in older patients with comorbidities who are ineligible for transplant, highlighting the need for careful patient selection due to a notable attrition rate following frontline treatment.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation questions	Response
Relevant comparators	
BR is an appropriate comparator for the first-line treatment of transplant-ineligible MCL. Other regimens sometimes used are R-CVP and R-CHOP.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Patients were enrolled in the ECHO trial if they were aged 65 years and older. Would patients who are younger than 65 years and not eligible for transplant be considered for acalabrutinib plus BR treatment?	pERC agreed with the clinical experts that patients younger than 65 years who are ineligible for transplant may be considered for acalabrutinib plus BR treatment, although this scenario is relatively uncommon.
Considerations for prescribing of therapy	
During the maintenance rituximab phase, rituximab was administered every 2 months for 12 doses along with oral acalabrutinib twice daily. In some jurisdictions, maintenance rituximab is administered every 3 months for 8 doses.	This is a comment from the drug programs to inform pERC deliberations.
CDA-AMC had previously recommended brexucabtagene autoleucel for the treatment of adult patients with relapsed or refractory MCL after 2 or more lines of systemic therapy. Prior therapy must have included an anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody therapy, and a BTKi. - Is there evidence to support sequencing brexucabtagene autoleucel as a second-line treatment if the first-line therapy contains all 3 components (anthracycline, anti-CD20 monoclonal antibody, and a BTKi)? - Can acalabrutinib and bendamustine be administered with rituximab biosimilars or subcutaneous rituximab? - If 1 drug of the combination of acalabrutinib, rituximab, and bendamustine needs to be discontinued, can the remaining drugs be continued?	pERC indicated that brexucabtagene autoleucel is currently approved and funded after 2 lines of therapy, and there is no evidence to support the sequencing of this CAR T-cell therapy immediately after acalabrutinib + BR. Funding policies regarding brexucabtagene autoleucel would need to be reassessed to account for the evolving therapeutic landscape. This is outside the scope of the present review. pERC agreed with the clinical experts that acalabrutinib and bendamustine can be administered with rituximab biosimilars or subcutaneous rituximab. pERC agreed with the clinical experts that if 1 drug of the combination of acalabrutinib, rituximab, and bendamustine needs to be discontinued, the remaining drugs can be continued.
Generalizability	
For patients who started on BR first-line treatment and are transplant-ineligible, should acalabrutinib be added to BR	pERC agreed with the clinical experts consulted by CDA-AMC that there are no studies directly addressing the question.

Implementation questions	Response
at the time of funding? If so, is there a maximum number of cycles of BR that would be given before considering not adding acalabrutinib?	Considering the PFS benefit of BTKis in second-line treatment, clinical experts stated it is unnecessary to offer acalabrutinib to patients who have already started BR as first-line therapy. pERC agreed with the clinical experts that funding for acalabrutinib should be restricted to patients who have not yet initiated BR therapy.
Funding algorithm	
Request initiation of a rapid provisional funding algorithm.	This is a comment from the drug programs to inform pERC deliberations.
Acalabrutinib may change the place in therapy of drugs reimbursed in subsequent lines.	This is a comment from the drug programs to inform pERC deliberations.
Care provision issues	
Acalabrutinib is an oral drug that is an enabler for implementation. However, additional pharmacy resources will be required for drug-drug interaction monitoring and dispensing.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
The OWG is concerned with the budget impact of the addition of acalabrutinib to BR.	This is a comment from the drug programs to inform pERC deliberations.
Rituximab biosimilars and subcutaneous rituximab have confidential negotiated prices. Bendamustine has multiple generics and confidential net prices.	This is a comment from the drug programs to inform pERC deliberations.

BR = bendamustine + rituximab; BTKi = Bruton tyrosine kinase inhibitor; CDA-AMC = Canada's Drug Agency; MCL = mantle cell lymphoma; OWG = Oncology Working Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (Oncovin), and prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing phase III, double-blind, placebo-controlled RCT (ECHO, N = 598) evaluating the efficacy and safety of acalabrutinib plus BR compared to placebo plus BR in adult patients with previously untreated MCL who are ineligible for ASCT was included in the sponsor-submitted systematic review. The ECHO trial was not designed to demonstrate the efficacy and safety of acalabrutinib in induction (combined with BR) and maintenance (combined with rituximab) phases separately. The primary end point was PFS assessed by IRC using the Lugano Classification. Key secondary end points included overall response rate per IRC and OS. Secondary end points outside the statistical hierarchy included PFS and overall response rate (investigator-assessed), duration of response, HRQoL, and safety end points. Patients were randomized in a 1:1 ratio to receive either acalabrutinib plus BR (n = 299) or placebo plus BR (n = 299). Randomization was conducted using an interactive voice and/or web response system and stratified by geographic region (North America versus Western Europe versus Other) and Simplified MCL International Prognostic Index (MIPI) score (low

risk [0 to 3] versus intermediate risk [4 to 5] versus high risk [6 to 11]). Eligible patients were recruited in 189 study centres in 26 countries, including 6 sites in Canada that enrolled a total of 25 patients.

Demographic and disease characteristics were well balanced between treatment groups. The median age of all patients was 71.0 years, ranging from 65 to 86 years. Most patients were male (female: 29.3%; male: 70.7%) and white (78.3%) and also included patients self-reporting as American Indian or Alaska Native, Asian, and multiple ethnicities or races. Nearly half (49.5%) of patients had an Eastern Cooperative Oncology Group performance status score of 0. All (100%) patients had histologically documented MCL, close to half (42.3%) of patients had a simplified MIPI score of 4 to 5 (intermediate risk), and the most reported MCL type was classic (80.4%). Generally, the baseline disease history was balanced across treatment groups, [REDACTED] was the most reported medical history in patients in the ECHO trial.

Efficacy Results

Only those efficacy outcomes identified as important for this review are reported. Efficacy and safety data were evaluated at a planned interim analysis with a data cut-off date of February 15, 2024. The median duration of follow-up was 46.1 months in the acalabrutinib plus BR group and 44.4 months in the placebo plus BR group.

Progression-Free Survival

At the of the interim analysis, 110 (36.8%) patients in the acalabrutinib plus BR group and 137 (45.8%) patients in the placebo plus BR group experienced a PFS event; among them, 57 (19.1%) had disease progression based on IRC assessment and 53 (17.7%) died in the acalabrutinib plus BR group, and 99 (33.1%) had disease progression and 38 (12.7%) died in the placebo plus BR group. The median PFS was 66.4 months (95% CI, 55.1 months to not estimable) in the acalabrutinib plus BR group and 49.6 months (95% CI, 36.0 to 64.1 months) in the placebo plus BR group. There was a statistically significant improvement in PFS in the acalabrutinib plus BR group compared with the placebo plus BR group (HR = 0.73; 95% CI, 0.57 to 0.94; P = 0.0160). The Kaplan-Meier estimate of PFS probability at 48 months was [REDACTED] (95% CI, [REDACTED] to [REDACTED]) for the acalabrutinib plus BR group, and [REDACTED] (95% CI, [REDACTED] to [REDACTED]) for the placebo plus BR group; the between-group difference was [REDACTED] (95% CI, [REDACTED] to [REDACTED]). Similar results were observed in the analysis of PFS based on investigator assessment (HR = 0.68; 95% CI, 0.53 to 0.88; nominal P = 0.0028). The PFS results were consistent across most prespecified and additional sensitivity analyses and subgroups except for females (n = 175; HR = 0.34; 95% CI, 0.19 to 0.58) and males (n = 425; HR = 0.91; 95% CI, 0.68 to 1.21). The clinical experts consulted for this review advised that the treatment effects observed for the subgroup analysis by female and male sex were likely attributable to chance.

Overall Survival

At the interim analysis, a total of 97 patients (32.4%) in the acalabrutinib plus BR group and 106 patients (35.5%) in the placebo plus BR group had died. The median OS was not estimable at the time of the interim analysis for both treatment groups, and there was no difference in the risk of death between acalabrutinib plus BR compared with placebo plus BR (HR = 0.86; 95% CI, 0.65 to 1.13; P = 0.2743). The Kaplan-Meier

estimate of OS probability at 48 months was [REDACTED] (95% CI, [REDACTED] to [REDACTED]) for the acalabrutinib plus BR group, and [REDACTED] (95% CI, [REDACTED] to [REDACTED]) for the placebo plus BR group, the between-group difference was [REDACTED] (95% CI, [REDACTED] to [REDACTED]). It is important to note that this analysis was not powered to detect a statistically significant difference in OS. The type I error rate in the OS analysis was not controlled for multiple comparisons, and results should be considered as supportive evidence with limited interpretability.

Health-Related Quality of Life

On cycle 48 day 1 (approximately 48 months of treatment), [REDACTED] of 299 ([REDACTED]) patients and [REDACTED] of 299 ([REDACTED]) patients contributed to the analysis of Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) total score. Patients in the acalabrutinib plus BR group reported an estimated least squares mean increase (improvement) from baseline in the FACT-Lym total score of [REDACTED] (standard error = [REDACTED]) compared to [REDACTED] points (standard error = [REDACTED]) in patients in the placebo plus BR group, the between-group difference was [REDACTED] points (95% CI, [REDACTED] to [REDACTED]; nominal P = [REDACTED]). The type I error rate in the FACT-Lym analysis was not controlled for multiple comparisons, and results should be considered as supportive evidence.

Harms Results

At the time of the interim analysis, 296 of 297 (99.7%) patients in the acalabrutinib plus BR group and 294 of 297 (99.0%) patients in the placebo plus BR group experienced at least 1 treatment-emergent AE (TEAE), with nausea (42.8% versus 37.7% for acalabrutinib plus BR versus placebo plus BR) being the most reported TEAE. A total of 205 (69.0%) patients in the acalabrutinib plus BR group and 184 (62.0%) patients in the placebo plus BR group reported at least 1 serious AE. TEAEs leading to discontinuation of study treatment were reported by 127 (42.8%) patients in the acalabrutinib plus BR group and 92 (31.0%) patients in the placebo plus BR group. The most common TEAE that caused treatment discontinuation was COVID-19 (4.7% versus 3.0%). A total of 97 of the 299 (32.4%) patients died in the acalabrutinib plus BR group and 106 of the 299 (35.5%) patients died in the placebo plus BR group during the study, including the crossover period. COVID-19 pneumonia (5.1% versus 3.4%) was the most reported AEs leading to death. The clinical experts consulted by CDA-AMC identified the following AEs as notable harms for the treatment with acalabrutinib: infections and infestations ([REDACTED] versus [REDACTED]), atrial fibrillation and/or flutter ([REDACTED] versus [REDACTED]), which were reported more frequently in the acalabrutinib plus BR group than the placebo plus BR group, and ventricular arrhythmias ([REDACTED] versus [REDACTED]), which were reported similarly between treatment groups. Hemorrhage (28.3% versus 17.2%) was an AE of clinical interest that was reported more frequently in the acalabrutinib plus BR group than the placebo plus BR group.

Critical Appraisal

As the ECHO trial is ongoing, results were only available from the interim analysis for this review. The upper bound of the 95% CI for median PFS in the acalabrutinib plus BR group was not estimable, and the median OS was not reached in either treatment group. The review team notes that the early reporting of the study results may lead to an overestimation of the treatment effect.²² Given that PFS is a surrogate outcome for OS, it remains uncertain whether these benefits will translate into an improvement in OS for

this trial because the OS data were not interpretable at the time of the interim analysis. Furthermore, OS data were confounded by substantial crossover of patients from the placebo plus BR arm to acalabrutinib plus BR upon progression. The study was not powered to detect a statistically significant difference in OS; moreover, duration of response and HRQoL were not part of the statistical testing strategy, and thus were not adjusted for multiple testing, limiting credible conclusions from these results. There was a notable attrition rate observed at cycle 48 day 1 in the analysis of HRQoL measurements (i.e., FACT-Lym and EQ-5D-5L) with only approximately [REDACTED] of patients contributing to the analysis. Moreover, more patients in the acalabrutinib plus BR group ([REDACTED]) provided HRQoL data than the placebo plus BR group ([REDACTED]). Given that withdrawal by patients was a common reason for study discontinuation, this would introduce bias because the characteristics of patients who remained in the study may differ from those who did not. Generally, the clinical experts commented that the trial eligibility criteria of the ECHO trial were standard but more strict than clinical practice, indicating that the ECHO trial included a healthier patient population that may not be reflective of all patients with MCL who are ineligible for ASCT in clinical practice.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal ECHO trial identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The reference points for the certainty of evidence assessment for PFS, OS, HRQoL were measured using FACT-Lym total score, and harms were set according to the presence of an important effect based on the established minimal important difference or thresholds agreed upon by clinical experts consulted for this review.

Table 3: Summary of Findings for Acalabrutinib Plus BR Versus Placebo Plus BR for Patients With Untreated MCL

Outcome and follow-up	Patients (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus BR	Acalabrutinib plus BR	Difference		
PFS							
Probability of being alive and progression-free at 48 months Follow-up (median): - Acalabrutinib plus BR: 46.1 months - Placebo plus BR: 44.4 months	598 (1 RCT)	HR = 0.73 (0.57 to 0.94)	per 1,000	per 1,000 (to per 1,000)	per 1,000 (to per 1,000)	Moderate ^a	Acalabrutinib plus BR likely results in a clinically important increase in the probability of being alive and progression-free at 48 months when compared with placebo plus BR.
OS							
Probability of being alive at 48 months Follow-up (median): - Acalabrutinib plus BR: 46.1 months - Placebo plus BR: 44.4 months	598 (1 RCT)	HR = 0.86 (0.65 to 1.13)	per 1,000	per 1,000 (to per 1,000)	per 1,000 (to per 1,000)	Moderate ^{b,c}	Acalabrutinib plus BR likely results in little to no clinically important difference in the probability of being alive at 48 months compared with placebo plus BR.
HRQoL							
Least squares mean change from baseline in the FACT-Lym total score at cycle 48 day 1 (0 [worse] to 168 [better]) Follow-up (median): Acalabrutinib plus BR: 46.1 months	(1 RCT)			()	to (to)	Low ^{c,d}	Acalabrutinib plus BR may result in little to no clinically important improvement in the FACT-Lym total score at cycle 48 day 1 compared with placebo plus BR.

Outcome and follow-up	Patients (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus BR	Acalabrutinib plus BR	Difference		
• Placebo plus BR: 44.4 months							
Harms							
Incidence of infections and infestations Follow-up (median): NR	594 (1 RCT)	NR	■ per 1,000	■ per 1,000 (■)	■ per 1,000 (■ to ■ per 1,000)	Moderate ^{c,e}	Acalabrutinib plus BR likely results in little to no clinically important difference in the incidence of infections and infestations compared with placebo plus BR.
Incidence of ventricular arrhythmias Follow-up (median): NR	594 (1 RCT)	NR	■ per 1,000	■ per 1,000	■ per 1,000 (■ to ■ per 1,000)	Low ^{c,f}	Acalabrutinib plus BR may result in little to no clinically important difference in the incidence of ventricular arrhythmias compared with placebo plus BR.
Incidence of atrial fibrillation and/or flutter Follow-up (median): NR	594 (1 RCT)	NR	■ per 1,000	■ per 1,000	■ per 1,000 (■ to ■ per 1,000)	Moderate ^{c,g}	Acalabrutinib plus BR likely results in little to no clinically important difference in the incidence of atrial fibrillation and/or flutter compared with placebo plus BR.

BR = bendamustine + rituximab; BTKi = Bruton tyrosine kinase inhibitor; CI = confidence interval; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; HR = hazard ratio; HRQoL = health-related quality of life; MCL = mantle cell lymphoma; MID = minimal important difference; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 1 level for serious imprecision. There is no established between-group MID for PFS at 48 months, but the clinical experts suggested that a 7% difference between groups in the probabilities of PFS at 48 months could be considered a threshold of minimal clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested a minimal clinically important difference between the 2 groups, whereas the lower bound of the 95% CI suggested no clinically important difference for acalabrutinib plus BR versus placebo plus BR based on this threshold. Additionally, PFS results were based on an interim analysis and the treatment effect may be overestimated. Although PFS is a widely used surrogate outcome for OS in oncology trials, the correlation between PFS and OS is not well established in MCL.

^bRated down 1 level for serious imprecision. There is no established between-group MID for OS at 48 months, but the clinical experts suggested that a 5% difference between groups in the probabilities of OS at 48 months could be considered a threshold of minimal clinical importance. The point estimate and the lower bound of the 95% CI for the between-group difference suggested no minimal clinically important difference between the 2 groups, whereas the upper bound of the 95% CI suggested a clinically important difference for acalabrutinib plus BR versus placebo plus BR based on this threshold. Additionally, OS results were based on an interim analysis and the treatment effect may be overestimated. The ECHO trial was not powered to evaluate OS. At the time of the data cut-off, data maturity was 34%. Given the trial design, allowed crossover, and data immaturity, the interpretability of these results is limited.

^cThe statistical testing for this outcome was not adjusted for type I error rate for multiple comparisons in the trial and should be considered as supportive evidence.

^dRated down 1 level for serious risk of bias due to missing data, given that the proportion of patients available for assessment diminished substantively over time. Rated down 1 level for serious imprecision. There is no established MID for between-group difference for FACT-Lym total score, but the estimated MID for the change from baseline is 7-point for increase. The point estimate and the upper bound of the 95% CI for the between-group difference suggested no clinically important increase, whereas the lower bound of the 95% CI suggested a clinically important difference between treatment groups based on a 7-point threshold identified in the literature.

^eRated down 1 level for serious imprecision. There is no established between-group MID for the incidence of infections and infestations, but the clinical experts considered that a 10% difference between groups at 48 months in the incidence of infections and infestations could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested no clinically important difference, whereas the lower bound of the 95% CI suggested a clinically important difference between treatment groups based on a 10% threshold.

^fRated down 2 levels for very serious imprecision. There is no established between-group MID for the incidence of ventricular arrhythmias, but the clinical experts considered that a 1% difference between groups in the incidence of ventricular arrhythmias could be considered a threshold of clinical importance. The point estimate for the between-group difference suggested no clinically important difference between the 2 groups, whereas the lower and upper bounds of the 95% CI suggested a clinically important difference in the incidence of ventricular arrhythmias for acalabrutinib plus BR versus placebo plus BR based on a 1% threshold, indicating possible clinically important benefit and harm with acalabrutinib plus BR compared to placebo plus BR. Additionally, the incidence of ventricular arrhythmias was based on a relatively low number of events in either treatment group.

^gRated down 1 level for serious imprecision. There is no established between-group MID for the incidence of atrial fibrillation and/or flutter, but the clinical experts considered that a 5% difference between groups in the incidence of atrial fibrillation and/or flutter could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested no clinically important difference, whereas the lower bound of the 95% CI suggested a clinically important difference between treatment groups based on a 5% threshold.

Source: ECHO Clinical Study Report (2024). Details included in the table are from the sponsor's Summary of Clinical Evidence.

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
- HRQoL (FACT-Lym)
- safety.

Long-Term Extension Studies

No long-term extension studies were submitted for this review.

Indirect Comparisons

No indirect comparisons were submitted for this review.

Studies Addressing Gaps in the Evidence From the Systematic Review

The ECHO trial initially used acalabrutinib 100 mg capsules, but as of February 27, 2023, Health Canada approved a 100 mg acalabrutinib maleate salt oral tablet formulation, which is now marketed to replace the capsule format that has not been supplied in Canada since July 31, 2024. The tablets reduce the impact of acid-reducing agents (e.g., proton pump inhibitors) on acalabrutinib. Dosing is identical for the formulations, and the tablets are smaller in volume. The sponsor submitted 2 phase I, open-label, randomized, crossover studies (D8220C00018 and D8223C00013) to assess the bioequivalence of acalabrutinib maleate film-coated tablet and acalabrutinib capsule. Results from the 2 studies concluded that acalabrutinib tablets and capsules are bioequivalent, indicating that the same efficacy and safety profile can be expected with the same dosing strength and schedule. Patients are able to coadminister tablets with acid-reducing agents such as proton pump inhibitors, and this removes the need to stagger dosing with H2 receptor antagonists and antacids. The CDA-AMC review team considers the D8220C00018 and D8223C00013 trials out of scope for this review because patients enrolled in the 2 trials were healthy patients without MCL. Therefore, the CDA-AMC review team acknowledges these studies but considers that they do not address gaps in the systematic review evidence for this review.

Economic Evidence

Cost and Cost-Effectiveness

- Acalabrutinib is available as 100 mg tablets. At the submitted price of \$142.77 per tablet, the cost of acalabrutinib is expected to be \$7,995 per patient per 28-day cycle, based on the Health Canada–recommended dosage. In combination with BR, the per-cycle cost of acalabrutinib is expected to be \$13,574 per patient. The combination regimen may be administered for up to 6 cycles. Following this, acalabrutinib may be continued with maintenance rituximab, which is estimated to cost \$9,035 per patient per 28-day cycle.
- Clinical efficacy in the economic analysis was derived from the ECHO trial, which compared acalabrutinib plus BR with placebo plus BR. Evidence submitted by the sponsor indicates that acalabrutinib plus BR results in a benefit in PFS; however, the treatment benefit in OS is uncertain because of immature data.
- The results of the CDA-AMC base case suggest that:
 - Acalabrutinib plus BR is predicted to be associated with higher costs to the health care system than BR alone (incremental costs = \$339,591), primarily driven by the higher drug acquisition costs associated with acalabrutinib.
 - Acalabrutinib plus BR is predicted to be associated with a gain of 0.74 life-years compared to BR alone. When the impact on HRQoL is also considered, acalabrutinib plus BR is predicted to be associated with a gain of 0.64 QALYs compared to BR alone.
 - The ICER of acalabrutinib plus BR compared to BR alone was \$533,458 per QALY gained in the CDA-AMC base case. The estimated ICER is uncertain because of uncertainty in the long-term survival estimates, comparative efficacy, and subsequent therapy assumptions. Given the unresolved uncertainty in the long-term comparative efficacy, the economic analysis may not accurately assess the impact on patient health. As such, the cost-effectiveness estimates are uncertain, and higher price reductions may be required to achieve a given WTP threshold.
- CDA-AMC estimates that the budget impact of reimbursing acalabrutinib for use in combination with BR for the treatment of adult patients with previously untreated MCL who are ineligible for ASCT will be approximately \$25.6 million over the first 3 years of reimbursement compared to the amount currently spent on comparators. The expenditure on acalabrutinib over this period is expected to be \$30.9 million (acalabrutinib plus BR = \$40.9 million). The actual budget impact of reimbursing acalabrutinib will depend on the number of patients treated and the type and proportion of subsequent therapies received following progression.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice Chair), Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: August 13, 2025

Regrets: Four expert committee member(s) did not attend.

Conflicts of interest: None



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