pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Acalabrutinib (CALQUENCE) **Submitted Reimbursement Request:** Acalabrutinib with or without obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) for whom a fludarabine-based regimen is inappropriate.	
Submitted By: AstraZeneca Canada Inc.	**Manufactured By:** AstraZeneca Canada Inc.
NOC Date: November 28, 2019	**Submission Date:** April 7, 2020
Initial Recommendation: October 29, 2020	**Final Recommendation:** January 8, 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 previously untreated CLL for whom a fludarabine-based regimen is inappropriate, if the following conditions are met:

- cost-effectiveness improved to an acceptable level
- feasibility of adoption (budget impact) is addressed.

Eligible patients include those who are 65 years of age or older, or between 18 and 65 years of age with comorbidities (defined as creatinine clearance between 30 to 69 mL/min or a cumulative Illness Rating Scale [CIRS] for geriatrics score > 6), who 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 chlorambucil-obinutuzumab, 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). pERC agreed that acalabrutinib monotherapy 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 or no detriment to QoL.

In making this recommendation, pERC considered there is also a clinical benefit of acalabrutinib in combination with obinutuzumab; however,

	pERC agreed that acalabrutinib monotherapy better aligns with patient values compared to the combination therapy with acalabrutinib and obinutuzumab, which has a similar magnitude of PFS benefit to monotherapy but greater toxicity and cost, and a less convenient mode of administration due to intravenous obinutuzumab. Therefore, pERC does not recommend reimbursement of acalabrutinib in combination with obinutuzumab. pERC concluded that, at the submitted price, acalabrutinib monotherapy is not considered cost-effective compared to chlorambucil-obinutuzumab in patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate. Limitations with the submitted model suggest that there is uncertainty associated with the results of the economic analysis. 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. A price reduction for acalabrutinib would improve the likelihood that it is a cost-effective treatment for patients with previously untreated CLL who are fludarabine ineligible and would improve the budget impact.
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 monotherapy, 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 approximately 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.

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

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

Per iwCLL guidelines, treatment of CLL is often deferred in asymptomatic patients with early stage disease until there is evidence of progressive, symptomatic, or active disease, as there is no evidence of a survival advantage with early treatment. The choice of treatment is determined by several factors that include the patient's age, performance status, comorbidities, organ function, and the presence of high-risk cytogenetics or molecular features associated with poor prognosis (i.e., chromosome 17p or 11q deletion, TP53 mutation, unmutated immunoglobulin heavy chain variable [IgHV]) and patient preference. For fit, younger CLL patients without high-risk features, first-line treatment in Canada is chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR). However, the proportion of patients who receive FCR is relatively small, as most patients are diagnosed at an older age and are unable to tolerate the toxicities of this regimen. Accordingly, the chemoimmunotherapy regimen of chlorambucil-obinutuzumab combination (CHL-OBI) is often used for patients who cannot tolerate FCR due to age or impaired renal function. More recently, targeted therapies including Bruton's tyrosine kinase (BTK) inhibitors are available and preferred due to their superior efficacy in patients with and without high-risk molecular features and their improved tolerability. Ibrutinib is a first-generation BTK inhibitor that is funded in many Canadian jurisdictions for the first-line treatment of CLL patients who have high-risk cytogenetics. Ibrutinib is also used in unfit patients who do not have high-risk cytogenetics, but to a lesser extent due to inconsistent public funding for this indication. Other publicly funded options include bendamustine-rituximab (BEN-RIT) and chlorambucil-rituximab (CHL-RIT). While highly efficacious therapeutic options exist for patients with previously untreated CLL, pERC agreed that given the incurable nature of CLL, there is a need to have therapeutic choices that offer improved disease control, reduced toxicities, improved tolerability, lower cost, and provide patients with options to best meet their individual needs and preferences.

pERC deliberated on the results of one international, multi-centred, randomized, open-label, three-arm, phase III superiority trial (ELEVATE-TN; n = 535) of combination therapy with acalabrutinib and obinutuzumab (ACA-OBI) and acalabrutinib monotherapy (ACA), respectively, compared to CHL-OBI in adult patients with untreated CLL. Eligible patients were 65 years of age or older, or between 18 and 65 years of age with comorbidities (defined as creatinine clearance between 30 mL/min to 69 mL/min or CIRS for geriatrics score > 6), and must have had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) between 0 and 2 , and active disease meeting one or more of the iwCLL 2008 criteria. Patients were excluded from the trial if they had received a prior systemic therapy for CLL, had known central nervous system lymphoma or leukemia, prolymphocytic leukemia, history of or suspected Richter's syndrome, significant cardiovascular disease (CVD), or required concomitant medication with warfarin (or equivalent vitamin K antagonists). Patients in the CHL-OBI treatment group were permitted to crossover to receive ACA upon disease progression. pERC discussed that most patients in ELEVATE-TN had high-risk features (ranging from 65.4% to 72.9% across groups), and therefore, the most appropriate treatment comparator for these patients would be ibrutinib and not CHL-OBI.

The primary efficacy end point of the ELEVATE-TN trial was independent review committee assessment (IRC) of PFS for the comparison of ACA-OBI versus CHL-OBI. IRC-assessed PFS for the comparison of ACA versus CHL-OBI was evaluated as a secondary end point and was included in the hierarchical statistical testing of outcomes. 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 28.3 months. When compared to CHL-OBI, both ACA-OBI and ACA were shown in the trial to be associated with a statistically significant reduction in the risk of disease progression or death (ACA-OBI versus CHL-OBI: hazard ratio [HR] = 0.10;

95% CI, 0.06 to 0.17; P < 0.0001); ACA versus CHL-OBI: HR = 0.20; 95% CI, 0.13 to, 0.30; P < 0.0001). pERC noted that the PFS benefit of ACA-OBI and ACA was consistent across all pre-specified patient subgroup analyses performed. pERC also considered the results of a post-hoc analysis performed by the sponsor to explore the relative efficacy of ACA-OBI and ACA in terms of IRC-assessed PFS, which showed a reduction in the risk of disease progression or death with ACA-OBI compared to ACA (HR = 0.49; 95% CI, 0.26 to 0.95). pERC discussed that this analysis was not prospectively planned or powered to compare PFS between the acalabrutinib treatment groups and therefore was exploratory in nature. pERC concluded that the results of this analysis should be interpreted with caution and that the relative PFS of ACA-OBI versus ACA remains uncertain. In terms of overall survival (OS), pERC noted the OS data were immature at the time of the primary efficacy analysis. Due to the treatment crossover allowed in the trial, pERC acknowledged that the longer-term OS data may be confounded by crossover and the use of other subsequent post-trial treatments. Considering treatment crossover and the chronic nature of CLL, pERC agreed with the Clinical Guidance Panel (CGP)'s conclusion that PFS is the most appropriate end point to assess the clinical efficacy of acalabrutinib, and the statistically significant PFS benefits observed in the trial with ACA-OBI and ACA are clinically meaningful.

pERC deliberated on the safety data from ELEVATE-TN. pERC observed that due to differences in the treatment regimens being compared (i.e., continuous therapy with acalabrutinib versus fixed duration of CHL-OBI) treatment exposure was much longer in the ACA-OBI and ACA groups, at 27.7 months, compared to approximately 5.6 months with CHL-OBI. The most common adverse events (AEs) associated with acalabrutinib in either treatment group were diarrhea and headache. pERC discussed that the CGP identified cardiac toxicity to be a concern with acalabrutinib, which pERC noted is characteristic of BTK inhibitors as a class (i.e., ibrutinib). In the trial, any-grade cardiac events occurred in a similar proportion of patients in the ACA-OBI (14.0%) and ACA (14.0%) groups and these proportions were approximately two times greater than that observed in the CHL-OBI group (7.7%). pERC discussed that the incidence of cardiac toxicity may be higher when acalabrutinib is used in clinical practice considering patients with significant CVD were excluded from the ELEVATE-TN trial. Bleeding and infections of any grade also occurred in a higher proportion of patients in the acalabrutinib groups compared to CHL-OBI, while hypertension was observed in similar proportions of patients in all groups. The incidence of grade 3 or higher AEs was noticeably increased in the combination treatment groups, at 70.2% and 69.8% and mainly attributed to neutropenia in the ACA-OBI and CHL-OBI groups, respectively, compared to 45.3% in the ACA group. The need for treatment interruption, dose reduction, and treatment discontinuation of acalabrutinib due to AEs was higher in the ACA-OBI group compared to ACA. Serious AEs (SAEs) occurred in more patients treated with acalabrutinib (38.8% for ACA-OBI, and 31.8% for ACA) compared to CHL-OBI (21.9%). Based on these safety data, pERC agreed with the CGP that the side effects of acalabrutinib were as expected and generally considered manageable with no new safety signals. pERC concluded that the toxicity associated with ACA monotherapy was less when compared to ACA-OBI and CHL-OBI.

pERC also discussed the health-related QoL data from the ELEVATE-TN trial, which was assessed as an exploratory outcome and measured using the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC-QLQ-C30), the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-Fatigue), and the 5-dimension EuroQol (EQ-5D) questionnaire. The QoL results showed [redacted] Based on these QoL data, pERC concluded that there is no detriment to QoL outcomes with either ACA-OBI or ACA when compared to CHL-OBI. *(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 on the input received from one joint submission from two patient advocacy groups, Lymphoma Canada and CLL Canada (formerly 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 either ACA or ACA-OBI indicated that the treatment managed all their symptoms, except for fatigue in some patients. pERC noted that treatment-related fatigue was cited as the side effect that most impacted patients' QoL. pERC discussed that ACA monotherapy aligns with more patient values; compared to ACA-OBI, monotherapy has similar efficacy, less toxicity, and offers a more convenient oral administration, the latter of which is an important consideration for a primarily elderly patient population. pERC noted that acalabrutinib may not be affordable for all patients considering oral therapies are not funded equally across Canada.

In addition to the ELEVATE-TN trial, pERC also deliberated on the results of a series of matched indirect comparisons (MAICs) submitted by the sponsor that indirectly compared the efficacy and safety of ACA-OBI and ACA with relevant treatment options. pERC's deliberation focused on the MAICs to ibrutinib, the most appropriate comparator in this patient population. The MAIC results showed that ACA-OBI and ACA both had similar clinical efficacy, in terms of PFS and OS, to ibrutinib monotherapy. In terms of safety, ACA monotherapy was associated with a reduced likelihood of all-grade cardiac toxicity and grade 3 or higher infections compared to ibrutinib monotherapy; while ACA-OBI was associated with an increased likelihood of all-grade neutropenia compared to ibrutinib monotherapy. pERC acknowledged, however, that the CADTH Methods Team identified several limitations of the 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 ELEVATE-TN trial for most comparisons in the MAICs. The CADTH Methods Team noted that these reductions in sample size suggest there were substantial differences in the patient populations of included trials, and likely important generalizability concerns associated with the ELEVATE-TN patients who were included in each MAIC analysis compared to the overall ELEVATE-TN patient population. Considering these limitations, and in the absence of direct head-to-head trials comparing acalabrutinib regimens to ibrutinib, pERC concluded that no conclusions can be drawn from the MAIC results on the comparative efficacy of either ACA-OBI or ACA to ibrutinib monotherapy.

pERC discussed at length whether a reimbursement recommendation should be made for both ACA-OBI and ACA. In reaching their recommendation, pERC considered that both regimens offer a PFS benefit of similar magnitude, however, it was clear to the Committee that ACA monotherapy better aligns with patient values compared to ACA-OBI, which has greater toxicity and cost, and a less convenient mode of administration due to intravenous obinutuzumab. pERC noted that this opinion is supported by the conclusions of the CGP and by the majority of registered clinicians providing input, who indicated a strong preference for ACA monotherapy over ACA-OBI and did not see a role for the use of ACA-OBI in any particular patient subgroup. Therefore, based on the available clinical evidence, pERC concluded that reimbursement should be limited to ACA monotherapy for patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate.

Upon reconsideration of the Initial Recommendation, pERC reviewed the feedback received from all stakeholder groups and focused its deliberation on the feedback received from PAG, which was the only stakeholder group that did not fully support early conversion of the Initial Recommendation to a Final Recommendation. PAG requested that a more explicit statement be added to the recommendation to note that although the sponsor sought reimbursement for both ACA-OBI and ACA monotherapy, pERC did not recommend reimbursement for ACA-OBI. pERC agreed with PAG, and for clarity, added a statement to the recommendation that ACA-OBI is not recommended for reimbursement.

pERC deliberated on the cost-effectiveness of ACA and ACA-OBI compared with BEN-RIT, ibrutinib, and CHL-OBI for patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate. pERC noted limitations with the indirect comparisons used to inform the economic evaluation, which limited the ability to perform the sequential analysis. As such, pERC concluded that the cost-effectiveness of acalabrutinib compared with treatments such as ibrutinib and BEN-RIT is unknown. Based on the existing clinical evidence, pERC considered that the comparison based on the extrapolated ELEVATE-TN trial data represented a more appropriate comparison. pERC concluded that ACA was associated with lower costs and greater quality-adjusted life years (QALYs) than ACA-OBI (i.e., dominant) and that ACA was not cost-effective versus CHL-OBI at the submitted price. Given the level of uncertainty associated with the economics findings, pERC considered that a price reduction for acalabrutinib is

required to improve the likelihood that it is a cost-effective treatment. pERC noted the evidence was only applicable to the reimbursement request population and that the lack of clinical data in the broader Health Canada-approved population highlights that the cost-effectiveness in the broader Health Canada-approved population is unknown.

Upon reconsideration of the Initial Recommendation, PAG also requested that the condition of feasibility of adoption (i.e., budget impact) be added to the recommendation to address concerns on the affordability of ACA monotherapy. Upon pERC obtaining more information on the nature of the request, PAG indicated that based on real-world use of ibrutinib in Canadian jurisdictions, where dose reductions are more frequent when compared to the rate observed for ACA in the ELEVATE-TN trial, clinicians may prefer to use ACA instead of ibrutinib for reasons related to toxicity. In the absence of data on how long patients may be on treatment with ACA, PAG had concerns about the budget impact should ACA be better tolerated by patients than ibrutinib, since the drug is to be taken until disease progression or unacceptable toxicity. pERC considered this a reasonable request considering the lack of long-term data on ACA, and therefore agreed the condition of feasibility of adoption was appropriate.

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
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups, Lymphoma Canada and CLL Canada (formerly CLLPAG)
- input from registered clinicians: one clinician on behalf of the Cancer Care Ontario Drug Advisory Committee (CCO DAC) and seven clinicians on behalf of Lymphoma Canada
- input from CADTH's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- Two patient advocacy groups: Lymphoma Canada and CLL Canada
- One registered clinician from the CCO DAC
- PAG
- The sponsor, Astra Zeneca Canada Inc.

The pERC Initial Recommendation was to recommend the reimbursement of acalabrutinib as monotherapy in adult patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate, conditional on the related cost-effectiveness improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the sponsor, patient advocacy groups, and registered clinicians all agreed with the Initial Recommendation, and PAG agreed in part with the Initial Recommendation. PAG requested that pERC add to the recommendation an explicit statement on the reimbursement status of ACA-OBI since the combination is included in the reimbursement request; and that the condition of feasibility of adoption (i.e., budget impact) be added to the recommendation to address concerns on the affordability of ACA monotherapy.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review was to evaluate the safety and efficacy of acalabrutinib, with or without obinutuzumab, compared to existing treatment options for adult patients with previously untreated CLL for whom a fludarabine-based treatment regimen is inappropriate.

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

The pCODR systematic review included one international, multi-centre, randomized, open-label, phase III superiority trial of ACA-OBI and ACA, respectively, compared to CHL-OBI in adult patients with untreated CLL. The ELEVATE-TN trial was conducted across 18 countries in 142 centres, including five sites in Canada that enrolled a total of 22 Canadian patients. Eligible patients were randomized in a 1:1:1 ratio to ACA-OBI, ACA, or CHL-OBI. [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.)* In the ACA treatment groups, patients received ACA for continuous cycles until disease progression (PD) or unacceptable toxicity; and in the ACA-OBI treatment group, patients received ACA combined with six cycles of intravenous obinutuzumab starting in cycle 2. In the CHL-OBI group, patients received oral chlorambucil combined with intravenous obinutuzumab for six cycles. Treatment crossover was permitted for patients in the CHL-OBI group to receive ACA monotherapy after confirmation of PD if they continued to meet study eligibility criteria and had not received any new systemic therapy before initiation of acalabrutinib.

Patient populations: Previously untreated, median age of 70 years, and ECOG 0 or 1; majority of patients with high-risk features

Eligible patients were 65 years of age or older, or between 18 and 65 years of age with comorbidities (defined as creatinine clearance between 30 mL/min to 69 mL/min or a CIRS for geriatrics score greater

than 6), had to have an ECOG PS between 0 and 2 and active disease meeting one or more of the iwCLL 2008 criteria. The trial excluded patients who had received prior systemic therapy for CLL, had known central nervous system 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 535 eligible patients were randomized to receive ACA-OBI (n = 179), ACA (n = 179), and CHL-OBI (n = 179). Demographic and disease characteristics were generally balanced between the treatment groups. The median age of patients was 70 years (interquartile range [IQR] = 66 to 75). At baseline, most patients had an ECOG PS of 0 or 1 (93.6%). In terms of cytogenetics and molecular features, overall, 9.2% (n = 49) had a chromosome 17p deletion, 17.8% (n = 95) had a chromosome 11q deletion, 11.4% (n = 61) had a TP53 mutation, and 63.2% (n = 338) had unmutated IgHV. The patients in the ACA-OBI group had a lower proportion of patients with high-risk molecular features compared to patients in the ACA and CHL-OBI groups (high-risk features by treatment group: 65.4%, 72.1%, 72.9%, respectively). The median time from initial diagnosis was approximately six months shorter in the ACA group (24.4 months) compared to the ACA-OBI (30.5 months) and CHL-OBI (30.7 months) groups. There was a higher proportion of patients with a high-risk CLL International Prognostic Index (CLL-IPI) score in the ACA group (74.9%) compared to the ACA-OBI (64.2%) and CHL-OBI (67.2%) groups. A higher proportion of patients in the ACA group (27.9%) had Rai stage III disease compared to CHL-OBI (22.6%). Taking multiple factors into account, the ACA group may have had a less favourable prognosis due to shorter time from diagnosis and a higher proportion of patients with high-risk disease as per CLL-IPI, stage III disease as per Rai staging, bulky disease, and high-risk molecular features.

Key efficacy results: Statistically significant and clinically meaningful PFS benefit with acalabrutinib-based regimens compared to CHL-OBI; OS data immature

Patients were assessed for tumour response and disease progression in accordance with iwCLL 2008 criteria. All primary and secondary efficacy endpoints 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 February 8, 2019) after a median duration of follow-up of 28.3 months (IQR: 25.6, 33.1). The key efficacy outcomes deliberated by pERC included the primary end point, IRC-assessed PFS for the comparison of ACA-OBI to CHL-OBI, and key secondary endpoints that included IRC-assessed PFS for the comparison of ACA monotherapy to CHL-OBI, and OS comparing ACA-OBI and ACA, respectively, to CHL-OBI.

Primary End Point:

- IRC-assessed PFS (ACA-OBI versus CHL-OBI): based on a total of 14 (7.8%) IRC-assessed PFS events in the ACA-OBI group and 93 (52.5%) PFS events in the CHL-OBI group, the ELEVATE-TN trial met its primary end point. The median PFS was not reached in the ACA-OBI group and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. ACA-OBI demonstrated a statistically significant reduction in the risk of disease progression or death relative to CHL-OBI (HR = 0.10; 95% CI, 0.06 to 0.17; P < 0.0001).

Secondary End Points:

- IRC-assessed PFS (ACA versus CHL-OBI): the median PFS was not reached in the ACA group (95% CI, 34.2 to not estimable) and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. ACA demonstrated a statistically significant reduction in the risk of disease progression or death relative to CHL-OBI (HR = 0.20; 95% CI, 0.13 to, 0.30; P < 0.0001).

- OS: Since statistical significance of overall response rate (ORR) was not reached (see below), the OS results for the comparison of ACA to CHL-OBI were considered descriptive based on hierarchal statistical testing. OS data were considered immature and the median OS had not been reached in any treatment group. A total of nine patients (5.0%) in the ACA-OBI group, 11 patients (6.1%) in the ACA group, and 17 patients (9.6%) in the CHL-OBI group had died. The OS trends favoured ACA-OBI (HR = 0.47; 95% CI, 0.21 to 1.06; P < 0.0001) and ACA (HR= 0.60; 95% CI, 0.28 to 1.27) compared to CHL-OBI.

The results of pre-specified subgroup analyses for IRC-assessed PFS defined by demographic and disease characteristics showed a consistent PFS benefit in favour of ACA-OBI and ACA compared to CHL-OBI. A post-hoc, exploratory analysis was conducted to compare IRC-assessed PFS between the two acalabrutinib treatment groups, which showed a reduction in the risk of disease progression or death

(i.e., 51%) with ACA-OBI compared to ACA (HR = 0.49; 95% CI, 0.26 to 0.95). A P value was not assigned due to the exploratory nature of this analysis.

ORR was another key efficacy outcome of the ELEVATE-TN trial. At the interim analysis, there was an absolute difference in ORR of 15% between the ACA-OBI and CHL-OBI treatment groups, which was statistically significant (P < 0.0001); the best ORR in the ACA-OBI group was higher at 94% (95% CI, 89 to 97) compared to 79% (95% CI, 72 to 84) in the CHL-OBI group. In the ACA group, the ORR was 86% (95% CI, 80 to 90), which represented an absolute increase of 7% compared to the CHL-OBI group that did not reach statistical significance (P = 0.08).

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

[redacted]

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Safety: ACA monotherapy has less toxicity compared to ACA-OBI and CHL-OBI

A total of 526 patients were included in the analyses of safety in the ELEVATE-TN trial, which included 178 in the ACA-OBI group, 179 in the ACA group, and 169 in the CHL-OBI group. The median duration of treatment with ACA was 27.7 months in both ACA-based treatment groups, while the median duration of treatment with obinutuzumab was 5.5 months and 5.6 months in the ACA-OBI and the CHL-OBI treatment groups, respectively. The median duration of treatment with chlorambucil was 5.5 months in the CHL-OBI group. At the time of the data cut-off date, a similar proportion of patients in the acalabrutinib treatment groups were actively receiving treatment (79.3%) and no patients were still receiving treatment with CHL-OBI. A total of 45 patients (25.4%) crossed over from CHL-OBI to ACA. Overall, few trial patients received a subsequent therapy after study drugs were discontinued. A total of 2.8%, 6.1%, and 5.6% of patients in the ACA-OBI, ACA, and CHL-OBI treatment groups, respectively, received a subsequent therapy.

A similar proportion of patients experienced any-grade AEs in the three treatment groups (96.1% in the ACA-OBI group, 95.0% in the ACA group, and 98.8% in the CHL-OBI group). The most common any-grade AEs in the ACA-OBI and ACA groups included headache (39.9% and 36.9%, respectively) and diarrhea

(38.8% and 34.1%, respectively). In the ACA-OBI group, this was followed by neutropenia (31.5%), fatigue (28.1%), and contusion (23.6%); and in the ACA group, this was followed by nausea (22.3%), fatigue (18.4%), cough (18.4%), and upper respiratory tract infection (18.4%). In the CHL-OBI group, the most common any-grade AEs included neutropenia (45.0%), infusion-related reactions (39.6%), nausea (31.4%), diarrhea (21.3%), and pyrexia (20.7%).

Grade 3 or higher AEs were increased in the ACA-OBI (70.2%) and CHL-OBI treatment groups (69.8%) compared to the ACA group (49.7%). The most common grade 3 or higher AEs in the ACA-OBI group included neutropenia (29.8%), thrombocytopenia (8.4%), and anemia (5.6%). Similarly (although in a higher proportion of patients) in the CHL-OBI group, 41.4%, 11.8%, and 7.1% experienced neutropenia, thrombocytopenia, and anemia, respectively. In the ACA group, neutropenia (9.5%) and anemia (6.7%) were the most common grade 3 or higher AEs. A greater proportion of patients in the ACA-OBI group experienced an any-grade SAE (38.8%) compared to the ACA (31.8%) and CHL-OBI (21.9%) groups. Pneumonia was the most common any-grade SAE, and grade 3 or higher SAEs were reported in both the ACA-OBI (any grade: 6.7%; grade ≥ 3: 4.5%) and ACA groups (any grade: 2.8%; grade ≥ 3: 2.2%). In the CHL-OBI group, the most common SAEs were tumour lysis syndrome (4.7%; all were grade ≥ 3) and febrile neutropenia (4.1%; all were grade ≥ 3).

Any-grade cardiac events occurred in a similar proportion of patients in the ACA-OBI (14.0%) and ACA (14.0%) groups, and these proportions were higher than what was observed in the CHL-OBI group (7.7%). Similarly, bleeding of any grade (ACA-OBI: 42.7%; ACA: 39.1%) and infections of any grade (ACA-OBI : 69.1%; ACA: 65.4%) occurred in a higher proportion of patients in the acalabrutinib groups compared to the CHL-OBI group (bleeding: 11.8% and infections: 43.8%).

A higher proportion of patients interrupted treatment with acalabrutinib due to AEs in the ACA-OBI group (n = 60; 33.7%) compared to patients in the ACA group (n = 28; 15.6%); and a similar proportion of patients interrupted treatment with obinutuzumab in both the ACA-OBI (n = 18; 10.1%) and CHL-OBI treatment groups (n = 21; 12.4%). More patients in the ACA-OBI treatment group required a dose reduction of acalabrutinib due to an AE (n = 14; 7.9%) compared to patients in the ACA group (n = 5; 2.8%). Dose reductions of obinutuzumab were not permitted in the trial. In the ACA-OBI group, 11.2% of patients withdrew from treatment due to AEs compared to 8.9% in the ACA group and 14.1% in the CHL-OBI group.

There were 21 deaths (3.9%) attributed to AEs (occurring within the 30 days of last dose and beyond 30 days) and included four in the ACA-OBI group, six in the ACA group, and 11 in the CHL-OBI group.

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

Overall, ELEVATE-TN 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 the 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 endpoints 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 (i.e., continuous therapy with acalabrutinib versus the fixed duration of treatment with CHL-OBI). The longer treatment exposure may result in bias in favour of the acalabrutinib treatment groups as patients in the fixed duration treatment group do not have a similar opportunity to prolong PFS with continuous therapy.
- Since patients in the CHL-OBI 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 CHL-OBI group completing assessments at each assessment time point. The smaller, select group of patients that continued to complete PRO assessments in the CHL-OBI

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 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 any treatment group. The long-term OS data from the trial could be confounded by the treatment crossover of patients in the CHL-OBI group to ACA and by the use of post-trial treatments.
- In the ELEVATE-TN trial, acalabrutinib demonstrated efficacy in patients with or without high-risk molecular features. Based on current Canadian clinical practice, the most relevant treatment comparator for this patient subgroup would be ibrutinib and not CHL-OBI. In the absence of a direct trial comparison of acalabrutinib-based regimens and ibrutinib, the sponsor submitted a series of MAICs that indirectly compared the efficacy and safety of ACA (monotherapy) and ACA-OBI to ibrutinib and other relevant comparators for the treatment of patients with previously untreated CLL. After matching the summary baseline characteristics of patients between the ELEVATE-TN trial and five comparator trials (RESONATE-2, iLLUMINATE, CLL-14, ALLIANCE, and CLL 11), the MAIC results showed that ACA was similar in clinical efficacy (PFS and OS) when compared to ibrutinib monotherapy; and was associated with a statistically significant improvement in clinical efficacy (PFS or OS) when compared to ibrutinib plus obinutuzumab (IBR-OBI), BEN-RIT, CHL-RIT, and venetoclax plus obinutuzumab (VEN-OBI). The MAIC results showed that ACA-OBI was similar in efficacy (PFS and OS) compared to ibrutinib, IBR-OBI, and VEN-OBI; and associated with a statistically significant improvement in clinical efficacy (PFS) compared with BEN-RIT and CHL-RIT. In terms of safety, the results of the MAIC suggested that ACA had a reduced likelihood of AEs that included any-grade major hemorrhage and grade 3-4 atrial fibrillation and hypertension when compared with ibrutinib, IBR-OBI, and BEN-RIT; and a reduced likelihood of all-grade neutropenia and infections when compared to VEN-OBI and CHL-RIT. However, ACA was associated with a statistically significant increase in leukopenia compared to VEN-OBI and CHL-RIT. ACA-OBI was associated with a reduced likelihood of all-grade atrial fibrillation when compared with IBR-OBI and BEN-RIT, and grade 3-4 neutropenia when compared to VEN-OBI. However, ACA-OBI was associated with a statistically significant increase in neutropenia compared to ibrutinib, and a statistically significant increase in leukopenia when compared to VEN-OBI and CHL-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 terms of patient and study characteristics, and reduced sample size of the ELEVATE-TN trial across various comparisons after matching, which suggests that there were substantial differences in patients between the ELEVATE-TN and comparator trials, and likely important generalizability concerns associated with the ELEVATE-TN patients included in the MAIC analyses compared to the overall ELEVATE-TN patient population. Due to the methodological limitations associated with the MAICs, the CADTH Methods Team concluded the MAIC 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. For patients who cannot tolerate fludarabine-based treatment, CHL-OBI is often used as first-line treatment. In recent years, however, targeted therapies have become available and are preferred due to their superior efficacy in patients with or without high-risk features and their improved tolerability. Ibrutinib is a first-generation BTK inhibitor that is funded in many Canadian jurisdictions for the first-line treatment of patients who have high-risk cytogenetics. Ibrutinib is also used in unfit patients who do not have high-risk cytogenetics, but to a lesser extent due to inconsistent public funding across Canada. Other publicly funded options include BEN-RIT and CHL-RIT. While highly efficacious therapeutic options exist for patients with previously untreated CLL, there remains a desire to have therapeutic choices that offer reduced toxicities, improved tolerability, and lower cost, and treatments that provide patients with options to best meet their individual needs and preferences. Having an additional treatment option with acalabrutinib, which is a second generation BTK inhibitor with fewer off-target effects on other kinases, theoretically should minimize its AE profile as compared to ibrutinib, and thus may provide an alternative treatment choice when other drugs in the same space are contraindicated for a patient.

Registered clinician input: Acalabrutinib effective regardless of high-risk features; preference for ACA monotherapy among most clinicians

Two registered clinicians, one from Cancer Care Ontario (CCO) (one clinician) and another on behalf of Lymphoma Canada (seven clinicians), provided input for the review of acalabrutinib for previously untreated CLL. The clinicians from Lymphoma Canada indicated they all had experience administering acalabrutinib for CLL; whereas, the CCO clinician did not specify this information. Clinicians indicated that the appropriate comparators for first-line therapy include CHL-OBI and ibrutinib for high-risk patients. They estimated that approximately 50% of fludarabine-ineligible patients in Canada are currently treated with ibrutinib monotherapy as first-line treatment although there is variation in provincial funding for this drug.

Both clinician inputs stated that current data suggest that acalabrutinib is effective in all CLL patients who are fludarabine ineligible regardless of high-risk features. However, there were contrasting views whether ACA as monotherapy or ACA-OBI is the preferred regimen for first-line treatment of CLL. The opinion of the clinicians from Lymphoma Canada was that the data for ACA-OBI are not strong enough to justify the added costs and toxicity of combination therapy and they anticipated no groups of patients for which they would consider ACA-OBI based on the current evidence. Conversely, the one clinician from CCO believed that ACA-OBI would be the preferred regimen based on the pivotal trial results and it would replace the current standard of CHL-OBI. The inability for patients to concurrently use a proton-pump inhibitor was noted as a deterrent to treatment with acalabrutinib.

The clinicians indicated a preference for administering acalabrutinib over ibrutinib in patients of advanced age who are at risk of cardiovascular events (e.g., atrial fibrillation and hypertension) due to reported rates of cardiac related deaths with ibrutinib. Outside of these concerns they stated they would administer acalabrutinib in any patient for whom they would consider treatment with ibrutinib, as they expect acalabrutinib to be associated with lower toxicity but comparable efficacy.

PATIENT-BASED VALUES

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

Two patient groups, Lymphoma Canada and the CLLPAG, contributed to a joint input on the review of acalabrutinib for previously untreated CLL. 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, with the most common conventional therapies being FCR followed by BEN-RIT. The most common oral therapies received by patients 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 intravenous 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, 22 patients and nine patients had frontline treatment experience with ACA (monotherapy) and ACA-OBI, respectively. More than two-thirds of ACA patients (68%) and more than three-quarters of ACA-OBI patients (78%) reported that acalabrutinib managed all their symptoms. The only symptoms reported to be unmanaged by acalabrutinib in more than 10% of patients in either treatment-experience group were fatigue and lack of energy (26%). Among those who experienced treatment-related side effects, muscle or joint pain, and headaches were the most reported side effects in the ACA and ACA-OBI treatment-experience groups, respectively. Reduced blood counts appeared to be more common among patients treated with ACA-OBI and included anemia, thrombocytopenia, and neutropenia being reported more often. Treatment-related fatigue was reported to have a "significant" or "very significant" impact on QoL, while treatment-related headache was never reported to have a "significant" or "very significant" impact on QoL in both treatment-experience groups. Overall, acalabrutinib was reported to be an effective treatment with mild side effects allowing for patients to maintain or regain a good QoL.

ECONOMIC EVALUATION

Acalabrutinib is supplied as a 100 mg oral capsule at submitted price of $135.98 per capsule. When used as monotherapy (ACA), acalabrutinib 100 mg is taken twice daily until disease progression. When used in combination with obinutuzumab (ACA-OBI), acalabrutinib 100 mg is taken twice daily until disease progression, and obinutuzumab 1,000 mg is administered intravenously every four weeks for a total of six cycles. The cost per 28-day cycle of ACA was estimated to be $7,615. When used in combination with obinutuzumab the cost per cycle ranges from $7,615 to $24,049.

The sponsor submitted a cost-utility analysis comparing costs and quality-adjusted life years (QALYs) for ACA compared with currently available treatment options for the treatment of patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate (ibrutinib monotherapy and chlorambucil in combination with obinutuzumab (CHL-OBI) as base case comparators, bendamustine in combination with rituximab (BEN-RIT) additionally included in a scenario analysis). Costs and QALYs were modelled over a 20-year time horizon based from a public health care payer perspective. The modelled population is in line with the ELEVATE-TN trial population and the sponsor's reimbursement request but does not align with the Health Canada-approved population that includes all previously untreated CLL patients. The sponsor indicated that acalabrutinib had not been studied in the broader Health Canada-approved population, and since there are no clinical data to support an economic analysis in patients who are appropriate for a fludarabine-based regimen, this analysis could not be provided. This rationale was considered reasonable justification. The sponsor presented analyses for ACA-OBI within scenario analyses. The sponsor submitted a three-state semi Markov model costing of Progression-free (PF), Progressed disease (PD) and Death states. All patients entered the model in the PF state and received first-line treatment until PD or death. Once in the PD state, patients receive subsequent treatment. Time to progression (TTP) and time to death (TTD) were used to inform the transition probabilities from the PF to PD states, and PD to Death states, respectively. TTP and TTD for ACA, ACA-OBI, and CHL-OBI were derived using parametric survival models fitted to ELEVATE-TN trial patient data. Comparative efficacy of ACA and ACA-OBI versus ibrutinib or BEN-RIT was derived as hazard ratios (HRs) from MAICs.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Comparative efficacy for acalabrutinib with and without obinutuzumab when compared with ibrutinib monotherapy and BEN-RIT was derived from multiple MAICs. The CADTH clinical review highlighted several concerns about the internal validity of MAIC results given the substantial heterogeneity in the populations included, differences in effect modifiers, and in the design of included studies.
- The submitted model applied fixed TTP and TTD curves based on PFS and OS, and these curves have integrated relative hazards between interventions making it impossible to perform crucial scenario analyses or test structural uncertainties with the model.

Given the limitations associated with the comparative clinical evidence, the cost-effectiveness of acalabrutinib, as monotherapy or in combination with obinutuzumab, in patients with previously untreated CLL who are fludarabine-eligible is unknown. Furthermore, CADTH was unable to undertake sequential analyses that included the most relevant comparator currently available (ibrutinib) due to the sponsor's use of multiple MAICs for comparative efficacy. These MAICs were associated with

methodological uncertainty, such that any differences between treatments are associated with unknown magnitude. Therefore, CADTH reanalyses that considered corrections to the sponsor's model and alternate cost sources do not address the key identified limitations.

The comparison of ACA with CHL-OBI (and ACA-OBI) using the best available data from the ELEVATE-TN trial suggests that ACA is more effective and more costly than CHL-OBI (incremental cost-effectiveness ratio [ICER] = $65,672 per QALY), and associated with greater QALYs and fewer costs compared with ACA-OBI (i.e., dominant). A price reduction of at least 4% for acalabrutinib is required to achieve an ICER of $50,000 per QALY for ACA compared with CHL-OBI.

ADOPTION FEASIBILITY

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

The sponsor's budget impact analysis was associated with notable uncertainties due to limited information of key model drivers, including population size, treatment uptake, and treatment displacement, and acalabrutinib combination use. CADTH reanalyses suggested the estimated budget impact may range from $225,335 to $400,259 over three years in the population aligned with the reimbursement request based on the submitted and publicly available prices, though could be higher if acalabrutinib displaces treatments other than ibrutinib. 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.

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

- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH 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 acalabrutinib for previously untreated 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 Provincial Advisory Group 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 patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate. PAG is seeking clarity on whether the following patients would be eligible for treatment with acalabrutinib in the first-line setting:	
• Patients with an ECOG performance status score greater than 2	• Based on the eligibly criteria of the ELEVATE-TN 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 acalabrutinib. 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 acalabrutinib.
• Patients older than 65 years who do not match the following trial inclusion criteria: a) Creatinine clearance 30 to 69 mL/min OR b) A score higher than six on the Cumulative Illness Rating Scale-Geriatric.	• pERC agreed with the CGP that patients with a CIRS-geriatric score of <7 and with renal function that is sufficiently preserved (i.e., creatinine clearance of >69mL/min) may be eligible for more intensive therapy such as BEN-RIT. BEN-RIT has not been directly compared to acalabrutinib and therefore it is not known whether BEN-RIT eligible patients would experience a similar or greater clinical benefit from acalabrutinib.
• Patients with creatinine clearance less than 30 mL/minute	• The safety and efficacy of acalabrutinib has not been established in patients with creatinine clearance less than 30 mL/min, and therefore pERC considered these patients ineligible for acalabrutinib.
• Patient with platelets less than 25×10^9/L and densely packed bone marrow	• In the ELEVATE-TN trial, a platelet count ≥ 50 × 109 /L, or ≥ 30 × 109 /L in patients with documented bone marrow involvement, and without transfusion support seven days before assessment was required. Patients with transfusion-dependent thrombocytopenia were excluded from the trial. The safety and efficacy of acalabrutinib has not been established in patients with impaired hematopoiesis and associated thrombocytopenia with bleeding risk. Therefore, pERC agreed with the CGP that acalabrutinib-based therapy could be considered in clinically stable, non-bleeding patients, provided that clinical caution and careful risk/benefit assessment be implemented before using acalabrutinib-based therapy. Another option is to consider a brief course of CLL debulking therapy with non-myelosuppressive or minimally myelosuppressive therapy first (e.g., a trial of corticosteroids), and if platelets counts subsequently improve, to institute acalabrutinib-based therapy.
• CD20-negative CLL	• pERC agreed with the CGP that eligible patients for acalabrutinib would need to meet WHO criteria for CLL. The level of CD20 is characteristically low in CLL

	compared to normal B cells and other B-cell lymphoproliferative disorders. In rare cases of CLL, CD20 may be negative; in these situations, specialized hematopathology diagnostic assessment would be required to render a confident diagnosis of CLL. In this situation, ACA monotherapy would be reasonable to consider.
• Patients with known CNS lymphoma or leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome	• The safety and efficacy of acalabrutinib has not been established in these subgroups of patients with CLL, and therefore pERC considers these patients ineligible for acalabrutinib.
Implementation factors	
Treatment with acalabrutinib should continue until disease progression or unacceptable toxicity. 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. pERC noted, however, that since BCR inhibitors including ACA can result in treatment-related lymphocytosis, especially during the first few months of therapy (and up to 12 months after treatment initiation), an isolated increase in lymphocytosis in patients who are otherwise well, early after treatment initiation, should not be considered grounds for CLL 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 acalabrutinib ± obinutuzumab and overall sequencing of all treatments available for CLL. In particular, PAG would need information on the following aspects:	
• Preferential use of acalabrutinib versus ibrutinib in high-risk patients, and of acalabrutinib, ibrutinib, BEN-RIT, or CHL-OBI in FCR-ineligible patients.	• pERC agreed with the CGP that there is currently no direct or robust indirect evidence to justify the preferential use of acalabrutinib or ibrutinib, or for the first-line use of acalabrutinib versus BEN-RIT in FCR-ineligible patients. Based on the superior PFS results reported in the ELEVATE-TN trial, acalabrutinib is preferred over CHL-OBI.
• Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter.	• As noted above, pERC agreed there is no preferred therapy.
• Use of ACA-OBI. A cohort treated with this combination was included in the ELEVATE-TN trial. At this time, it is unclear what population would benefit the most from the addition of obinutuzumab. PAG also seeks guidance on whether obinutuzumab can be subsequently discontinued, and what patient factors would drive such a decision.	• pERC agreed with the CGP that there is no compelling indication for ACA-OBI over ACA alone. The ELEVATE-TN trial was not powered to compare ACA monotherapy with ACA-OBI. Significant toxicities were associated with the combination regimen including neutropenia, infections and infusion-related reactions. Further, the need to administer obinutuzumab as an intravenous infusion increases patient, hospital, pharmacy, and nursing time as compared to monotherapy.
• Sequencing of ibrutinib and acalabrutinib. Is there information on cross-resistance between	• pERC agreed with the CGP that there is limited evidence on the safe and efficacious use of a BTK

BTK inhibitors that could inform whether one can be used when the other has failed?	inhibitor after the failure of another drug of the same class. Therefore, after first-line acalabrutinib intolerance or failure, a CLL therapy drug of another class would instead need to be considered. Regarding the role of next-line acalabrutinib after ibrutinib intolerance, pERC noted that acalabrutinib 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 acalabrutinib. Therefore, pERC agreed with the CGP that in cases of ibrutinib intolerance, a careful, individualized switch from ibrutinib to acalabrutinib is reasonable in selected CLL patients. pERC agreed that therapeutic switches in the other direction (i.e., from acalabrutinib to ibrutinib) will be rare and may be considered in individual patients.
• Appropriateness of therapies after failure on acalabrutinib e.g., VEN-RIT, BEN-RIT, CHL-OBI.	• If acalabrutinib failure occurs (i.e., CLL non-responsiveness or progression), next-line therapy depends on multiple patient and disease-related factors. pERC agreed with the CGP that optimal therapeutic approaches consist of choosing a drug from a different therapeutic class that is likely to be active in CLL, such as venetoclax (± rituximab), idelalisib, or cellular therapy.

ACA = acalabrutinib; BEN-RIT = bendamustine plus rituximab; ACA-OBI = acalabrutinib plus obinutuzumab; CGP = clinical guidance panel; CHL-OBI = chlorambucil plus obinutuzumab; CLL= chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, and rituximab; IgHV = immunoglobulin heavy chain; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; VEN-RIT = venetoclax plus rituximab.