pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the CADTH pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *Procedures for the CADTH pan-Canadian Drug Review*, which are available on the CADTH website. The Final Recommendation will be posted on the pCODR website once available and will supersede this Initial Recommendation.

Drug: Acalabrutinib (CALQUENCE)

Submitted Reimbursement Request: As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Submitted by: AstraZeneca Canada Inc.

Manufactured by: AstraZeneca Canada Inc.

NOC date: November 28, 2019

Submission date: April 7, 2020

Initial Recommendation issued: October 29, 2020

Approximate per patient drug costs, per month (28 days)	Acalabrutinib costs $135.98 per 100 mg capsule. At the recommended dose of 100 mg twice daily, acalabrutinib monotherapy costs $275 per day and $7,615 per 28-day cycle.

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions**[a]
☐ **Do not reimburse**

[a] If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of acalabrutinib as monotherapy in adult patients with relapsed or refractory CLL who have received at least one prior therapy, if the following condition is met:

- Cost-effectiveness being improved to an acceptable level.

Eligible patients must have received at least one prior systemic therapy, have active disease according to one or more of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria, and good performance status. Treatment with acalabrutinib should be continued until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that, compared to investigator's choice of either idelalisib-rituximab or bendamustine-rituximab, there is a net clinical benefit of acalabrutinib monotherapy based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), a manageable toxicity profile, and no apparent detriment to quality of life (QoL) with an improvement in fatigue (observed in both treatment groups). pERC agreed that acalabrutinib aligns with patient values by providing an additional oral treatment option that improves disease control with less toxicity, has manageable side effects, an improvement in fatigue, and maintenance of/no detriment to QoL.

pERC concluded that, at the submitted price, acalabrutinib monotherapy is not considered cost-effective when compared to investigator's choice

	(idelalisib-rituximab/bendamustine-rituximab) in patients with active CLL who have received at least one prior systemic therapy. A reduction in price for acalabrutinib is required to improve cost-effectiveness to an acceptable level. pERC acknowledged the lack of a direct or robust indirect comparison to ibrutinib, the most appropriate comparator in this patient population, and was unable to draw a conclusion on the relative clinical efficacy and safety of acalabrutinib to ibrutinib. Due to these limitations, the cost-effectiveness estimates of acalabrutinib compared to ibrutinib are uncertain.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-effectiveness** Given that pERC was satisfied that there is a net clinical benefit of acalabrutinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of acalabrutinib. pERC noted that a reduction in the price of acalabrutinib would be required to improve cost-effectiveness to an acceptable level. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia in Canada and primarily affects older adults, with a median age at diagnosis of 71 years. Most patients are diagnosed at an early stage with an estimated median survival of over 10 years. The five-year survival rate of patients with CLL in Canada is 83%. Despite these relatively high survival rates, CLL remains an incurable disease. Most patients will have a partial response to initial therapy but will inevitably relapse requiring multiple lines of therapy. Treatment strategies in the relapsed setting depend on the number and intensity of previous lines of therapy, duration of response to prior lines of therapy, as well as patient comorbidities.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

For patients with CLL that is relapsed or refractory (R/R) to standard therapies including fludarabine, alkylating drugs, and rituximab — all current components of front-line therapy — the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib has emerged as the standard second-line drug, although there are few randomized trials examining optimal sequencing of available treatments for R/R CLL. Ibrutinib and idelalisib-rituximab (IDELA-RIT) are treatment options that are broadly funded for this indication in Canada; however, IDELA-RIT is less commonly used than ibrutinib because of greater toxicity with the combination and relative ease of administration of ibrutinib. Elderly patients may be treated with chemoimmunotherapy such as bendamustine-rituximab (BEN-RIT), although funding of this combination is not consistent across Canada and it is associated with hematologic toxicity and infections. Venetoclax as monotherapy or combined with rituximab (VEN-RIT) are also funded for R/R CLL and primarily used in patients where treatment with a BTK inhibitor has failed. Ibrutinib, venetoclax, and idelalisib are treatment options for R/R CLL irrespective of high-risk molecular features including a 17p deletion or TP53 mutation. While efficacious therapeutic options exist for patients with R/R CLL, pERC agreed that given the incurable nature of CLL, there is a need to identify therapies that are active in subsequent lines of treatment and activity that is independent of genetic subtype as well as intolerance to currently available molecularly targeted drugs.

pERC deliberated on the results of one international, multi-centred, randomized, open-label, phase III superiority trial (ASCEND; n = 358) of acalabrutinib monotherapy (ACA) compared to investigator's choice of either IDELA-RIT or BEN-RIT for patients with R/R CLL who had received at least one prior line of therapy. Eligible patients were those aged 18 years or older and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) between 0 and 2. Patients must have received at least one prior line of systemic therapy, however, patients with previous exposure to B-cell lymphoma 2 (BCL-2) inhibitors (e.g., venetoclax) or B-cell receptor (BCR) inhibitors including BTK inhibitors (e.g., ibrutinib) or phosphoinositide 3-kinases (PI3K) inhibitors (e.g., idelalisib) were excluded. Also excluded were patients who had known central nervous system (CNS) lymphoma or leukemia, prolymphocytic leukemia, history of or suspected Richter's syndrome, had significant cardiovascular disease (CVD), or required concomitant medication with warfarin (or equivalent vitamin K antagonists). Patients in the investigator's choice group could crossover to ACA upon confirmation of disease progression. pERC noted that the comparator treatments in the control group of the ASCEND trial, IDELA-RIT or BEN-RIT, are not the most relevant treatment comparators for R/R CLL. Most patients in the investigator's choice control group were treated with IDELA-RIT (77% versus 23% with BEN-RIT), which, as noted above, is an infrequently used regimen in Canadian clinical practice. The Clinical Guidance Panel (CGP) noted that the ASCEND trial population was enriched for higher risk patients for whom BEN-RIT therapy was considered inappropriate. pERC agreed that ibrutinib is considered the most appropriate comparator to ACA, as it is currently the most frequently used treatment for R/R CLL in Canada regardless of molecular features.

The primary end point of the ASCEND trial was the independent review committee (IRC)-assessed PFS. The primary efficacy analysis was based on the trial meeting its primary end point at the pre-specified interim analysis after a median duration of follow-up of 16.1 months (range = 0.03 to 22.4). The trial demonstrated a statistically significant reduction in the risk of disease progression or death with ACA compared to investigator's choice of IDELA-RIT or BEN-RIT. A final descriptive analysis performed after a median of 22 months of follow-up, based on investigator's assessment of PFS, was consistent with the

interim analysis and confirmed that the PFS benefit was maintained. pERC noted that the results of overall response rate (ORR), a key secondary efficacy outcome was not statistically different between groups. Based on hierarchical statistical testing, the evaluation of the remaining secondary efficacy outcomes, including overall survival (OS) and duration of response (DOR), were considered descriptive analyses. The confidence limits around the estimate of OS indicated no difference between the treatment groups at either the interim analysis or the final descriptive analysis. For DOR, the data at the interim analysis indicated a longer DOR in favour of ACA compared to investigator's choice therapy. pERC acknowledged that longer-term OS data could be confounded by treatment crossover and the use of post-trial treatments; considering this and the long natural history of CLL, pERC agreed with the CGP's conclusion that PFS is the most appropriate end point to assess the clinical efficacy of ACA. pERC discussed that the PFS benefit of ACA was consistent across all pre-specified patient subgroup analyses performed that included patients with high-risk features (i.e., immunoglobulin heavy chain [IgHV] gene, 17p deletion, 11q deletion, and/or TP53 mutation) and multiple lines of prior therapy. Based on these data, pERC concluded that the PFS benefit associated with ACA is clinically meaningful. pERC noted that this conclusion is supported by the CGP and all registered clinicians who provided input for this submission.

pERC deliberated on the safety data from the ASCEND trial. pERC observed that due to differences in the treatment regimens being compared (i.e., continuous therapy with ACA; and continuous therapy with idelalisib versus fixed duration of rituximab and bendamustine) treatment exposure was longer in ACA group at 15.7 months compared to investigator's choice treatments. In the investigator's choice group, the median duration of treatment in patients treated with idelalisib and rituximab was 11.5 months and 5.5 months, respectively; and the median duration of treatment of patients treated with bendamustine and rituximab was 5.6 months and 5.5 months, respectively. The most common adverse events (AEs) among patients in the ACA group were headache, neutropenia, and diarrhea. pERC discussed that the CGP identified cardiac toxicity to be a concern with ACA, which pERC noted is characteristic of BTK inhibitors as a class (i.e., ibrutinib). Any-grade cardiac events occurred in a higher proportion of patients treated with ACA (13%), primarily due to atrial fibrillation (5%), compared to IDELA-RIT (8%) and BEN-RIT (9%); however, grade 3 or higher cardiac events were more frequent in patients treated with BEN-RIT (9%), with a similar event rate observed in patients treated with ACA (3%) and IDELA-RIT (3%). Any-grade bleeding was higher in patients treated with ACA compared to investigator's choice treatments but grade 3 or higher major bleeding events and any-grade hypertension were similar between the treatment groups. pERC discussed that the incidence of cardiac toxicity may be higher when ACA is used in clinical practice considering patients with significant CVD were excluded from the ASCEND trial. The incidence of grade 3 or higher AEs was noticeably increased among patients who were treated with IDELA-RIT compared to ACA and BEN-RIT; and the need for dose reduction and treatment discontinuation due to AEs was higher in both investigator's choice treatments compared to ACA. Serious AEs (SAEs) also occurred in a much higher proportion of patients treated with IDELA-RIT compared to patients treated with ACA or BEN-RIT, where rates of SAEs were similar. Based on these safety data, pERC agreed with the CGP that the side effects of ACA were as expected and considered manageable with no new safety signals. pERC concluded that the toxicity associated ACA was less when compared to investigator's choice treatments, particularly when compared to IDELA-RIT.

pERC deliberated on the health-related QoL data from the ASCEND trial, which was measured using the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-Fatigue), a secondary end point of the trial; as well as the European Organization for Research and Treatment of Cancer 30-item core quality of life (EORTC-QLQ-C30) and 5-dimension, 5-level EuroQol (EQ-5D-5L) questionnaires, which were exploratory outcomes. [redacted] Based on these QoL data, pERC concluded that there is no apparent detriment to QoL outcomes with ACA when compared to investigator's choice of IDELA-RIT or BEN-RIT. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This*

information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

pERC deliberated the input received from one joint submission from two patient advocacy groups, Lymphoma Canada and the Chronic Lymphocytic Leukemia Patient Advocacy Group (CLLPAG), and noted that patients with CLL value having additional treatment options that improve disease control, have manageable side effects, improve QoL, have ease of use (i.e., oral therapy), and are accessible and affordable. Most of the patients who had experience with ACA for R/R CLL had been diagnosed more than 10 years ago. Half of the patients reported that all their CLL symptoms were managed by ACA; the most common being increased lymphocyte count, fatigue and lack of energy, and enlarged lymph nodes. pERC noted that the ability of ACA to address disease-related fatigue was variable among patients in the sample. The most frequently reported side effects of ACA included diarrhea, headache, and muscle or joint pain. Most patients noted that treatment side effects had no impact or some impact on their QoL. Patients described the side effects of ACA as mild, and that they were able to maintain good QoL while on treatment. Based on the input provided, pERC concluded that ACA aligns with patient values by providing an additional oral treatment option that improves disease control with less toxicity and more tolerable side effects. pERC noted, however, that ACA may not be affordable for all patients considering oral therapies are not funded equally across Canada.

In addition to the ASCEND trial, pERC also deliberated the results of matching adjusted indirect comparisons (MAICs) submitted by the sponsor that indirectly compared the efficacy and safety of ACA to ibrutinib monotherapy and VEN-RIT for the treatment of patients with R/R CLL. pERC's deliberation focused on the MAIC to ibrutinib, the most appropriate comparator in this patient population. The MAIC results suggested that ACA has a similar clinical efficacy in terms of PFS and OS compared to ibrutinib. Overall, safety outcomes favoured treatment with ACA; compared to ibrutinib, ACA was associated with a reduced likelihood of all-grade diarrhea, fatigue, peripheral edema, anemia and hypertension, and an increased risk of grade 3-4 anemia. pERC noted that the CADTH Methods Team identified several limitations of the submitted MAICs. These included the use of unanchored comparisons, which are associated with an increased risk of producing biased treatment effect estimates, and a significant heterogeneity across included trials related to patient and study characteristics that had resulted in using a reduced sample size from the ASCEND trial for both comparisons in the MAICs. The CADTH Methods Team noted that the reductions in sample size suggest there were substantial differences in the patient populations of included trials, and likely important generalizability concerns associated with the ASCEND trial patients who were included in each MAIC analysis compared to the overall ASCEND patient population. Considering these limitations, and in the absence of a direct head-to-head trial comparing ACA to ibrutinib, pERC concluded that no conclusions can be drawn from the MAIC results on the comparative efficacy of ACA to ibrutinib.

pERC deliberated on the cost-effectiveness of ACA compared with ibrutinib, IDELA-RIT, IDELA-RIT/BEN-RIT, and VEN-RIT for patients with CLL who have received at least one prior systemic therapy. pERC noted the lack of direct or robust indirect evidence to inform the comparisons of ACA versus ibrutinib and ACA versus VEN-RIT. As such, the cost-effectiveness of ACA compared with ibrutinib or VEN-RIT is uncertain. Based on the clinical evidence, pERC considered that the comparison based on the extrapolated ASCEND trial data represented a more appropriate comparison. pERC concluded that ACA was not cost-effective at the submitted price versus investigator's choice (IDELA-RIT/BEN-RIT) or IDELA-RIT. A reduction in drug price would be required to improve cost-effectiveness to an acceptable level.

pERC deliberated on the input from PAG, regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups, Lymphoma Canada and CLLPAG
- input from registered clinicians: one clinician on behalf of Cancer Care Ontario and seven clinicians on behalf of Lymphoma Canada
- input from CADTH's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review was to evaluate the safety and efficacy of ACA as monotherapy compared to existing treatment options for adult patients with CLL who have received at least one therapy.

Studies included: One open-label, randomized phase III superiority trial (ASCEND)

The pCODR systematic review included one international, multi-centred, open-label, phase III superiority trial of ACA compared to investigator's choice of either IDELA-RIT or BEN-RIT for patients with R/R CLL who had received at least one line of therapy. The trial was conducted across 25 countries in 102 centres including six sites in Canada that enrolled a total of 13 Canadian patients. [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 30, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* Eligible patients were randomized in a 1:1 ratio to receive oral ACA for continuous cycles until disease progression or unacceptable toxicity, or investigator's choice of oral idelalisib in combination with up to eight doses of IV rituximab or IV BEN-RIT for up to six cycles. Patients who received investigator's choice of IDELA-RIT or BEN-RIT could crossover to ACA following confirmation of disease progression if eligibility criteria were maintained.

Patient populations: Median age of 67 years, ECOG PS of 0 or 1, BCL-2 inhibitor and BCR inhibitor naive, median of 1 or 2 prior therapies

Eligible patients were 18 years of age or older, with an ECOG PS between 0 and 2, CD20-postitive disease, active disease meeting one or more of the iwCLL 2008 criteria. Patients must have received at least one prior line of systemic therapy; however, patients previously treated with a BCL-2 inhibitor (e.g., venetoclax) or a BCR inhibitor, such as BTK inhibitors (e.g., ibrutinib) or phosphoinositide 3-kinases (PI3K) inhibitors (e.g., idelalisib), were excluded. The trial also excluded patients who had known CNS lymphoma or leukemia, prolymphocytic leukemia, a history of or suspected Richter's syndrome, significant CVD, or required concomitant medication with warfarin (or equivalent vitamin K antagonists).

A total of 310 eligible patients were randomly assigned to receive ACA (n = 155) or investigator's choice (n = 155) of IDELA-RIT (n = 119) or BEN-RIT (n=36). Demographic and disease characteristics were generally balanced between the treatment groups. The median age was 67 years (range = 32 to 90). At baseline, most patients had an ECOG PS of 0 or 1 (87%), 48.7% of patients had bulky disease (lymph node ≥ 5 cm), 60.6% had any constitutional symptoms, and 53.2% had any cytopenias. In terms of differences, the median time from initial diagnosis to randomization was longer in the ACA group (85.3 months) compared to the investigator's choice group (79.0 months) by approximately five months. In terms of high-risk features, 15.8% of patients had a 17p deletion, 26.8% had an 11q deletion, and 23.5% had a TP53 mutation, which were generally balanced between the groups. There was a higher proportion of patients with unmutated IgHV in the investigator's choice group (80.6%) compared to the ACA group (76.1%). There was also a higher proportion of patients in the ACA group who received just one prior line of therapy (53%) compared to the investigator's choice group (43%); the median number of prior therapies in each group was one and two, respectively. Taking multiple factors into account, the ACA group may have had a

more favourable prognosis due a longer time between initial diagnosis to randomization, a higher proportion of patients with Rai stage I disease, and a higher proportion of patients who received one prior therapy compared to the investigator's choice treatment group.

Key efficacy results: Statistically significant and clinical meaningful PFS benefit with ACA compared to IDELA-RIT and BEN-RIT; OS data immature

Patients were assessed for tumour response and disease progression in accordance with iwCLL 2008 criteria. All primary and secondary efficacy end points were controlled for multiplicity and tested for statistical significance according to a fixed, sequential hierarchy.

The primary efficacy analysis was based on a pre-specified interim analysis (data cut-off date of January 15, 2019) after a median follow-up duration of 16.1 months (range = 0.03 to 22.4). A descriptive final analysis was conducted after a median follow-up of 22 months based on investigator assessment (data cut-off date of August 1, 2019). The key efficacy outcomes deliberated by pERC included the primary end point, IRC-assessed PFS, and the key secondary end point of OS.

Primary End Point:

- IRC-assessed PFS: based on a total of 27 (17.4%) IRC-assessed PFS events in the ACA group and 68 (43.9%) PFS events in the investigator's choice group. The median PFS was not reached in the ACA group and was 16.5 months (95% CI, 14.0 to 17.1) in the investigator's choice group. ACA demonstrated a statistically significant reduction in the risk of disease progression or death relative to investigator's choice of IDELA-RIT or BEN-RIT (hazard ratio [HR] = 0.31; 95% CI, 0.20 to 0.49; P < 0.0001). The results of the final analysis for this outcome based on the INV assessment were consistent (HR = 0.27; 95% CI, 0.18 to 0.40) with the interim analysis.

Secondary End Points:

- OS: Since statistical significance of ORR was not reached (see below), the OS results were considered descriptive based on hierarchal statistical testing. At the time of the interim analysis the OS data were considered immature and the median OS had not been reached in either treatment group. A total of 15 (10%) patients in the ACA group and 18 (12%) patients in the investigator's choice group had died (IDELA-RIT: n = 13; BEN-RIT: n = 5) and there was no difference between the treatment groups (HR = 0.84; 95% CI, 0.42 to 1.66). The results of the final analysis for this outcome were consistent (HR = 0.78; 95% CI, 0.44 to 1.40) with the interim analysis results.
- IRC-assessed ORR: There was an absolute difference in ORR of 5.8% between the treatment groups that did not reach statistical significance at the time of the interim analysis (P = 0.22). In the ACA group, the ORR was 81.3% (95% CI, 74.5 to 86.6) compared to 75.5% (95% CI, 68.1 to 81.6) in the investigator's choice treatment group.
- IRC-assessed DOR: Results for DOR were also considered descriptive based on hierarchal statistical testing. The DOR was not reached in the ACA group and was 13.6 months (95% CI, 11.9 to not reached) in the investigator's choice treatment group, which represents a prolongation in DOR in favour of ACA compared to investigator's choice (HR = 0.33; 95% CI, 0.19 to 0.59).

The results of pre-specified subgroup analyses for IRC-assessed PFS (based on the interim analysis) defined by demographic and disease characteristics showed a consistent PFS benefit in favour of ACA for almost all patient subgroups examined (a few subgroups were limited by small sample size). A post-hoc exploratory analysis of IRC-assessed PFS by the type of investigator's choice therapy also showed a PFS benefit of ACA when compared against IDELA-RIT (HR = 0.29; 95% CI, 0.18 to 0.46) and BEN-RIT (HR = 0.36; 95% CI, 0.19 to 0.69) individually. The results of the final analysis for this comparison were consistent with the interim analysis results.

Patient-reported outcomes: No clinically meaningful differences between groups for most QoL measures; fatigue improved in all treatment groups

Patient-reported health-related QoL was assessed in the ASCEND trial and measured using the FACIT-Fatigue questionnaire, a secondary end point of the trial, and the EORTC-QLQ-C30 and EQ-5D-5L questionnaires, which were exploratory outcomes.

[redacted]

[redacted]

[redacted]

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Safety: ACA has less toxicity compared to IDELA-RIT and comparable toxicity to BEN-RIT

A total of 307 patients were included in the analyses of safety in the ASCEND trial, which included 154 in the ACA group and 153 in the investigator's choice group (118 received IDELA-RIT and 35 received BEN-RIT). The median duration of treatment with ACA was 15.7 months. The median duration of treatment in investigator's choice group in patients treated with IDELA-RIT was 11.5 months and 5.5 months for idelalisib and rituximab, respectively. For patients treated with investigator's choice of BEN-RIT, the median duration of treatment of bendamustine and rituximab was 5.6 months and 5.5 months, respectively. At the time of the data cut-off date, 80% of patients were still receiving treatment in the ACA group, compared to 31.9% of patients assigned to IDELA-RIT, and no patients assigned to BEN-RIT. A total of 35 patients (23%) crossed over from investigator's choice to ACA. Overall, few patients received a subsequent therapy after study drugs were discontinued (8.4% in the ACA group and 7.1% in the investigator's choice group) reflecting the relatively short duration of follow-up in the trial.

A similar proportion of patients in each treatment group experienced AEs of any grade (93.5% in the ACA group, and 94.8% in the investigator's choice group that included 99.2% of patients treated with IDELA-RIT and 80.0% of patients treated with BEN-RIT). The most common any-grade AEs in the ACA group were headache (22.1%), neutropenia (19.5%), and diarrhea (18.2%). In the investigator's choice group, diarrhea (46.6%), neutropenia (44.9%), pyrexia (17.8%), and cough (15.3%) were the most common AEs in patients treated with IDELA-RIT; and neutropenia (34.3%), fatigue (22.9%), infusion-related reaction (22.9%), nausea (20.0%), and pyrexia (17.1%) were the most common AEs in patients treated with BEN-RIT.

Grade 3 or higher AEs were increased in the investigator's choice group among patients treated with IDELA-RIT (89.8%) compared to BEN-RIT (48.6%) and compared to the ACA group (49.4%). The most frequently occurring grade 3 or higher AEs in both treatment groups was neutropenia, which occurred in a higher proportion of patients in the investigator's choice group (IDELA-RIT: 39.8%; BEN-RIT: 31.4%) compared to the ACA group (15.6%). This was followed by anemia (11.7%) and pneumonia (5.2%) in the ACA group. In the investigator's choice group, for patients treated with IDELA-RIT, the most frequently occurring grade 3 or higher AEs after neutropenia were diarrhea (23.7%), pneumonia (8.5%) and alanine aminotransferase increased (8.5%); and in patients treated with BEN-RIT, the next most common was anemia (8.6%). SAEs occurred in 28.6% of patients in the ACA group and 49.0% of patients treated with investigator's choice (IDELA-RIT: 55.9%; BEN-RIT: 25.7%). A higher proportion of patients treated with IDELA-RIT experienced a grade 3 or higher SAE (50.8%) compared to BEN-RIT (25.7%) and the ACA group (26.6%). Among patients treated with ACA, the most frequent SAE was pneumonia (5.2%). In the investigator's choice group, the most frequent SAEs were diarrhea (13.6%) and pneumonia (8%) in patients treated with IDELA-RIT, and no SAEs affected more than one patient treated with BEN-RIT.

Any grade cardiac events occurred in a higher proportion of patients treated with ACA (13%), primarily due to atrial fibrillation (5%), compared to IDELA-RIT (8%) and BEN-RIT (9%). Grade 3 or higher cardiac events occurred in more patients treated with BEN-RIT (9%), with a similar event rate observed in the ACA (3%) and IDELA-RIT (3%) treatment groups. Any-grade bleeding occurred was higher patients treated with ACA (26%) compared to IDELA-RIT (8%) and BEN-RIT (6%); however, grade 3 or higher AEs including major bleeding events were similar between the treatment groups.

A higher proportion of patients treated with IDELA-RIT in the investigator's choice group interrupted treatment (58%), primarily due to AEs, compared to BEN-RIT (11%) and to the ACA group (23%). Dose reductions were also higher in the investigator's choice group and were required in more patients treated with idelalisib (47%) compared to bendamustine (17%) and compared to patients in the ACA group (8%). Similarly, fewer treatment discontinuations due to AEs occurred in the ACA group (10.4%) compared to the investigator's choice group (IDELA-RIT: 52.5%; BEN-RIT: 17.1%).

Treatment-emergent AEs that led to death occurred in six (4%) patients in the ACA group and seven (5%) patients treated with investigator's choice of IDELA-RIT (n = 5) or BEN-RIT (n = 2).

Limitations: Open-label design, disproportionate completion of patient-reported outcome assessments between treatment groups, OS data immature and confounded by treatment crossover, no direct comparison to ibrutinib

Overall, the ASCEND trial was a well conducted phase III RCT. The CADTH Methods Team identified the following key limitations of the trial:

- The open-label trial design is susceptible to multiple biases (e.g., reporting, performance and detection bias) as patients and investigators were not blinded to study treatment. It is possible that biases by both investigators and patients may have influenced the assessment of more subjective outcomes including safety and QoL. The primary end point, IRC-assessed PFS, and secondary end points including IRC-assessed ORR and OS, were unlikely influenced by the study design as the IRC was blinded to the study treatment assignment of patients.
- Due to differences in dosing regimens and modes of administration of the study treatments there was an unequal comparison of treatments in terms of treatment exposure. The continuous therapy with ACA may continue to provide clinical benefit (particularly in delaying progression) compared to a therapy of fixed duration since the disease is being actively treated for a longer period. The longer treatment exposure may result in bias in favour of the ACA treatment group as patients receiving a fixed duration treatment do not have a similar opportunity to prolong PFS with continuous therapy.
- Since patients in the investigator's choice group completed active treatment earlier, compliance with ongoing PRO assessments was reduced. Patient completion rates for each PRO instrument declined over time in each treatment group but the decline was disproportionate, with less patients in the investigator's choice group completing assessments at each assessment time point. The smaller, select group of patients that continued to complete PRO assessments in the investigator's choice group may not be representative of all patients randomized to this treatment group, and thus there is some uncertainty around whether the results obtained are generalizable to the broader ASCEND trial population.
- The OS data were considered immature and not interpretable at the time of the primary efficacy analysis based on a low number of events and the median OS not being reached in each treatment group. The long-term OS data from the trial may be confounded by the treatment crossover of patients in the investigator's choice group to ACA and by the use of post-trial treatments. In addition, any further analysis of OS will be considered a descriptive analysis.
- There were some imbalances in baseline disease characteristics, which suggest the ACA group may have had a more favourable prognosis at baseline compared to the investigator's choice group and these differences may have influenced efficacy outcomes. Compared to the investigator's choice group, patients in the ACA treatment group had a longer time from initial diagnosis to randomization, a slightly higher proportion of patients with Rai stage I disease, and a higher proportion of patients who received only one therapy. The most concerning of these imbalances was the 10% difference between treatment groups in patients who received just one therapy. This difference, in combination with the other imbalances observed between the groups, has the potential to confound efficacy results in favour of ACA.

- IDELA-RIT, the comparator treatment received by most patients in the investigator's choice group is not a commonly used treatment regimen in Canadian clinical practice. Based on current practice, the most relevant treatment comparator for ACA would be ibrutinib monotherapy. In the absence of a direct trial comparison of ACA and ibrutinib, the sponsor submitted MAICs that indirectly compared the efficacy and safety of ACA to ibrutinib and VEN-RIT for the treatment of patients with R/R CLL. After matching the summary baseline characteristics between the ASCEND trial and comparator trials (RESONATE and MURANO), the MAICs results showed that ACA has a similar efficacy in terms of PFS and OS compared to ibrutinib and VEN-RIT. Safety outcomes favoured treatment with ACA for both comparisons; compared to ibrutinib, ACA was associated with a reduced likelihood of all-grade diarrhea, fatigue, peripheral edema, anemia, and hypertension; and compared to VEN-RIT, ACA was associated with a reduced likelihood of all-grade diarrhea and neutropenia, and SAEs. Conversely, the risk of grade 3-4 anemia was significantly increased among patients treated with ACA compared to ibrutinib, and the risk of all grade headache was significantly increased among patients treated with ACA compared to VEN-RIT. The CADTH Methods Team identified several limitations of the submitted MAICs that included the use of unanchored analyses, heterogeneity among the included trials in patient and study characteristics, and reduced sample size of the ASCEND trial across both comparisons after matching, which suggests that there were substantial differences in patients between the ASCEND and comparator trials, and likely important generalizability concerns associated with the ASCEND patients included in the MAIC analyses compared to the overall ASCEND patient population. Due to the methodological limitations associated with the MAICs, the CADTH Methods Team concluded the results should be interpreted with caution.

Need and burden of illness: Incurable and chronic nature of CLL requires additional treatment options to address individual patient needs and preferences

Despite relatively high survival rates, CLL remains an incurable disease. Patients with CLL either die as a result of bone marrow failure (typically from infection or bleeding) or as a result of CLL transformation to an aggressive non-Hodgkin lymphoma, a process known as Richter's transformation. Most patients will have a partial response to initial therapy but will inevitably relapse requiring multiple lines of therapy. Treatment strategies in the relapsed setting depend on the number and intensity of previous lines of therapy, DOR to prior lines of therapy, as well as patient comorbidities. Ibrutinib has emerged as the standard second-line treatment for R/R CLL. Ibrutinib and IDELA-RIT are treatment options that are broadly funded for R/R CLL in Canada; however, IDELA-RIT is less commonly used because of greater toxicity attributed to idelalisib and the relative ease of administration of ibrutinib. Elderly patients may be treated with chemoimmunotherapy such as BEN-RIT, although funding of this combination is less consistent across Canada and it is associated with hematologic toxicity and infections. Venetoclax as monotherapy or combined with rituximab are also funded and primarily used in patients who experience disease progression with ibrutinib. Despite the availability of efficacious treatment options, there remains an unmet need for additional therapies in CLL. Given the long natural history of the disease and the inevitability of relapse, treatments are needed that improve disease control, have lower toxicity, improved tolerability, and that provide patients with options to best meet their individual needs and preferences. ACA is a second generation BTK inhibitor that has a higher BTK selectivity with fewer off-target effects on other kinases, that theoretically should minimize its AE profile as compared to ibrutinib. ACA therefore may provide an additional treatment option with a different safety profile for patients who have contraindications or intolerance to currently available treatments.

Registered clinician input: Unmet need for ACA in patients intolerant to ibrutinib, and in patients with cardiac concerns

Two registered clinicians, one from Cancer Care Ontario (one clinician) and another on behalf of Lymphoma Canada (seven clinicians), provided input for the review of ACA for R/R CLL. The clinicians from Lymphoma Canada indicated they all had experience administering ACA for CLL while the Cancer Care Ontario clinician had minimal experience. The clinicians indicated that the appropriate comparators for ACA in R/R CLL include ibrutinib, IDELA-RIT, VEN-RIT, and BEN-RIT. They also noted that most clinical experts would not consider chemoimmunotherapy as an appropriate treatment option for patients with CLL who have relapsed after previous chemoimmunotherapy. The clinicians considered ACA to address a clinical unmet need in two specific patient groups: patients who do not tolerate ibrutinib, and patients who are not suitable candidates for ibrutinib due to cardiac toxicity. Regarding patients demonstrating an intolerance to ibrutinib, the clinicians stated there is no reason not to administer ACA in patients who have stopped ibrutinib without evidence of disease progression. They noted that the evidence suggests that ibrutinib and ACA exhibit similar effectiveness and tolerability. Regarding patients with cardiac concerns, the clinicians indicated a preference for using ACA in anticoagulated patients, patients with

cardiac comorbidities (e.g., atrial fibrillation), those at risk of cardiovascular events (e.g., dysrhythmias and hypertension), and in patients of advanced age. In terms of sequencing and priority of treatments, the clinicians indicated that ACA could be used in the second-line or beyond, like ibrutinib, after chemoimmunotherapy and prior to venetoclax; and in the third-line setting after venetoclax-based therapy. All clinicians indicated a preference for ACA over IDELA-RIT due to the side effect profile and poor tolerance of the latter, which may result in the need for infusions and patients discontinuing the combination therapy before being able to derive as much benefit as would be expected from ACA. There was a less uniform opinion among clinicians on the preference between ACA and VEN-RIT. Overall, the Lymphoma Canada clinicians believe there is no reason to conclude that one sequence of therapy (i.e., BCL-2 inhibitor then BTK inhibitor or vice versa) would be superior to another based on presently available clinical data.

PATIENT-BASED VALUES

Experience of patients with R/R CLL: Fatigue, frequent infections, and reduced blood counts important disease symptoms to control; need for additional treatment options with less side effects

Two individual patient groups, Lymphoma Canada and the CLLPAG, contributed to a joint input for the review of ACA as monotherapy for the treatment of R/R CLL in patients who have received at least one prior therapy. Data were gathered from three online surveys where most survey respondents were from Canada, the US, and the UK. Patients with CLL indicated they experience increasing symptoms as their disease progresses; ongoing fatigue, frequent infections, and reduced blood counts are common symptoms that patients identified as important to control. Patients cited fatigue and lack of energy, frequent infections, and shortness of breath as the symptoms that affect QoL on an ongoing basis. Patients and caregivers reported ongoing anxiety and worry due to the illness. Psychosocial aspects of CLL that were mentioned included difficulties with concentration and the influence of the disease on personal image and emotions; and mood swings were highlighted as interfering with patients' performance, ability to work, travel, day-to-day-activities, family, friendships, and intimate relations.

Patients reported being treated with two previous therapies, on average, and the most commonly received regimens included fludarabine, cyclophosphamide and rituximab, followed by BEN-RIT as conventional IV therapies. The most common oral therapies received included ibrutinib (most common), venetoclax, and idelalisib. Fatigue, reduced blood counts, nausea, diarrhea, and infections were cited by patients as being the most concerning side effects associated with current therapies for CLL. The patient groups highlighted that the symptoms experienced, the course of illness, and response and tolerance to therapies varied significantly across CLL patients, thus emphasizing the patients' value and need for additional effective treatment options with fewer and more tolerable side effects. Patients did not strongly agree that current therapies manage disease symptoms. Oral therapies were highlighted to have less of an impact on QoL compared to IV therapies based on fewer clinical visits, lower rates of treatment-related fatigue, restored activity level, tolerability of treatment, and lower number and frequency of infections.

Patient values, experience on or expectations for treatment: disease control, less toxicity, improved QoL, and access to affordable oral therapies

Patients indicated they value and prioritize new treatments that can offer increased effectiveness (i.e., disease control), decreased toxicity, improved QoL, accessible and affordable treatments, and access to oral therapies. Of those surveyed, input was provided by 20 patients who had treatment experience with ACA for R/R CLL with most patients diagnosed more than 10 years ago. Half of patients reported that all their CLL symptoms were managed by ACA, with the most common symptoms being increased lymphocyte count, fatigue and lack of energy, and enlarged lymph nodes. Conversely, the most common symptoms that patients reported as not managed by ACA included fatigue, frequent infections, and pain. The ability of ACA to address fatigue was variably reported among patients. The most reported side effects of ACA included diarrhea, headache, and muscle or joint pain. Most patients indicated that treatment side effects had no impact or some impact on their QoL, and aspects of daily living, ability to spend time with family and friends, travel, fulfill family obligations, and perform household chores were cited as being improved by treatment with ACA. Overall, patients reported that ACA was an effective treatment with mild side effects that enabled them to maintain or regain a good QoL. Further, ACA was considered by some patients to be a less toxic alternative to ibrutinib; half of the patient respondents had previously received ibrutinib and all of them had discontinued treatment with ibrutinib due to intolerable side-effects.

ECONOMIC EVALUATION

ACA is supplied as a 100 mg oral capsule at the submitted price of $135.98 per capsule. ACA 100 mg is taken twice daily until disease progression. The per-cycle (28 days) cost of acalabrutinib was estimated to be $7,615.

The sponsor submitted a cost-utility analysis comparing costs and outcomes for ACA (monotherapy) compared with currently available treatment options for the treatment of patients with CLL who have received at least one prior therapy, excluding BCL2 inhibitor or BTK inhibitor (i.e., R/R CLL). For the base case, ACA was compared to ibrutinib. Scenario analyses were performed in which pairwise comparisons were made with IDELA-RIT, IDELA-RIT / BEN-RIT, and VEN-RIT. The modelled population is aligned with the Health Canada approved indication, the sponsor's reimbursement request, and the cohort of patients who enrolled in the ASCEND trial. Costs and quality-adjusted life-years (QALYs) were modelled over a 15-year time horizon based from a public health care payer perspective. The sponsor submitted a partitioned survival model consisting of the following health states: progression free (PF), disease progression, and death. At the start of the model, all patients were assumed to be PF in the second-line setting and, over time, the proportion of patients who progress on second-line treatment was estimated as the difference between the proportion of living patients (estimated from the OS curve), and the proportion of PF patients (estimated from the PFS curve). Parametric survival models fitted to the ASCEND trial PFS and OS data were used to inform the comparison of ACA with IDELA-RIT/BEN-RIT and IDELA-RIT. Comparative efficacy data for ibrutinib and VEN-RIT were derived using a MAIC, which incorporated PFS and OS data from the RESONATE trial for ibrutinib and from the MURANO trial for VEN-RIT. Individual patient data from the ACA group in the ASCEND trial were weighted to ensure the mean baseline characteristics in the ASCEND trial matched those reported for patients in the comparator trials.

CADTH identified that the key limitation with the sponsor's pharmacoeconomic analysis involved MAIC-derived hazard ratios that introduced significant uncertainty into the model that was insufficiently explored and integrated into the economic analysis.

Given the limitations associated with the comparative clinical evidence that could not be addressed, including the lack of head-to-head comparison of ACA and comparators other than IDELA-RIT/BEN-RIT and limited evidence on PFS and OS data beyond the trial, CADTH reanalysis results are associated with uncertainty.

CADTH estimated that ACA was dominant (lower total costs [$2,644] and higher total QALYs [0.12]) compared to ibrutinib. However, scenario analyses suggest that even slight variations in the clinical assumptions have large implications on the predicted outcomes, which in some cases rendering ACA less effective than ibrutinib. This is largely because the clinical evidence derived from MAICs suggests the efficacy of ACA is not significantly different from other targeted therapies, including ibrutinib. Based on the head-to-head evidence from the ASCEND trial, ACA was associated with higher costs and greater QALYs, with incremental cost-effectiveness ratio (ICERs) of $142,169 per QALY and $129,522 per QALY when compared to IDELA-RIT/BEN-RIT and IDELA-RIT, respectively. A price reduction of at least 17% for ACA is required to achieve an ICER of $50,000 per QALY compared with either IDELA-RIT/BEN-RIT, or IDELA-RIT. Compared to VEN-RIT, ACA was dominated (i.e., higher costs and fewer QALYs). A price reduction of more than 80% for ACA is required to achieve an ICER of at $50,000 per QALY compared with VEN-RIT, assuming VEN-RIT is considered a key comparator.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: submitted budget impact analysis is associated with substantial uncertainty

The sponsor's BIA was associated with notable uncertainties and discrepancies in the estimation of the population size, and assumptions regarding the displacement of less expensive comparators by ACA. CADTH reanalyses suggested that introducing ACA to the market may save between $1,960,051 and $2,972,943 over three years based on the submitted and publicly available prices. Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair
- Dr. W. Dominika Wranik, who was not present for the meeting.

Avoidance of conflicts of interest

All members of the CADTH pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of ACA for R/R CLL, through their declarations, no members had a real, potential, or perceived conflict; therefore, based on application of the *pCODR Conflict of Interest Guidelines* no members were excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and PAG input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The sponsor, as the primary data owner, did not agree to the disclosure of patient-reported QoL data, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *pCODR Disclosure of Information Guidelines*.

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.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC recommendation
Eligible patient population	
The reimbursement request is for the treatment of patients with CLL who have received at least one prior therapy. PAG is seeking clarity on whether the following patients would be eligible for treatment with ACA in the R/R setting:	
• Patients who have had experience with ibrutinib or another BCR inhibitor (e.g., idelalisib), or patients having experienced a BCL-2 inhibitor. Is ACA active in these patients?	• Within the ASCEND trial, patients had previously received therapy that included conventional chemotherapy, purine analogues, and anti-CD20 monoclonal antibodies. However, there were no patients who had previously received BTK inhibitors, PI3K inhibitors, or BCL-2 inhibitors. As such, there is no data to inform whether ACA would be safe and effective in patients previously exposed to BTK inhibitors, PI3K inhibitors, or BCL-2 inhibitors. Patients may have ibrutinib discontinued either because their CLL has proven refractory to it or because of the development of ibrutinib-related toxicity. pERC agreed with the CGP that the former group (ibrutinib-refractory) should not be eligible for ACA because non-cross-resistance with ibrutinib has not been demonstrated; however, when ibrutinib has been discontinued due to toxicity, ACA may be considered if its profile does not suggest cross-toxicity with ibrutinib. In Canadian practice, it is plausible that patients may have received front-line therapy with a PI3K or BCL-2 inhibitor on a clinical trial and are then found to be resistant or intolerant to these drugs. pERC agreed with the CGP that in these patients, the use of ACA may be reasonable, despite the lack of published evidence to support this.
• ECOG PS greater than 2	• Based on the eligibly criteria of the ASCEND trial, pERC agreed that patients would need to meet the criteria equating to a good performance status (i.e., ECOG PS of 0 to 2) to be eligible for ACA. However, for patients with an ECOG PS of 3 that can be attributed to disease-related symptoms and not comorbidities, pERC agreed that these patients may also be considered for treatment with ACA.
• Patients with known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome; patients with known CNS lymphoma or leukemia.	• The safety and efficacy of ACA has not been established in these subgroups of patients with CLL, and therefore pERC considers these patients ineligible for ACA.
Implementation factors	
PAG is seeking a clear definition of "disease progression" and "unacceptable toxicity" to help identify discontinuation criteria.	pERC agreed that CLL disease progression should be defined based on published iwCLL (2018) criteria for progression. Patients are continually evaluated for toxicity over the course of treatment and pERC agreed that treatment discontinuation due to toxicity should be determined by the individual patient and clinician.

Sequencing and priority of treatments	
PAG is seeking guidance on the appropriate place in therapy of ACA and overall sequencing of all treatments available for CLL. In particular, PAG would need information on the following aspects: • conditions under which ACA would be a preferred therapy versus ibrutinib, BEN-RIT, VEN-RIT, and IDELA-RIT.	• Conditions under which ACA would be a preferred therapy versus: ○ Ibrutinib: Ibrutinib and ACA have not been directly compared to one another; and in the absence of robust indirect evidence, pERC was unable to indicate a preference between these two drugs. pERC agrees with the CGP that that both ibrutinib and ACA are reasonable choices in relapsed or refractory CLL in patients who are BTK inhibitor naive. ○ BEN-RIT: Within the ASCEND trial, an exploratory subgroup analysis showed that PFS in the 155 patients assigned to ACA was superior to the 35 control patients who received BEN-RIT. Specifically, the estimated PFS at 12 months was 88% (95% CI, 81% to 92%) with ACA and 69% (95% CI, 50% to 82%) with BEN-RIT. SAEs occurred in 29% of patients treated with ACA, compared to 26% of patients treated with BEN-RIT. Based on these findings of a small exploratory subgroup, pERC agrees with the CGP that it is not possible to make definitive conclusions on the comparative efficacy of these drugs. It should be noted that BEN-RIT recipients in the ASCEND trial may have previously received bendamustine, provided that their response to previous bendamustine was ≥ 24 months. For those patients whose duration of response after bendamustine was < 24 months, this combination would not be a reasonable therapeutic choice. ○ VEN-RIT: This combination has not been directly compared to ACA; and in the absence of robust indirect evidence, pERC was unable to indicate a preference between ACA compared to VEN-RIT. pERC agrees with the CGP that both venetoclax-based therapy and ACA are reasonable choices in R/R CLL in patients who are BTK inhibitor naive. ○ IDELA-RIT: In the ASCEND trial, an exploratory subgroup analysis showed that PFS in the 155 patients assigned to ACA was superior to the 118 control patients who received IDELA-RIT. Specifically, the estimated PFS at 12 months was 88% (95% CI, 81% to 92%) with ACA and 68% (95% CI, 58% to 76%) with IDELA-RIT. SAEs occurred in 29% of patients treated with ACA, compared to 56% of patients treated with IDELA-RIT. Based on these findings, pERC agreed with the CGP that ACA represents a more efficacious and safe choice in patients with R/R CLL who are BTK inhibitor naive.

• Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter.	• pERC agreed with the CGP that preferred and alternative therapy in cases of intolerance of, or contraindication to ACA depends on the patients' treatment history, comorbid conditions, performance status, and CLL prognostic factors. Assuming that front-line therapy in CLL is transitioning to BTK inhibitors, therapeutic choices in the R/R CLL will be based around non-BTK-based, non-chemotherapeutic regimens. pERC noted that the CGP does not recommend treating with chemoimmunotherapy subsequent to failure of novel therapies, as there are insufficient data to support this therapeutic decision.
• Sequencing of ACA with other BCR inhibitors and VEN-RIT. There is a need for evidence of effectiveness in patients with failure to previous BCR inhibitors and VEN-RIT. There is a need for information on cross-resistance among BTK inhibitors to inform selection of subsequent therapies.	• ACA is a more specific (targeted) BTK inhibitor with fewer off-target effects on other kinases, which theoretically should minimize its AE profile as compared to ibrutinib. Evidence from a multi-centre phase II study suggests that some patients with ibrutinib intolerance might be able to tolerate subsequent standard dose ACA. Therefore, in cases of ibrutinib intolerance, pERC agreed with the CGP that a careful, individualized switch from ibrutinib to ACA is reasonable in selected CLL patients. pERC noted that according to the CGP, therapeutic switches in the other direction (i.e., from ACA to ibrutinib) are not well described in the published literature. One scenario where a switch from ACA to ibrutinib may be useful is in the setting of ACA-associated headache, which may not recur with ibrutinib. As noted previously, there are no data to support the role of ACA in patients who are resistant to ibrutinib. Similarly, there are no data assessing the role of ACA in patients who are resistant to, or intolerant of venetoclax-based regimens. In the case of venetoclax intolerance, pERC agreed with the CGP that the use of a drug from a different class (e.g., BTK inhibitors ibrutinib or ACA) is clinically acceptable.
• Appropriate time frame (if any) to consider ACA from last dose of ibrutinib in patients who received first-line ibrutinib for high-risk cytogenetics and had a break (without progression).	• pERC agreed that if ibrutinib is discontinued for any reason other than progression (e.g., toxicity or patient or physician choice), ACA can be considered when CLL progression requires treatment, regardless of the time since ibrutinib discontinuation.
• Overall most appropriate line of therapy for ACA. PAG remarked that patients who have progressed on ibrutinib cannot receive IDELA-RIT. PAG would like confirmation that the same situation prevails for ACA.	• pERC agreed with the CGP that it is not possible to make a confident recommendation about the most appropriate treatment line (i.e., first-line versus later lines) for ACA, as this decision depends on multiple patient and CLL-related variables, as well as the availability and funding of other first-line CLL active regimens. As BTK inhibitors are expected to play a progressively greater role in first-line therapy for CLL, the role of next line ACA in R/R CLL is likely to proportionately diminish in favour of regimens from a different class, such as venetoclax.
Companion diagnostic testing	
PAG seeks advice on whether patients with a high-risk genetic profile who progress on first-line	Chromosomal rearrangements in CLL, as measured by FISH, are dynamic, and can evolve throughout the disease course of CLL. Thus, pERC agreed with the CGP's recommendation of retesting if and/or when criteria for therapy are met, as

therapy should be retested for any biomarkers upon relapse.	these results influence prognosis and counselling as well as treatment pathways in CLL. pERC noted that IgHV mutational status is clinically relevant from a prognosis and counselling as well as treatment perspective, but it is stable throughout the diseases course of CLL and therefore retesting is not required.

ACA = acalabrutinib; BEN-RIT = bendamustine-rituximab; CGP = clinical guidance panel; CLL= chronic lymphocytic leukemia; IDELA-RIT = idelalisib-rituximab; FISH = fluorescence in situ hybridization; IgHV = immunoglobulin heavy chain; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; R/R = relapsed or refractory; VEN-RIT = venetoclax plus rituximab.